TiTAN CRETE
Tobacco treatment TrAining Network in Crete
Pharmacotherapy
Learning Objectives:

Describe principles in the use of pharmacotherapy and best practices in the use of first-line pharmacotherapies for smoking cessation.
Pharmacotherapy

All smokers trying to quit, except in the presence of special circumstances, should receive pharmacotherapy for smoking cessation.

3 “Generations”
NRT
bupropion
varenicline

“All smokers trying to quit, except in the presence of special circumstances, should receive pharmacotherapy for smoking cessation.”
<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Duration</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irritability / aggression</td>
<td>&lt; 4 weeks</td>
<td>50%</td>
</tr>
<tr>
<td>Depression</td>
<td>&lt; 4 weeks</td>
<td>60%</td>
</tr>
<tr>
<td>Restlessness</td>
<td>&lt; 4 weeks</td>
<td>60%</td>
</tr>
<tr>
<td>Poor concentration</td>
<td>&lt; 2 weeks</td>
<td>60%</td>
</tr>
<tr>
<td>Increase appetite</td>
<td>&gt; 10 weeks</td>
<td>70%</td>
</tr>
<tr>
<td>Light-headedness</td>
<td>&lt; 48 hours</td>
<td>10%</td>
</tr>
<tr>
<td>Night-time awakenings</td>
<td>&lt; 1 week</td>
<td>25%</td>
</tr>
<tr>
<td>Constipation</td>
<td>&gt; 4 weeks</td>
<td>17%</td>
</tr>
<tr>
<td>Mouth ulcers</td>
<td>&gt; 4 weeks</td>
<td>40%</td>
</tr>
<tr>
<td>Urges to smoke</td>
<td>&gt; 2 weeks</td>
<td>70%</td>
</tr>
</tbody>
</table>

The major meta-analyses include those of the Cochrane Collaboration, which examines in more than 40 analyses the effectiveness of different aspects of nicotine replacement therapy and the final report of the U.S. Surgeon General, co-ordinated by Michael C. Fiore, in the guide to smoking cessation for general practitioners. These data are consistent because they are based on the same studies. All these analyses reported the effectiveness of recommended treatments and are cited in this guide. These analyses report that smoking cessation treatment is not fully effective and that failures may occur as relapse during or after the treatment of tobacco addiction as a chronic disease.

The Cochrane Collaboration identified 132 trials of nicotine replacement products, 111 trials involving over 40,000 participants compared the different types of nicotine replacement therapy to a placebo or a control group without nicotine replacement therapy. RR (relative risk) of abstinence from all forms of substitute versus control is 1.58 (95% confidence interval [CI]: 1.50 to 1.66).

The RR for each type was:
- gum,
- patches,
- inhaler,
- nasal spray.

The results are independent of the duration of treatment, the intensity of the additional assistance provided or the context in which the NRT was issued. The effect is similar to a small group of studies to evaluate the use of nicotine replacement therapy without prescription. In the case of highly dependent smokers, there was a significant benefit of 4 mg gum compared with 2 mg gum, but evidence of a benefit of higher doses of patch are lower in the studies currently available. The lack of studies concerning high doses is regrettable.

The Cochrane Collaboration authors concluded that all commercially available forms of NRT (gum, transdermal patch, nasal spray, inhaler and sublingual tablets) can help smokers in their quit attempts and increase their chances of success. Substitutes increase the discontinuation rates of 50%-70%, regardless of type and dose.

**Figure 14:** Evolution of nicotine levels in the cerebral arteries with repeated nicotine consumption.

Nicotine replacement therapy delivers nicotine to the brain much more slowly than cigarettes, producing no peaks. It is thus able to saturate the nicotine receptors, so eliminating the need for nicotine, without stimulating the receptors, thus producing progressively fewer receptors, which after three months of NRT will return to normal number. However, these cells retain the memory of smoking and could be multiplied very rapidly on the cell membrane if smoking is resumed: tobacco dependence is therefore a chronic relapsing disease.
Kinetics of nicotine arterial blood after smoking a cigarette or NRTs

Graph showing the nicotine plasma levels in ng/ml as a function of time for different nicotine delivery methods:
- Cigarette
- Nasal spray
- Gum 4 mg
- Gum 2 mg
- Patch 21 mg

The graph illustrates the peak nicotine concentrations and the time it takes for nicotine levels to drop. The figure highlights the slower and more sustained nicotine delivery from patches compared to cigarettes and nasal spray.
NRT vs. Nicotine

- Absorbed more slowly via venous system
- Much lower levels of nicotine
- Helps minimize withdrawal and cravings
- Attenuated sympathomimetic response
- Flat dose-response curve of nicotine & CV effects
- **NO** Carbon monoxide! **NO** oxidants!
- 4,999+ other chemicals/mutagens are **not** present!
Figure 13: The two objectives of nicotine replacement therapy: decrease withdrawal syndrome (acute) and reduce addiction by reducing the number of receptors (chronic)
Nicotine Replacement Therapy

Patch
- 20 mg, 15 mg, 10 mg

Gum
- 2 mg, 4 mg

Inhaler
- 10 mg (per cartridge)
- 2 mg (absorbed)

Mouth Spray
- 1 mg per spray/dose
NRT – Patch

:: Available in 10mg, 15mg, 25 mg

:: Apply the patch to a clean, dry, non hairy area on the upper part of your body (arms, chest, back).

:: Replace the patch with a new one every 24 hours.

:: Remove the patch at bedtime, if you have difficulty sleeping.
NRT - Inhaler

- Fast Acting to address urges or cravings.
  - Nicotine delivered to oral cavity, throat & upper respiratory tract (a small fraction reaches the lungs)

- Provides hand to mouth motion of smoking

- 10 mg nicotine per cartridge
  - 4 mg can be extracted per cartridge
  - Only 2mg systemically absorbed
NRT - Gum

- Use gum once or twice at approximately the same frequency you would take a drag on a cigarette.
- Chew slowly until you can taste the nicotine or feel a slight tingling in your mouth, then stop chewing.
- Place the gum between your cheek and gum. After one minute, repeat the process until cravings are resolved.
- Avoid eating or drinking 15 minutes before or during use.
NRT Mouth Spray

- 1mg nicotine/spray dose
- 1-2 sprays every 30 to 60 minutes prn
- Maximum dosage is 4 sprays/hour
- Contains at least 150 sprays
How to use Mouth Spray

- First use, prime the spray pump
- Point spray nozzle as close to open mouth as possible and release
- Do not inhale to avoid getting spray down throat
- Refrain from swallowing for a few seconds

Possible Side Effects:
- Headache, nausea, vomiting, changes in taste, tingling sensation of the mouth
NRT Combination Therapy

NRT Patch

Flexible, short acting format:

Provides baseline dose of NRT throughout the day

Provides rapid relief from cravings and other withdrawal symptoms
Combination Therapy

Significantly higher cessation rates vs. monotherapy at 12 and 24 weeks\textsuperscript{6}

- Combination (15mg Patch + Gum) (n=149)
- 15mg Patch (n=150)

% Abstinent

- 12 weeks: 34.2% (p=0.039) vs. 22.7% (p=0.018)
- 24 weeks: 27.5% (p=0.018) vs. 15.3%
- 52 weeks: 18.1% vs. 12.7%

Weeks after start of treatment

Adapted from Kornitzer et al. 1995\textsuperscript{6}
Assessing Nicotine Addiction

1. Number of Cigarettes smoked per day

2. Time to First Cigarette

3. Patient History
Choosing the right dose

<table>
<thead>
<tr>
<th>Smokes ≥ 30 minutes of waking</th>
<th>Smokes ≤ 30 minutes of waking</th>
<th>TREATMENT GUIDE</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td></td>
<td>.: 10 mg for 6 weeks OR;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>.: use gum, inhaler or spray alone</td>
</tr>
<tr>
<td>10-19</td>
<td>&lt;10</td>
<td>.: 15mg daily for 6 weeks then;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>.: 10mg daily for 2 to 4 weeks</td>
</tr>
<tr>
<td>20-29</td>
<td>10-19</td>
<td>.: 25mg daily for 6 weeks then;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>.: 15mg daily for 2 weeks then;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>.: 10mg daily for 2 weeks <strong>or longer</strong></td>
</tr>
<tr>
<td>30-39</td>
<td>20-29</td>
<td>.: 25mg (25mg + 10 mg) daily for 6 weeks then;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>.: 25mg daily for 4 weeks then;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>.: 15mg daily for 2 weeks then;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>.: 10mg daily for 2 weeks <strong>or longer</strong></td>
</tr>
<tr>
<td></td>
<td>30-40</td>
<td>.: 35mg (25mg + 15mg) daily for 6 weeks then;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>.: 25mg daily for 4 weeks then;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>.: 15mg daily for 2 weeks then;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>.: 10mg daily for 2 weeks <strong>or longer</strong></td>
</tr>
<tr>
<td>40+</td>
<td></td>
<td>.: 40mg (25mg x 2) daily for 6 weeks then;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>.: 35mg (25mg + 10mg) daily for 2 weeks then;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>.: 25mg daily for 2 weeks then;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>.: 15mg daily for 2 weeks then;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>.: 10mg daily for 2 weeks <strong>or longer</strong></td>
</tr>
</tbody>
</table>

**WITH:**

Inhaler, gum, spray to be used as needed/required by the patient to manage cravings and withdrawal.
Heavy Smokers

- 20 or more Cigarettes
- Time to First Cigarette less than 5 mins (or 30 mins) from waking. Generally require higher doses of NRT

**Example:** 2 ppd (40 cigs) = 2 x 21 mg patches (42mg)

30-40 cigs/day = 35 mg

- Patch + Inhaler most often used
  - Inhaler used for breakthrough cravings
Titration of NRT

- If after initial application of Nicotine patch, withdrawal or cravings persist, add other forms of Nicotine Replacement Therapy (gum or inhaler to address cravings as necessary).

- If after 24 hours, cravings continue to persist, may add 7mg Nicotine patch (increase by 7mg increments only)
Remember...

Any patient who is likely to continue smoking is much ‘safer’ receiving NRT
Bupropion – How it works

• Helps to balance the chemicals in the brain
• Reduces nicotine cravings and withdrawal
Bupropion and The Biology of Nicotine Addiction

Nicotine deprivation causes two reactions:
1. Psychological Craving
2. Physiological Withdrawal Symptoms

Mesolimbic Dopamine System
nicotine stimulates release of dopamine

Locus Ceruleus
nicotine withdrawal may cause changes in the noradrenaline level

Bupropion – Dosage and duration

• Begin taking at least 7 days before quit date
• **Day 1-3:** 150 mg daily
• **Day 4 to Week 12:** 150 mg at breakfast and dinner (or at least 8 hours between doses)

• **OPTION TO:** Remain at 150 mg daily as side effects are dose dependant

• The usual duration is 12 weeks, however, some people may continue to take it up to 24 weeks.

• Take with full glass of water.
Bupropion Side Effects

- Dry mouth
- Insomnia
- Dizziness
- Difficulty concentrating
- Nausea
- Anxiety
- Constipation
- Shakiness
- Skin rash
- “I don’t feel right”
Bupropion - Side Effects

To address side effects:

• Ensure it is being taken properly with a full glass of water.

• May use OTC anti-nausea med. (eg. Ginger Gravol) if symptoms persist.

• Consider reducing dose by half (going back to 150mg twice a day) if symptoms are severe or intolerable.

• For severe mood changes – assess and follow product monograph - discontinuation may be advised.
Bupropion

Reduce dose from
150 bid to 150 mg/day

Side effects are dose dependent.
Varenicline

• How it works
• Contraindications
• Dosing
• Duration
• Side effects
New Medications and Approaches

Varenicline

Influences neurotransmitters and receptors
Addresses the neurochemistry of addiction
Varenicline ...a selective partial agonist of the $\alpha 4\beta 2$ nicotinic ACh receptor

- Provides relief from craving and withdrawal – *agonist* effect

- Blocks satisfaction and rewarding effects of nicotine – *antagonist* effect
**α4β2 nAChR Partial Agonists**

- **Smoking No Partial Ag**
- **No Smoking Partial Ag**
- **Smoking + Partial Ag**

<table>
<thead>
<tr>
<th>Smoking</th>
<th>No Smoking</th>
<th>Smoking + Partial Ag</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Partial Ag</td>
<td>Partial Ag</td>
<td>Antagonist</td>
</tr>
</tbody>
</table>

**α4β2 nAChR**

- **Nicotine**
  - Agonist: 100%
  - Partial Ag: 50%
  - Potential to relieve craving and withdrawal when quitting
  - Potential to block reinforcing effects when smoking

**Dual action of a partial agonist**
α4β2 Receptor

NICOTINE

CELL MEMBRANE

TiTAN CRETE
α4β2 Receptor

Varenicline

Cell Membrane
CO-Confirmed Continuous Abstinence - Wks 9-52

**Response Rate (%)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Varenicline</th>
<th>Bupropion</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>22.1</td>
<td>16.4</td>
<td>8.4</td>
</tr>
<tr>
<td>II</td>
<td>23.0</td>
<td>15.0</td>
<td>10.3</td>
</tr>
</tbody>
</table>

**OR (95% CI) p-value**

- **Varenicline vs. Placebo** (Study I): OR=3.13 (95% CI 1.97, 4.97) p<0.0001
- **Varenicline vs. Placebo** (Study II): OR=2.66 (95% CI 1.72, 4.11) p<0.0001
- **Bupropion vs. Placebo** (Study I): OR=1.45 (95% CI 0.98, 2.14) p=0.064
- **Bupropion vs. Placebo** (Study II): OR=1.72 (95% CI 1.16, 2.55) p<0.0062

**Total Participants**

- N=349 (Study I, Varenicline)
- N=329 (Study I, Bupropion)
- N=344 (Study I, Placebo)
- N=343 (Study II, Varenicline)
- N=340 (Study II, Bupropion)
- N=340 (Study II, Placebo)
Quit ‘Trajectories’

7-Day PP of Abstinence

- **Varenicline**
  - 50.4%
  - 36.4%
  - 35.2%
  - 30.6%
  - 23.5%
  - 17.3%

- **Bupropion**
  - 35.2%
  - 26.4%
  - 26.4%
  - 23.5%
  - 17.3%

- **Placebo**
  - 20.8%
  - 17.9%
  - 17.9%
  - 17.3%

Responders (%)

0 4 8 12 16 20 24 28 32 36 40 44 48 52
Varenicline - Contraindications

Do not use:

- If previous drug reaction to Varenicline
- If under age 18 yrs
- If pregnant or breastfeeding
- History of renal failure and is taking Cimetidine

Special Considerations (speak to MD)

- If using any form of NRT
- Recent history of nausea and vomiting in the past 2 months
- History of renal failure
Varenicline

• Begin taking 8 days before quit date
• **Day 1-3:** 0.5 mg daily
• **Day 4-7:** 0.5 mg at breakfast and dinner
• **Week 2 to Week 12:** 1 mg at breakfast and dinner

• **OPTION TO:** Remain at 0.5 mg at breakfast and dinner

• The usual duration is 12 weeks, however, some people may continue to take it up to 24 weeks.

• Take with full glass of water.
Varenicline – Side Effects

- Nausea (30%, 3% severe)
- Vomiting
- Trouble sleeping
- Headache
- Abnormal dreams
- Constipation
- Gas
- Allergic reaction (rare)
- Altered/depressed mood

- Avoid hazardous tasks until patients knows their reaction to medication
Varenicline - Side effects

- **To address side effects:**
  - Ensure it is being taken properly with a full glass of water.
  - For sleep disturbances, suggest med is taken earlier in the evening (at least 8 hours after morning dose)
  - May use Ginger Gravol if symptoms persist
  - Consider reducing dose by half (going back to 0.5mg twice a day) if symptoms are sever or intolerable.
  - For severe mood changes, refer to appropriate health care professional
Varenicline – Side Effects

• To address Nausea/Headache
  • Glass of Water
  • Dimenhydrinate

• Consider reducing dose by half
<table>
<thead>
<tr>
<th>Psychiatric Disorders</th>
<th>Varenicline (N=3091)</th>
<th>Placebo (N=2005)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (n)</td>
<td>% (n)</td>
</tr>
<tr>
<td><strong>Depressed mood disorders/disturbances</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>1.6 (51)</td>
<td>1.2 (24)</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>1.0 (32)</td>
<td>0.6 (12)</td>
</tr>
<tr>
<td><strong>Disturbances in thinking and perception</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thinking abnormal</td>
<td>0.4 (13)</td>
<td>0.1 (2)</td>
</tr>
<tr>
<td></td>
<td>0.2 (7)</td>
<td>-- (1)</td>
</tr>
<tr>
<td><strong>Mood disorders and disturbances NEC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affect liability</td>
<td>0.6 (20)</td>
<td>0.3 (6)</td>
</tr>
<tr>
<td>Mood swings</td>
<td>0.3 (10)</td>
<td>0.1 (2)</td>
</tr>
<tr>
<td>Apathy</td>
<td>0.2 (5)</td>
<td>-- (1)</td>
</tr>
<tr>
<td><strong>Psychiatric disorders NEC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.5 (16)</td>
<td>0.3 (6)</td>
</tr>
</tbody>
</table>
Varenicline, Smoking Cessation, and Neuropsychiatric Adverse Events

**Objective:** In 2009, the U.S. Food and Drug Administration issued a black box warning for varenicline regarding neuropsychiatric events. The authors used data from randomized controlled trials and from a large Department of Defense (DOD) observational study to assess the efficacy and safety of varenicline.

**Conclusions:** This analysis revealed no evidence that varenicline is associated with adverse neuropsychiatric events. The evidence supports the superior efficacy of varenicline relative to both placebo and bupropion, indicating considerable benefit without evidence of risk of serious neuropsychiatric adverse events, in individuals with and without a recent history of a psychiatric disorder.

## Comparison of Monotherapy and Combination Therapies

<table>
<thead>
<tr>
<th>Pharmacotherapy</th>
<th>Estimated OR (95% CI)</th>
<th>Estimated Abstinent Rate (95% CI)</th>
<th>Cost Per Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1.0</td>
<td>13.8</td>
<td>-</td>
</tr>
<tr>
<td>Nicotine Patch</td>
<td>1.9 (1.7-2.2)</td>
<td>23.4 (21.3-25.8)</td>
<td>$25-$30</td>
</tr>
<tr>
<td>High Dose Patch</td>
<td>2.3 (1.7-3.0)</td>
<td>26.5 (21.3-32.5)</td>
<td>$25-$30</td>
</tr>
<tr>
<td>Nicotine Inhaler</td>
<td>2.1 (1.5-2.9)</td>
<td>24.8 (19.1-31.6)</td>
<td>$40-$80</td>
</tr>
<tr>
<td>Nicotine Gum</td>
<td>1.5 (1.2-1.7)</td>
<td>19.0 (16.5-21.9)</td>
<td>$42</td>
</tr>
<tr>
<td>Bupropion</td>
<td>2.0 (1.8-2.2)</td>
<td>24.2 (22.2-26.4)</td>
<td>$15-$21</td>
</tr>
<tr>
<td>Varenicline</td>
<td>3.1 (2.5-3.8)</td>
<td>33.2 (28.9-37.8)</td>
<td>$36</td>
</tr>
<tr>
<td>Patch + Inhaler</td>
<td>2.2 (1.3-2.6)</td>
<td>25.8 (17.3-36.5)</td>
<td>$40-$60</td>
</tr>
<tr>
<td>Patch + Gum</td>
<td>2.6 (2.5-5.2)</td>
<td>26.5 (28.6-45.3)</td>
<td>$40-$60</td>
</tr>
<tr>
<td>Patch (long-term; &gt; 14 weeks) + ad lib NRT (gum or spray)</td>
<td>3.6 (2.5–5.2)</td>
<td>36.5 (28.6–45.3)</td>
<td>$40-$60</td>
</tr>
<tr>
<td>Patch + Bupropion</td>
<td>2.5 (1.9-3.4)</td>
<td>28.9 (23.5-25.1)</td>
<td>$40-$51</td>
</tr>
</tbody>
</table>

Pharmacological Treatments for Smoking Cessation

**CLINICAL QUESTION** Among the 3 first-line smoking cessation treatments (nicotine replacement therapy [NRT], bupropion, and varenicline), which is most effective in helping people who smoke achieve and maintain abstinence from smoking for at least 6 months, and what serious adverse events are associated with each?

**BOTTOM LINE** Higher rates of smoking cessation were associated with NRT (17.6%) and bupropion (19.1%) compared with placebo (10.6%). Varenicline (27.6%) and combination NRT (31.5%) (eg, patch plus inhaler) were most effective for achieving smoking cessation. None of the therapies was associated with an increased rate of serious adverse events.

- Cahill K., Stevens S., and Lancaster T. Pharmacological treatments for smoking cessation. JAMA Clinical Evidence Synopsis. 2014 311(2):
COMBINATION THERAPIES

• NRTs - excellent

• NRT + Bupropion – good

• NRT + Varenicline – emerging evidence

• Bupropion + Varenicline – emerging evidence

Problems with Pharmacotherapy

- Outdated concepts re: cessation
- “Myths” and “Misunderstandings”
- Rigid Application
- Inadequate Dosing Strategies
- Side effects

“Not a Magic Bullet!”