

# 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.**



3 “Generations”  
NRT  
bupropion  
varenicline

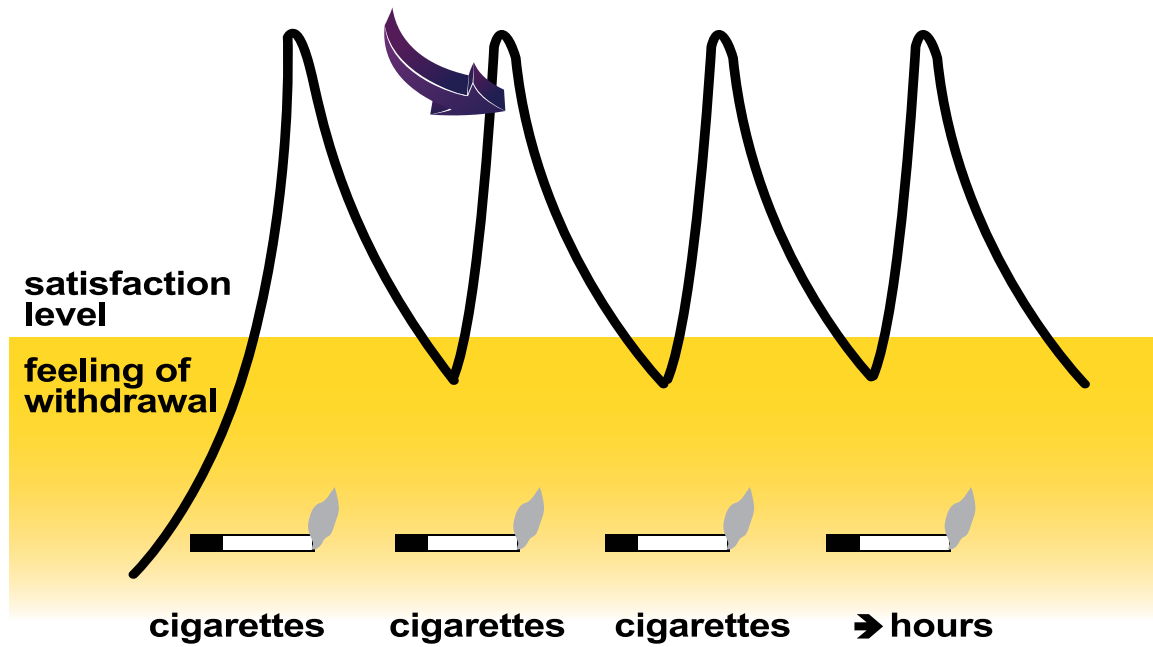
“All smokers trying to quit, except in the presence of special circumstances, should receive pharmacotherapy for smoking cessation.”



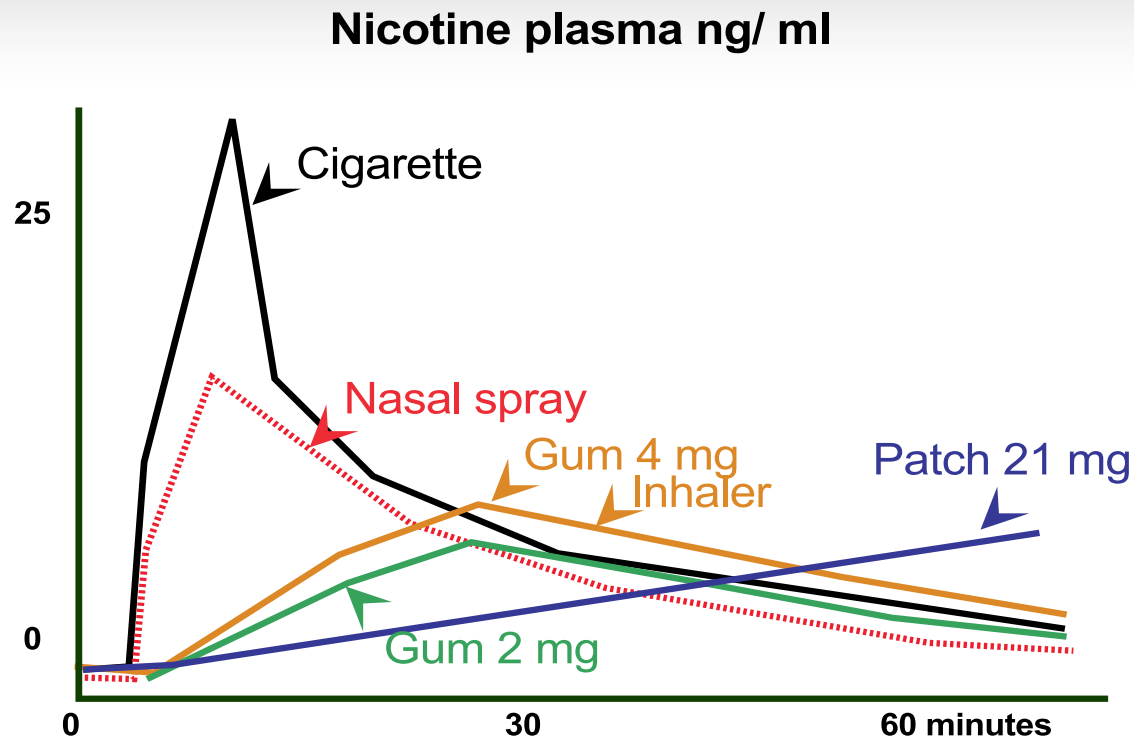
# Nicotine Withdrawal Symptoms

Symptoms	Duration	Prevalence
Irritability / aggression	< 4 weeks	50%
Depression	< 4 weeks	60%
Restlessness	< 4 weeks	60%
Poor concentration	< 2 weeks	60%
Increase appetite	> 10 weeks	70%
Light-headedness	< 48 hours	10%
Night-time awakenings	< 1 week	25%
Constipation	> 4 weeks	17%
Mouth ulcers	> 4 weeks	40%
Urges to smoke	> 2 weeks	70%

## NICOTINE CONCENTRATION IN BLOOD



# Kinetics of nicotine arterial blood after smoking a cigarette or NRTs

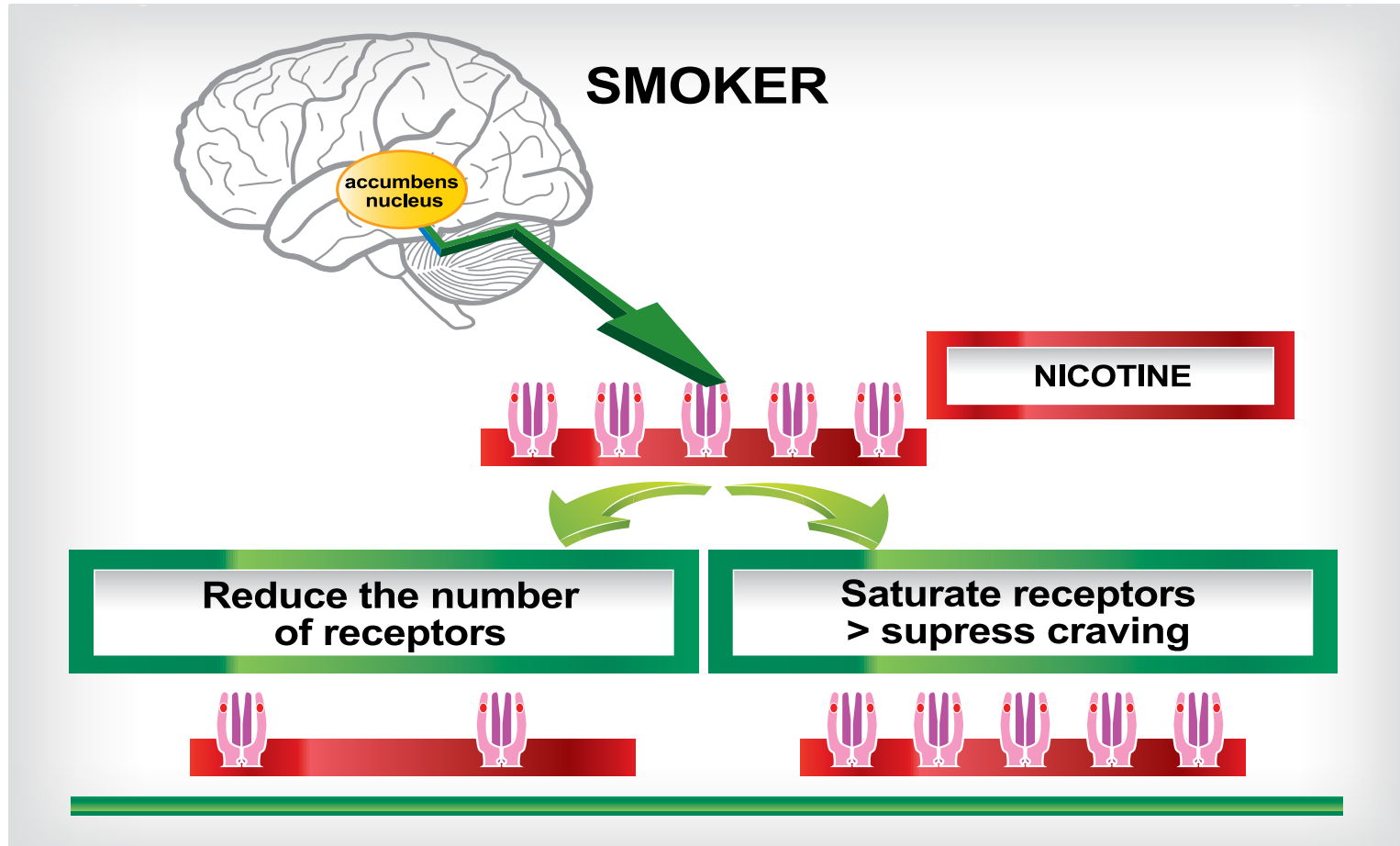


# NRT vs. Nicotine

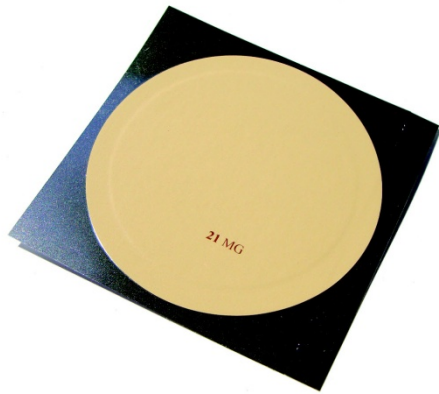
- Absorbed more slowly via venous system
- Much lower levels of nicotine
- Helps minimize withdrawal and cravings
- Attenuated sympathomimetic response
- Flat dose-response curve of nicotine & CV effects
- NO Carbon monoxide ! NO oxidants !
- 4,999+ other chemicals/mutagens are not present!



**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  
2mg, 4mg



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



Mouth Spray  
1mg 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

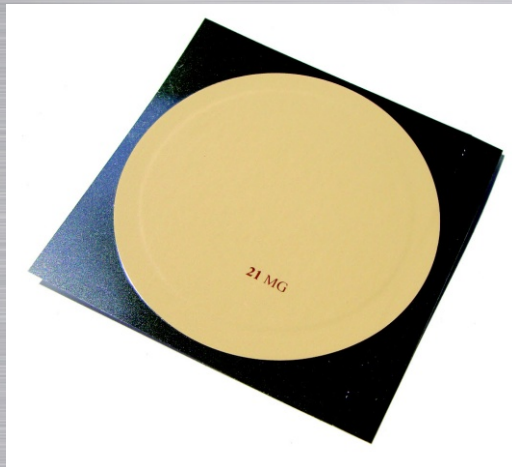
## Possible Side Effects:

- Headache, nausea, vomiting, changes in taste, tingling sensation of the mouth



# NRT Combination Therapy

**NRT Patch**



+

**Flexible, short acting format:**



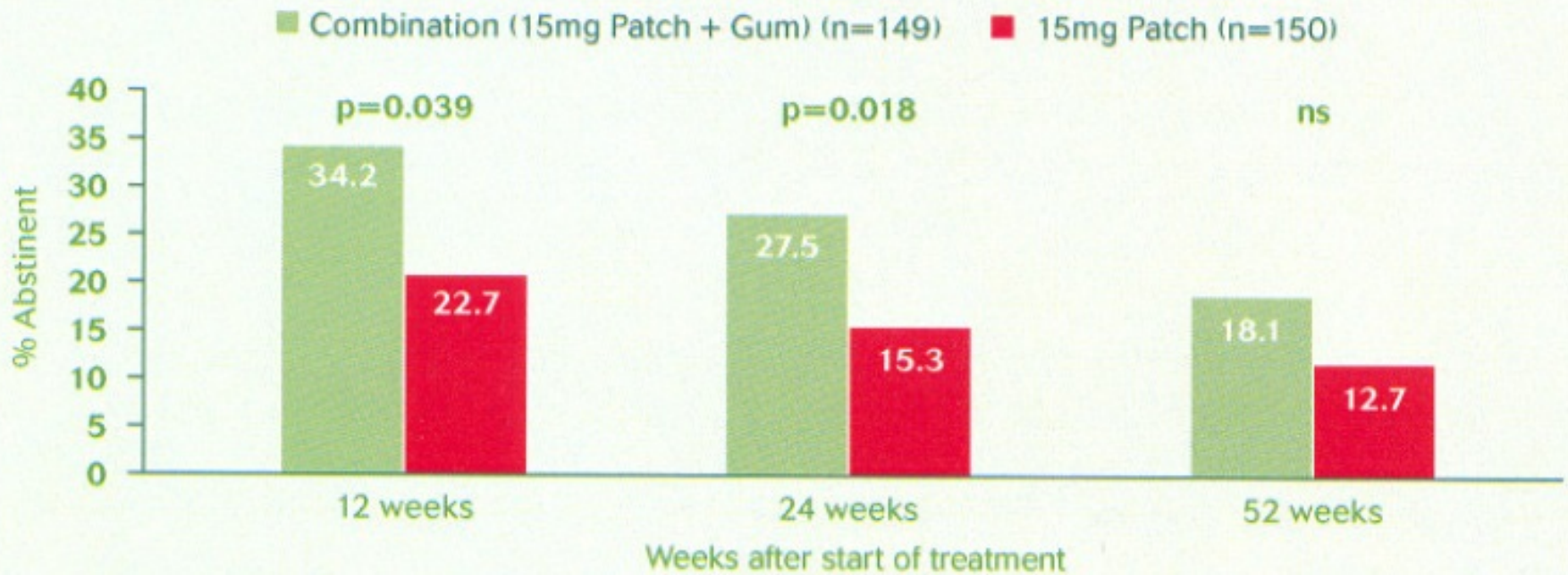
Provides baseline dose of NRT throughout the day

Provides rapid relief from cravings and other withdrawal symptoms



# Combination Therapy

Significantly higher cessation rates vs. monotherapy at 12 and 24 weeks<sup>6</sup>



Adapted from Kornitzer et al. 1995.<sup>6</sup>

# Assessing Nicotine Addiction

- 1. Number of Cigarettes smoked per day**
- 2. Time to First Cigarette**
- 3. Patient History**



# Choosing the right dose

Smokes ≥ 30 minutes of waking	Smokes ≤ 30 minutes of waking	TREATMENT GUIDE
<b>&lt;10</b>		<ul style="list-style-type: none"> <li>∴ <b>10 mg</b> for 6 weeks OR;</li> <li>∴ use gum, inhaler or spray alone</li> </ul>
<b>10-19</b>	<b>&lt;10</b>	<ul style="list-style-type: none"> <li>∴ <b>15mg</b> daily for 6 weeks then;</li> <li>∴ 10mg daily for 2 to 4 weeks</li> </ul>
<b>20-29</b>	<b>10-19</b>	<ul style="list-style-type: none"> <li>∴ <b>25mg</b> daily for 6 weeks then;</li> <li>∴ 15mg daily for 2 weeks then;</li> <li>∴ 10mg daily for 2 weeks <b>or longer</b></li> </ul>
<b>30-39</b>	<b>20-29</b>	<ul style="list-style-type: none"> <li>∴ <b>25mg</b> (25mg + 10 mg) daily for 6 weeks then;</li> <li>∴ 25mg daily for 4 weeks then;</li> <li>∴ 15mg daily for 2 weeks then;</li> <li>∴ 10mg daily for 2 weeks <b>or longer</b></li> </ul>
	<b>30-40</b>	<ul style="list-style-type: none"> <li>∴ <b>35mg</b> (25mg + 15mg) daily for 6 weeks then;</li> <li>∴ 25mg daily for 4 weeks then;</li> <li>∴ 15mg daily for 2 weeks then;</li> <li>∴ 10mg daily for 2 weeks <b>or longer</b></li> </ul>
<b>40+</b>		<ul style="list-style-type: none"> <li>∴ <b>40mg</b> (25mg x 2) daily for 6 weeks then;</li> <li>∴ 35mg (25mg + 10mg) daily for 2 weeks then;</li> <li>∴ 25mg daily for 2 weeks then;</li> <li>∴ 15mg daily for 2 weeks then;</li> <li>∴ 10mg daily for 2 weeks <b>or longer</b></li> </ul>
<b>WITH:</b>		
<b>Inhaler, gum, spray to be used as needed/required by the patient to manage cravings and withdrawal.</b>		

# 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...

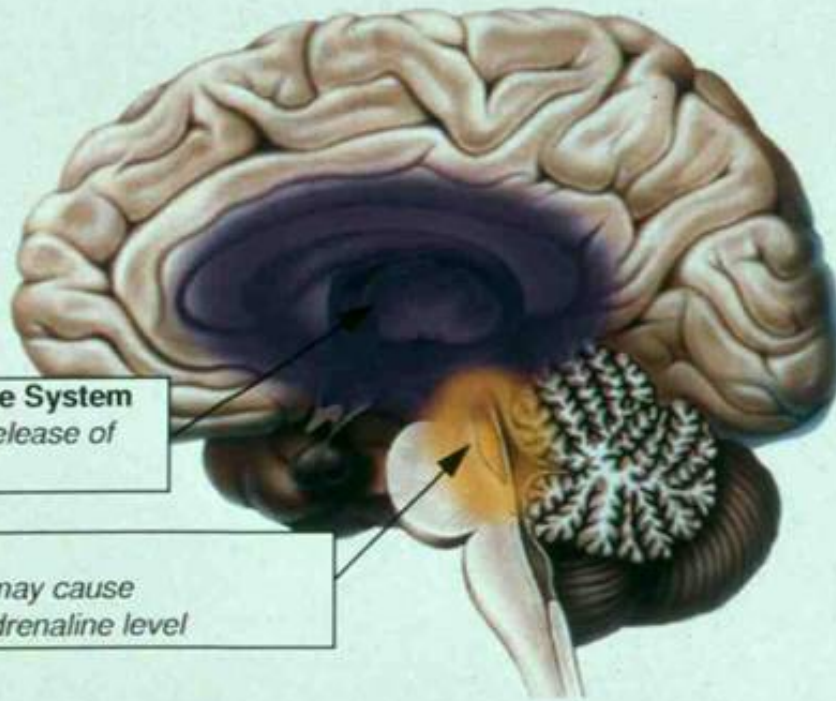
***Any patient who is likely to continue smoking is much 'safer' receiving NRT***

# Bupropion – How it works

- Helps to balance the chemicals in the brain
- Reduces nicotine cravings and withdrawal



# Bupropion and The Biology of Nicotine Addiction



**Mesolimbic Dopamine System**  
*nicotine stimulates release of dopamine*

**Locus Ceruleus**  
*nicotine withdrawal may cause changes in the noradrenaline level*

**Nicotine deprivation causes two reactions:**

1. Psychological Craving
2. Physiological Withdrawal Symptoms

# 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 Graval) 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**

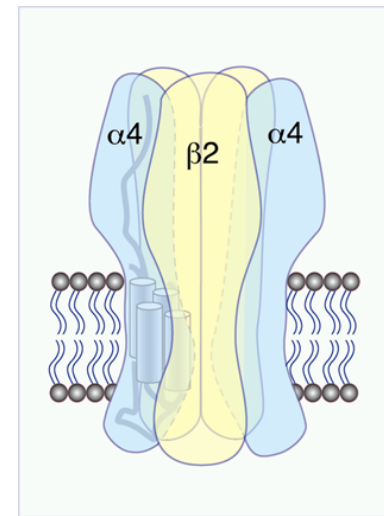
Side effects are dose dependent.

# Varenicline

- How it works
- Contraindications
- Dosing
- Duration
- Side effects

# New Medications and Approaches

**Varenicline**



$\alpha 4 \beta 2$  receptor

*Influences neurotransmitters and receptors*  
*Addresses the neurochemistry of addiction*



## Varenicline ...a selective partial agonist of the $\alpha4\beta2$ nicotinic ACh receptor

- Provides relief from craving and withdrawal – *agonist* effect
- Blocks satisfaction and rewarding effects of nicotine – *antagonist* effect

# $\alpha 4\beta 2$ nAChR Partial Agonists

Smoking  
No Partial Ag

No Smoking  
Partial Ag

Smoking  
+ Partial Ag

$\alpha 4\beta 2$  nAChR

Nicotine



Agonist



Response

100%

Part Ag



Partial Agonist



50%

Potential to relieve  
craving and withdrawal  
when quitting

Nicotine



Part ag



Antagonist

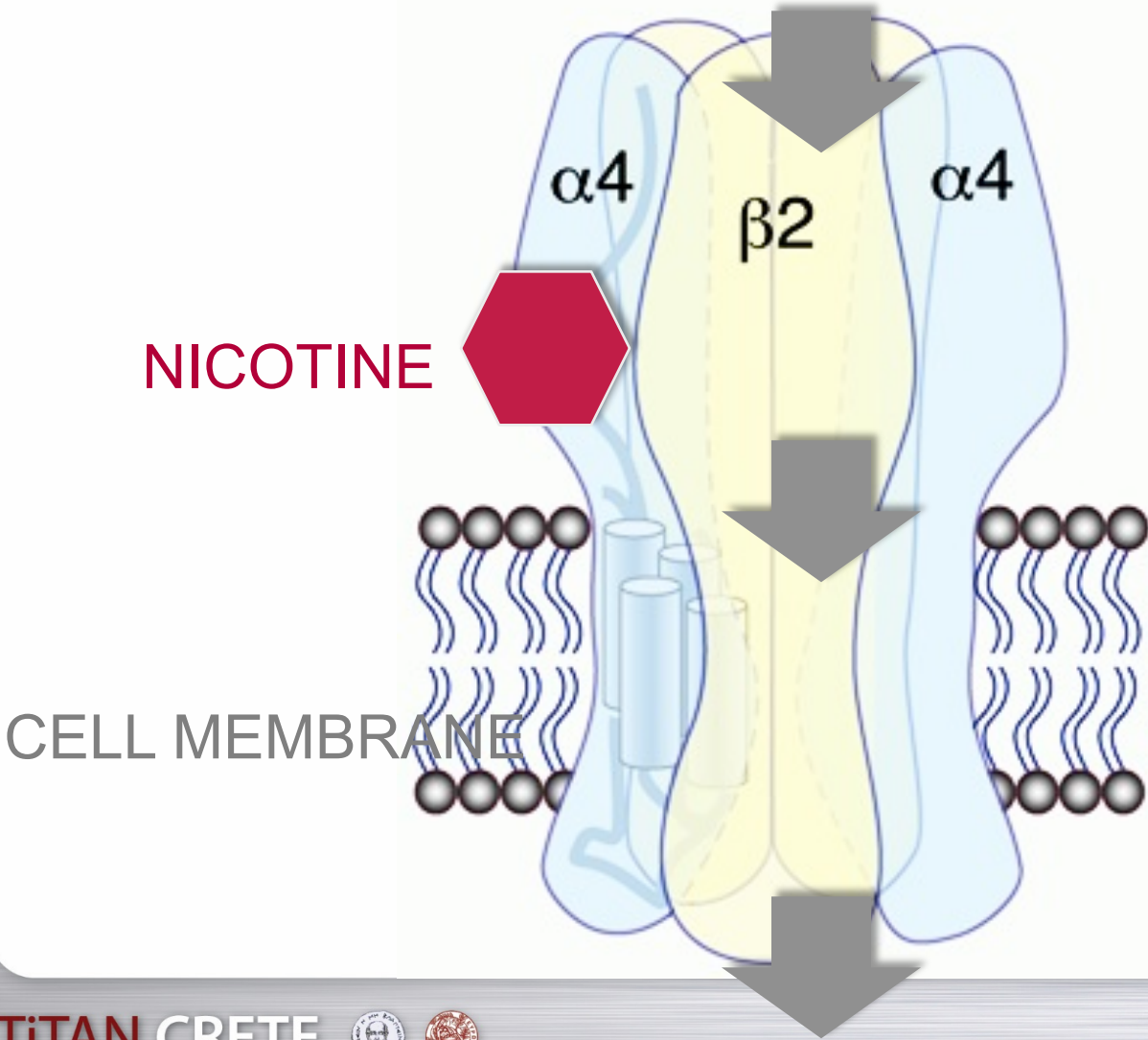


50%

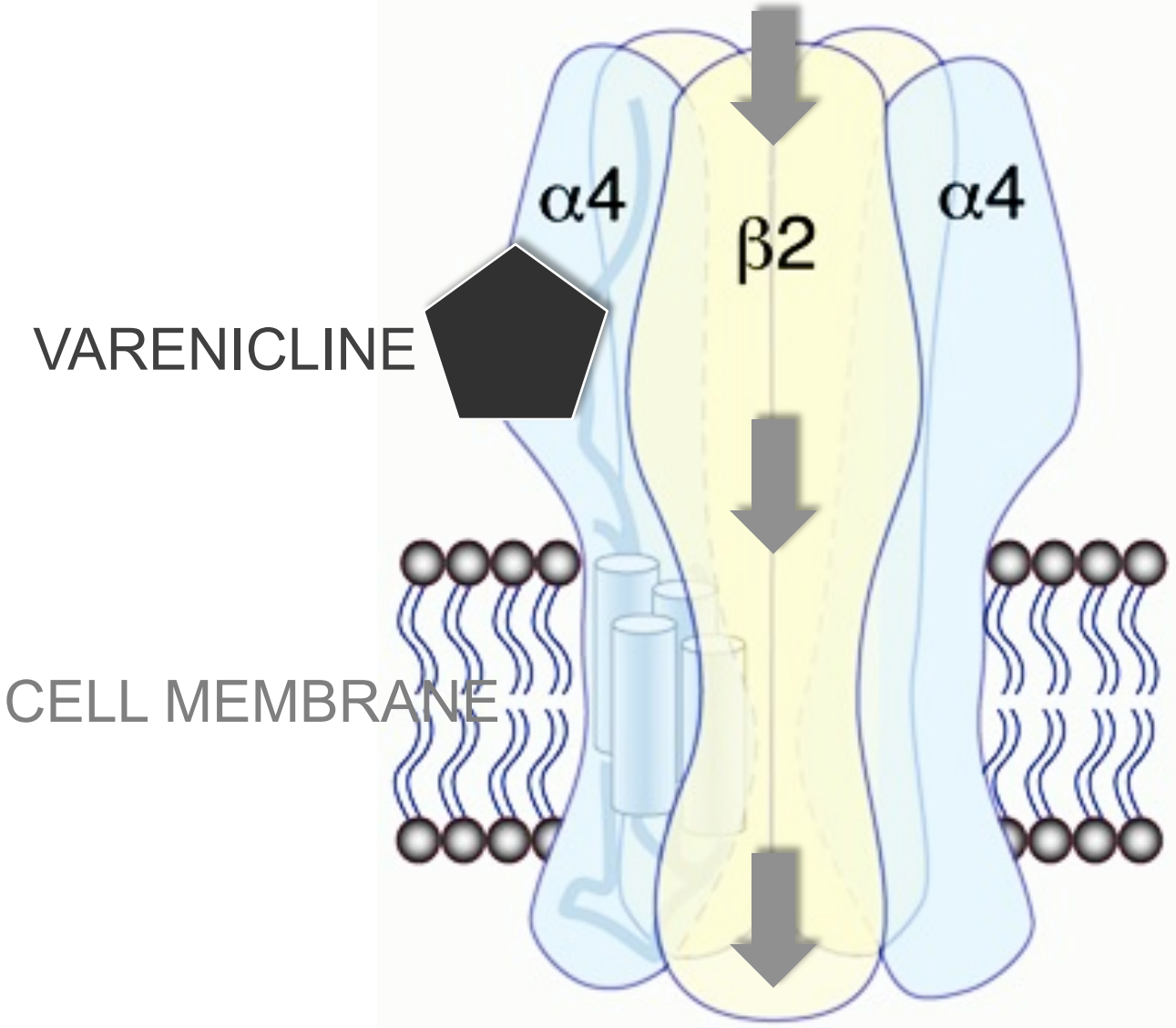
Potential to block  
reinforcing effects  
when smoking

Dual action of a partial agonist

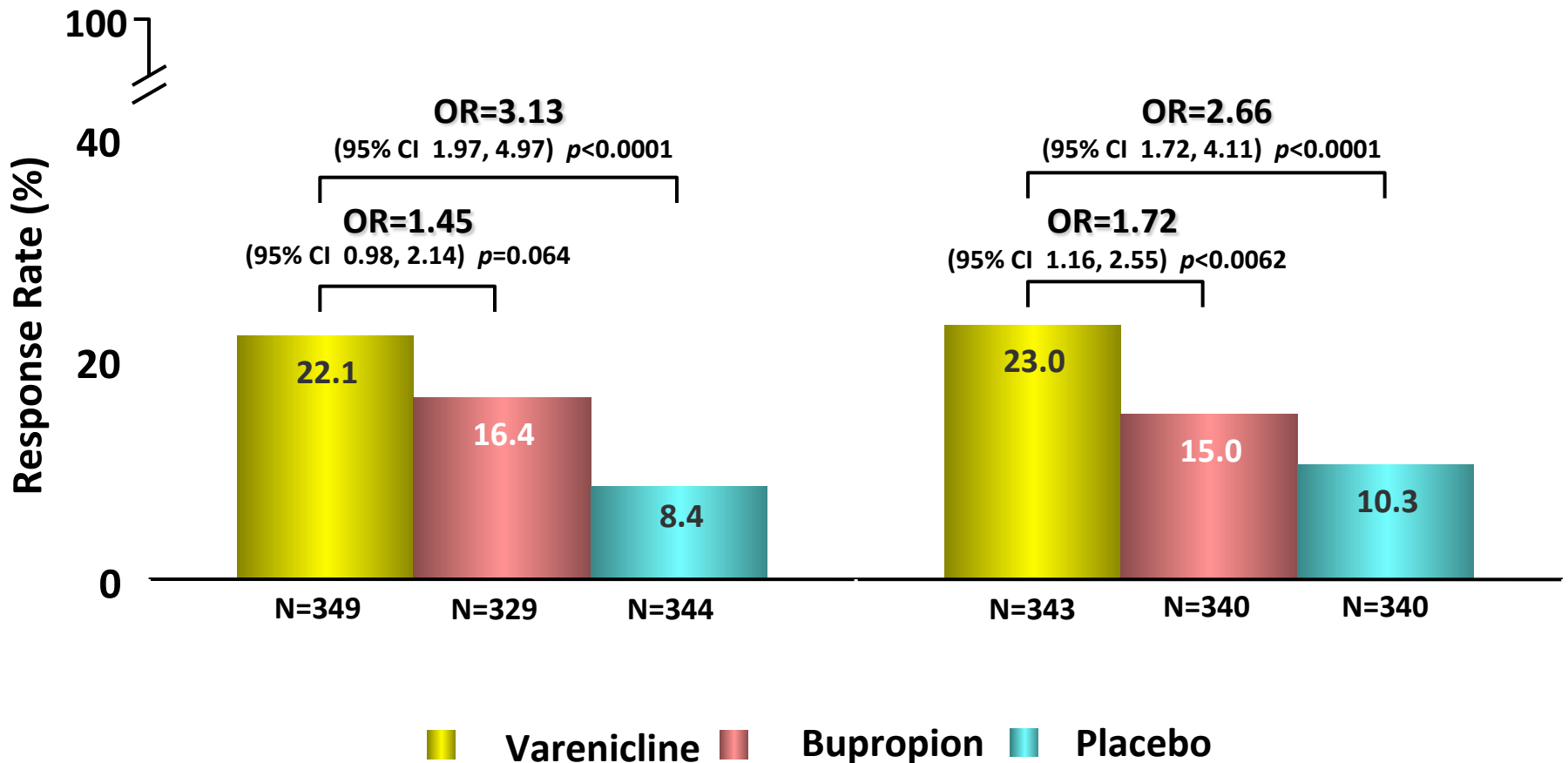
# $\alpha 4\beta 2$ Receptor



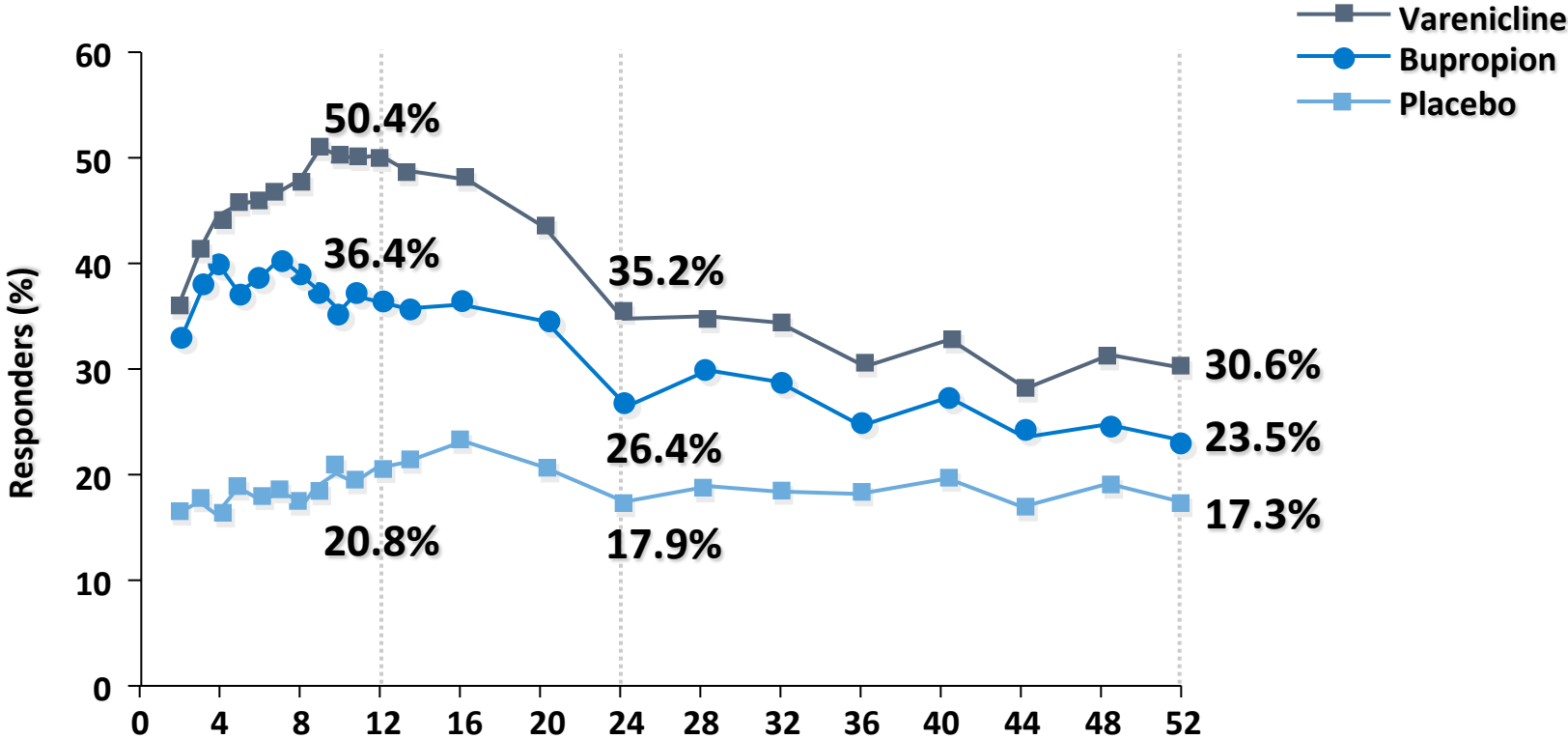
# $\alpha 4 \beta 2$ Receptor



# CO-Confirmed Continuous Abstinence - Wks 9-52



# Quitting 'Trajectories'



# 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 Gravalol if symptoms persist
  - Consider reducing dose by half (going back to 0.5mg twice a day) if symptoms are severe 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

# Neuropsychiatric Adverse Events

May 2010 Product Monograph p. 15

Psychiatric Disorders	Varenicline (N=3091)	Placebo (N=2005)
	% (n)	% (n)
<b>Depressed mood disorders/disturbances</b>	<b>2.8 (88)</b>	<b>1.9 (38)</b>
Depression	1.6 (51)	1.2 (24)
Depressed mood	1.0 (32)	0.6 (12)
<b>Disturbances in thinking and perception</b>	<b>0.4 (13)</b>	<b>0.1 ( 2)</b>
Thinking abnormal	0.2 ( 7)	-- ( 1)
<b>Mood disorders and disturbances NEC</b>	<b>2.4 (73)</b>	<b>1.5 (30)</b>
Affect lability	0.6 (20)	0.3 ( 6)
Mood swings	0.3 (10)	0.1 ( 2)
Apathy	0.2 ( 5)	-- ( 1)
<b>Psychiatric disorders NEC</b>	<b>0.5 (16)</b>	<b>0.3 ( 6)</b>



# 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.

Gibbons R.D, and Mann J.J. Varenicline, smoking cessation, and neuropsychiatric adverse events. 2013. Am J Psychiatry 170(12): 1460-67.

# Comparison of Monotherapy and Combination Therapies

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

# 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<sup>1</sup>**
- **NRT + Bupropion – good<sup>1</sup>**
- **NRT + Varenicline – emerging evidence<sup>2</sup>**
- **Bupropion + Varenicline – emerging evidence<sup>3</sup>**

1 Fiore et. al. Treating Tobacco Dependence Clinical Practice Guidelines. USDHHS. 2008. 2 Ebbert et. al. Nicotine Tob Research 2009; 11 (5); 572-6. 3 Ebbert et. al. Nicotine and Tobacco Research 2009; 11 (3): 234-9.



# Problems with Pharmacotherapy

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

*“Not a Magic Bullet!”*

# TiTAN CRETE



UNIVERSITY OF OTTAWA  
HEART INSTITUTE  
INSTITUT DE CARDIOLOGIE  
DE L'UNIVERSITÉ D'OTTAWA

OTTAWA MODEL  
FOR SMOKING CESSATION  
IN PRIMARY CARE  
MODÈLE D'OTTAWA  
POUR L'ABANDON DU TABAC  
EN SOINS PRIMAIRES

Global  Bridges  
Healthcare Alliance for Tobacco Dependence Treatment