

Basic and Clinical Pharmacology of Varenicline

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TRDRP Webcast
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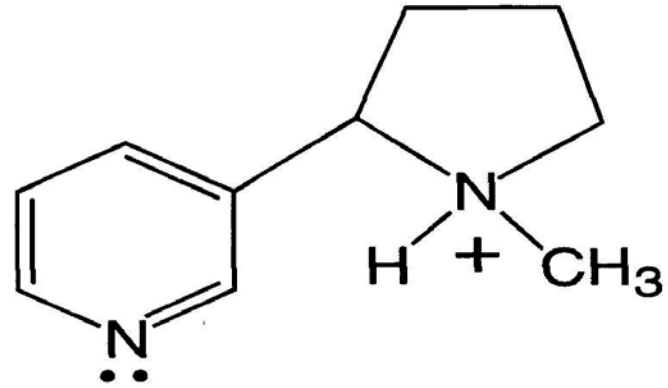
Disclosure Statement

Dr. Benowitz has served on the Pfizer Varenicline Worldwide Advisory Board and on the scientific steering committee of Pfizer-supported varenicline clinical trials.

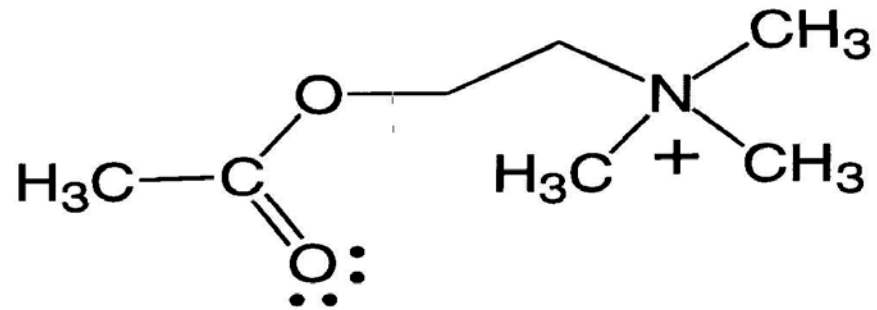
Objectives

- Overview of neurobiology of nicotine addiction
- Neurobiologic rationale for varenicline to treat tobacco dependence
- Clinical pharmacology of varenicline
- Possible mechanisms that might be involved in varenicline toxicity

Nicotine Addiction

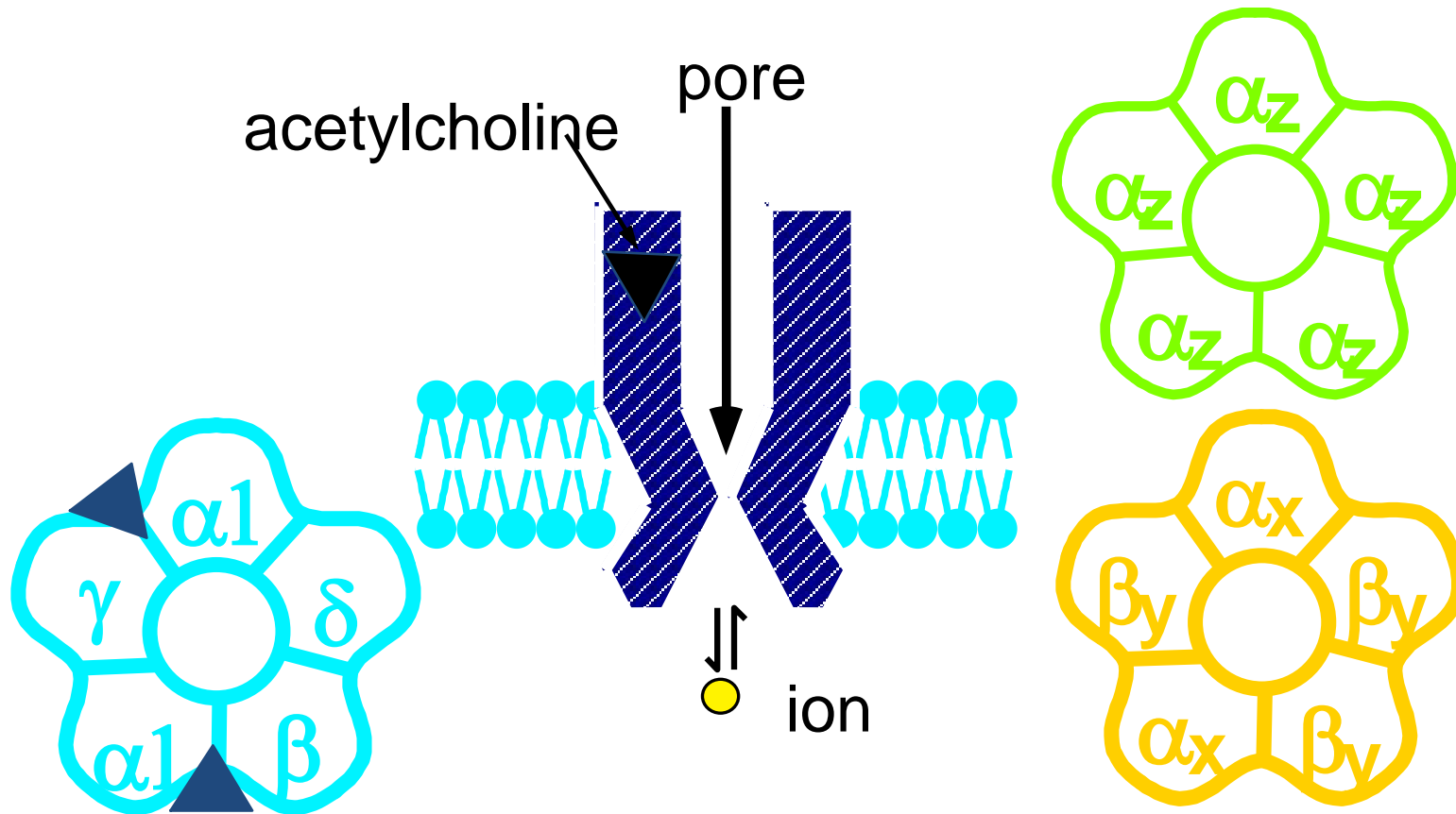


NICOTINE

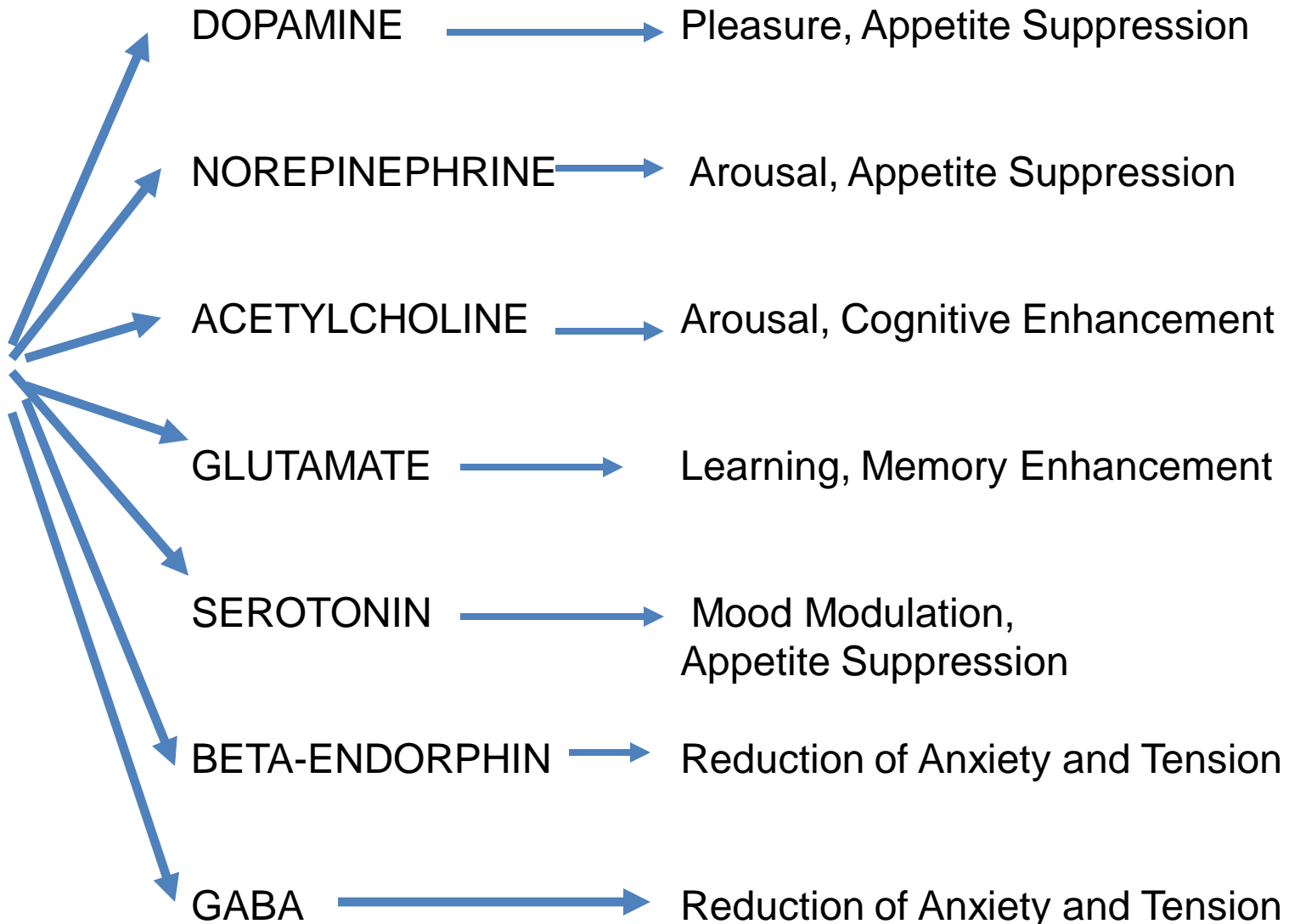


ACETYLCHOLINE

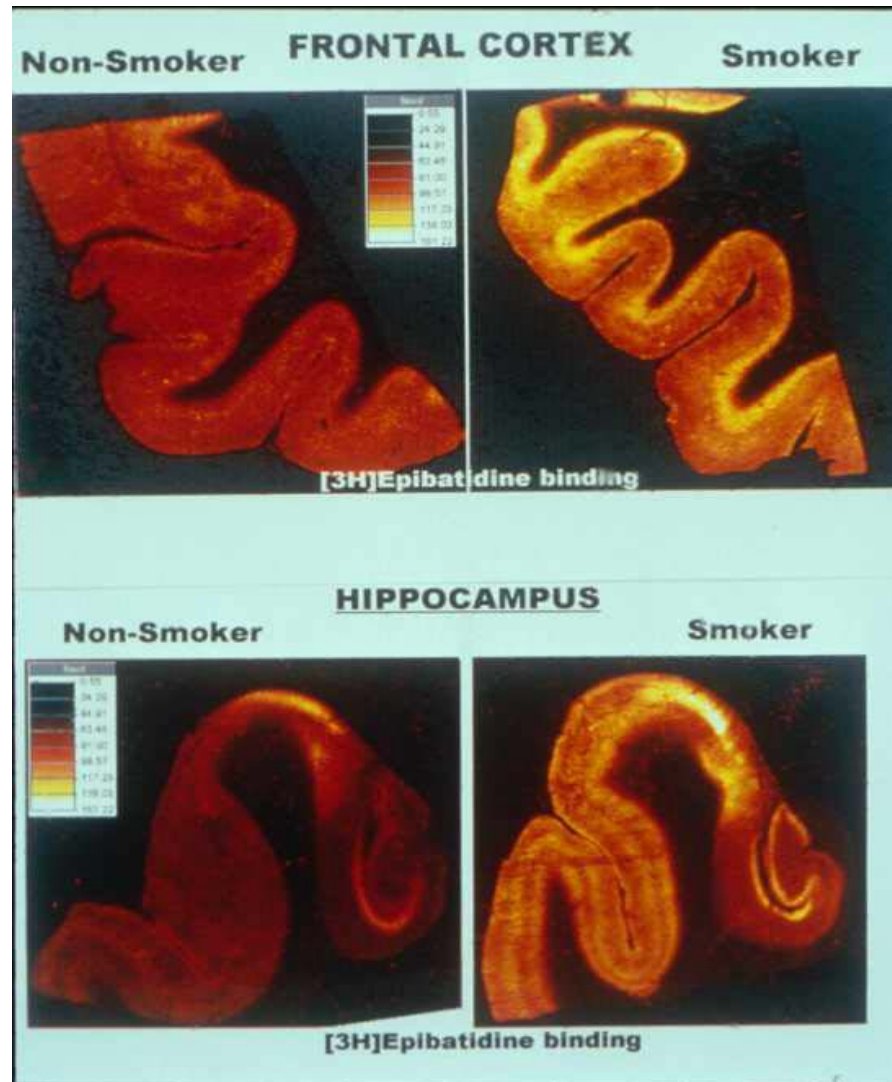
Structure of Nicotinic ACh Receptors



NICOTINE



Nicotinic Receptor Upregulation In Smokers

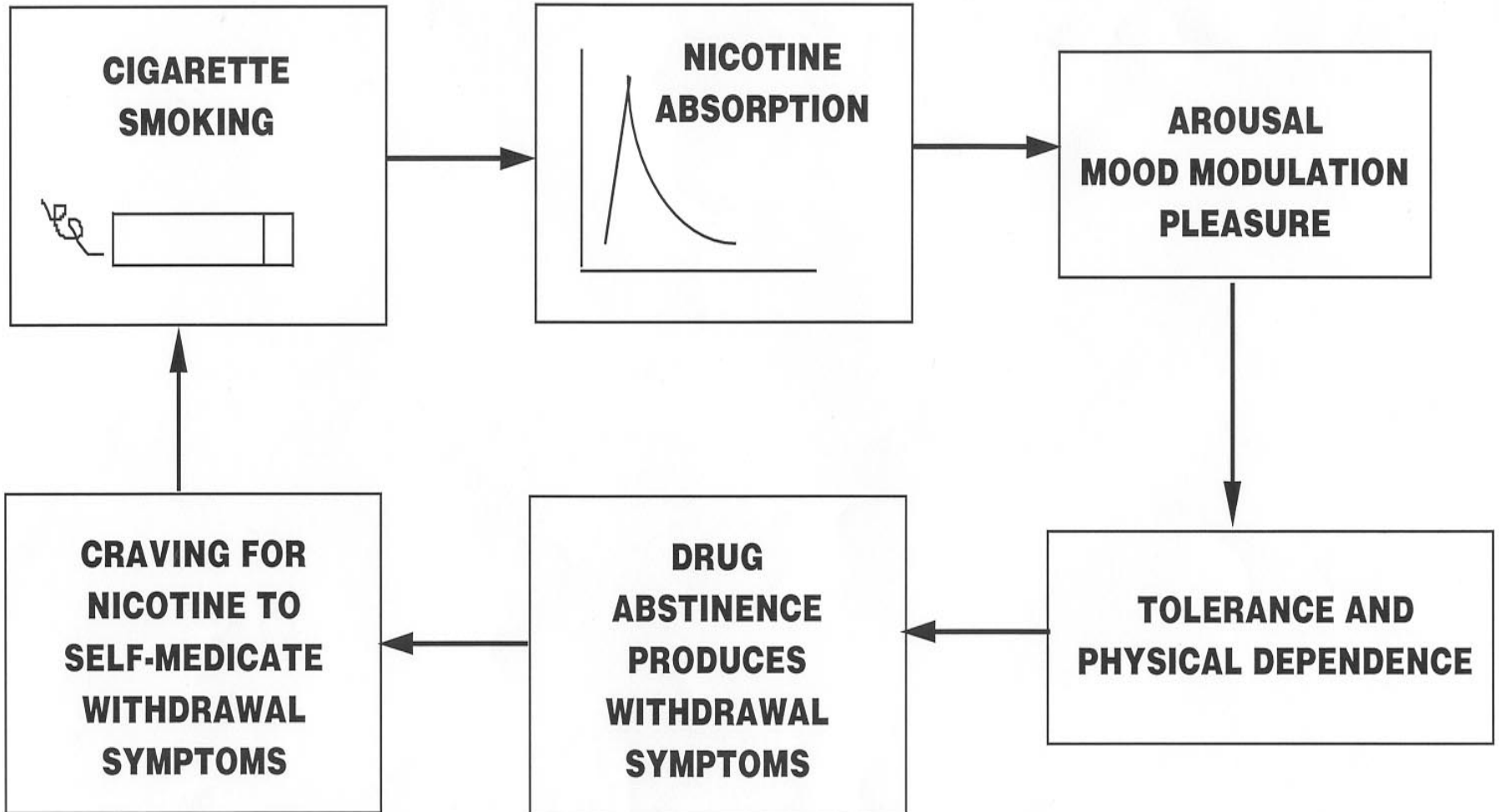


Tobacco Abstinence Symptom Clusters

(Gross and Stitzer)

- **PSYCHOLOGICAL DISTRESS:**
Irritability, Anger, Impatience, Anxiety
- **DIFFICULTY CONCENTRATING:**
Cognitive and Performance Impairment
- **HUNGER AND EATING:**
Weight Gain
- **TOBACCO CRAVING**
- **HEDONIC DYSREGULATION**

NICOTINE ADDICTION CYCLE

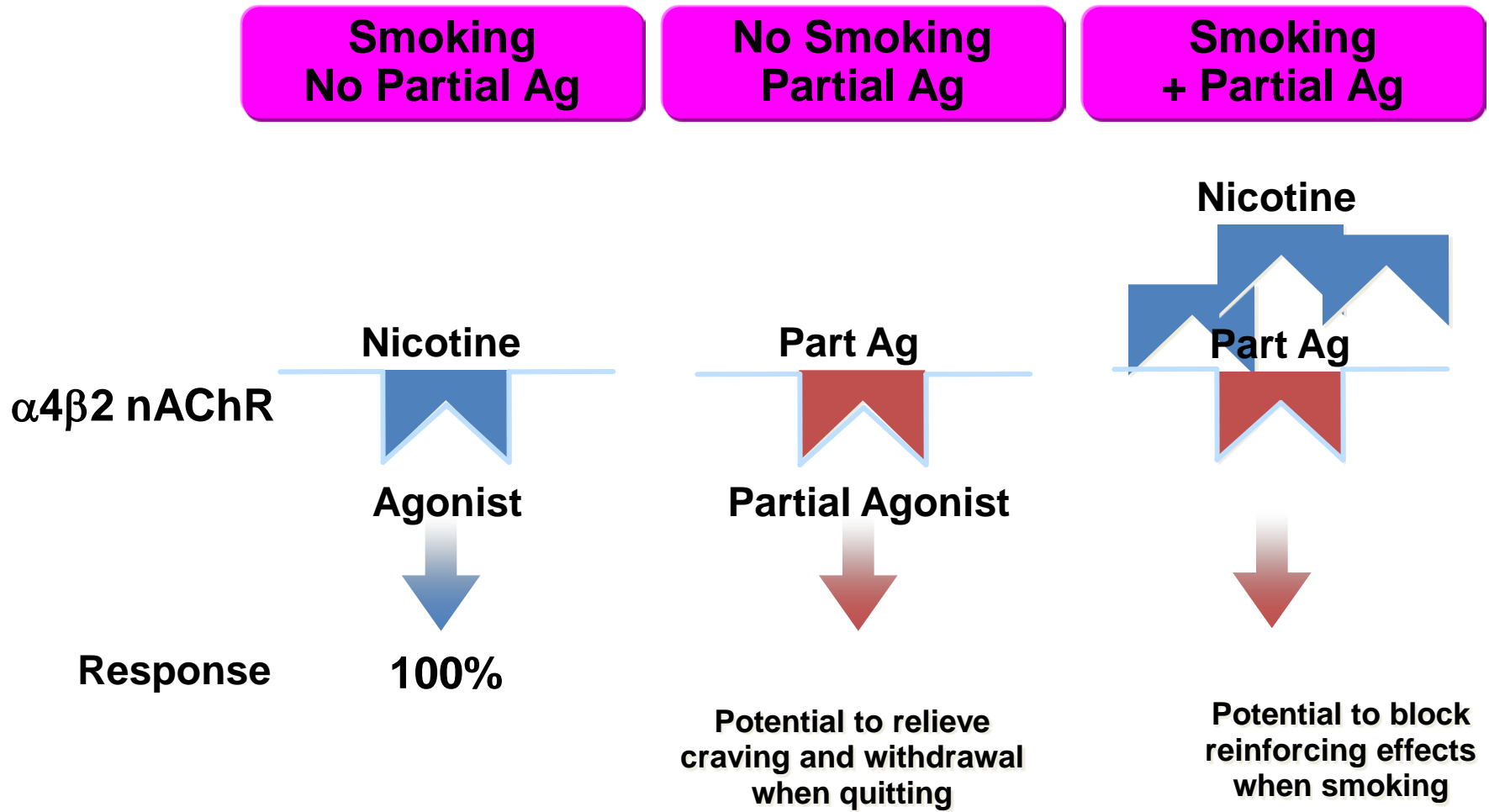


Basic Pharmacology of Varenicline

Receptor Pharmacology

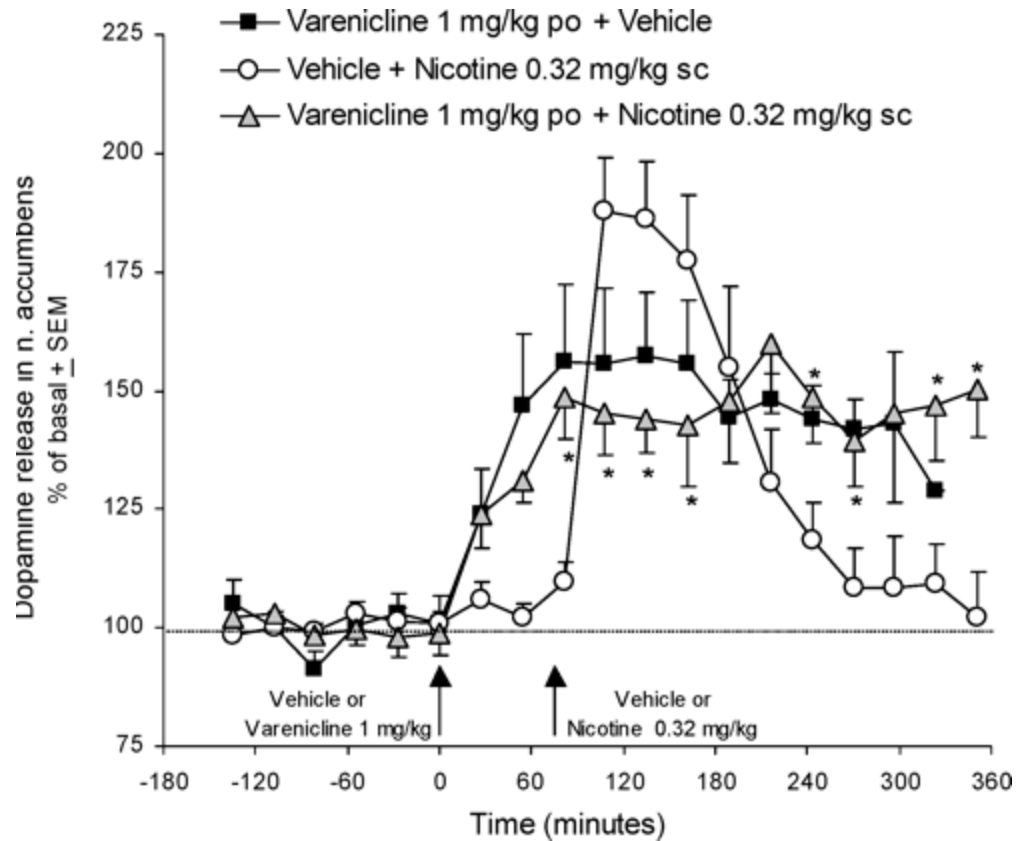
- Potent partial agonist at $\alpha 4\beta 2^*$ and $\alpha 6\beta 2^*$ receptors
- Activates nAChRs to ameliorate craving and withdrawal (50% of nicotine effect)
- Antagonizes nAChRs to reduce rewarding effects of nicotine
- May also desensitize nAChRs resulting in virtual full antagonism

Rationale for $\alpha 4\beta 2$ nAChR Partial Agonists



Dual action of a partial agonist

Nicotine, Varenicline and Brain Dopamine Release



Varenicline Actions on Other Receptors

$\alpha 7$ homomeric – full agonist

$\alpha 3\beta 4$ – weak agonist

5-HT₃ (serotonin) – full agonist

Varenicline Binding Affinity to Nicotinic Receptors

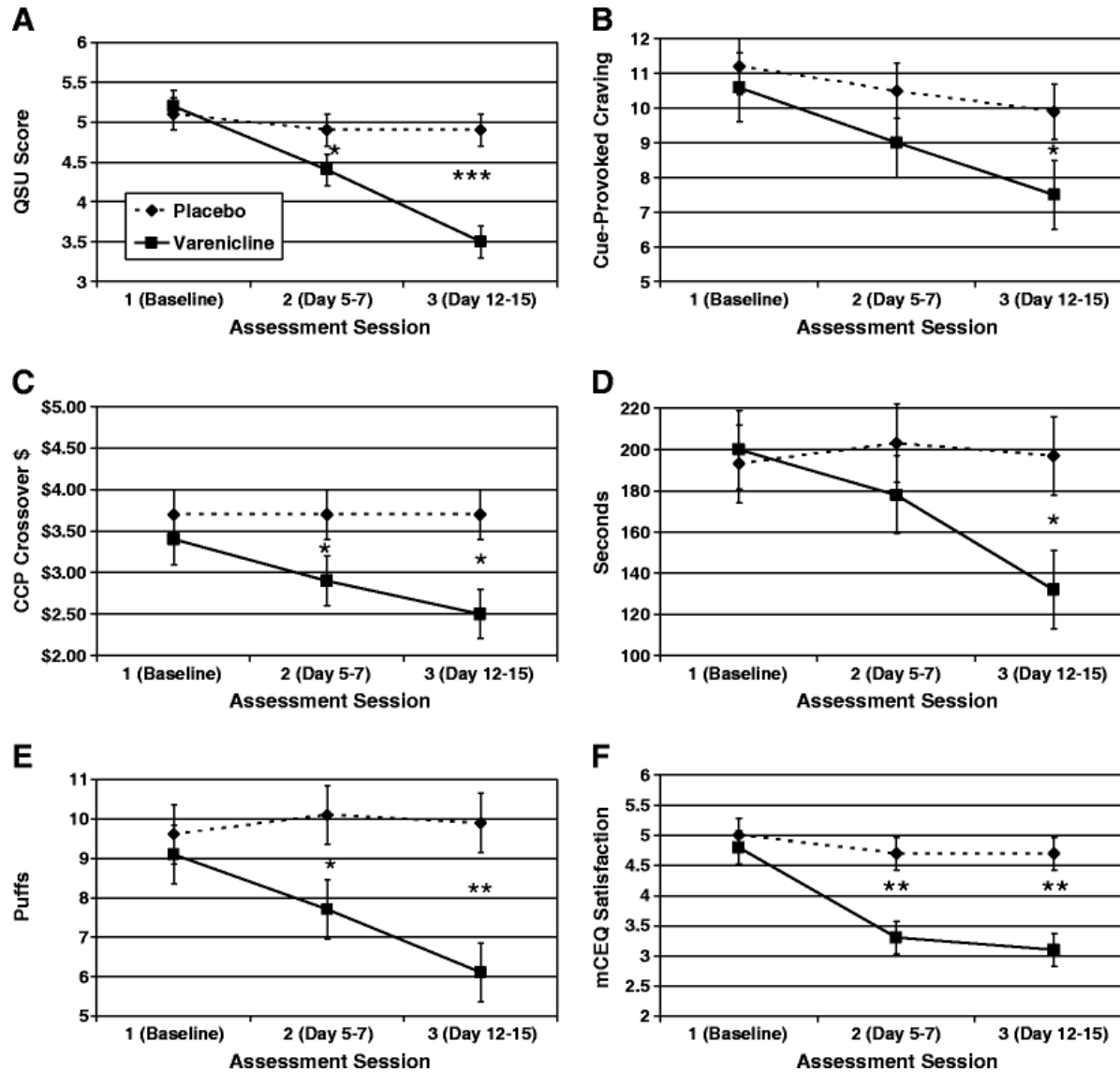
<u>nAChR</u>	<u>Ki or IC50 (nM)</u>
$\alpha 4\beta 2$	0.4
$\alpha 3\beta 4$	86
$\alpha 7$	125
$\alpha 6^*$	111

Clinical Pharmacology of Varenicline

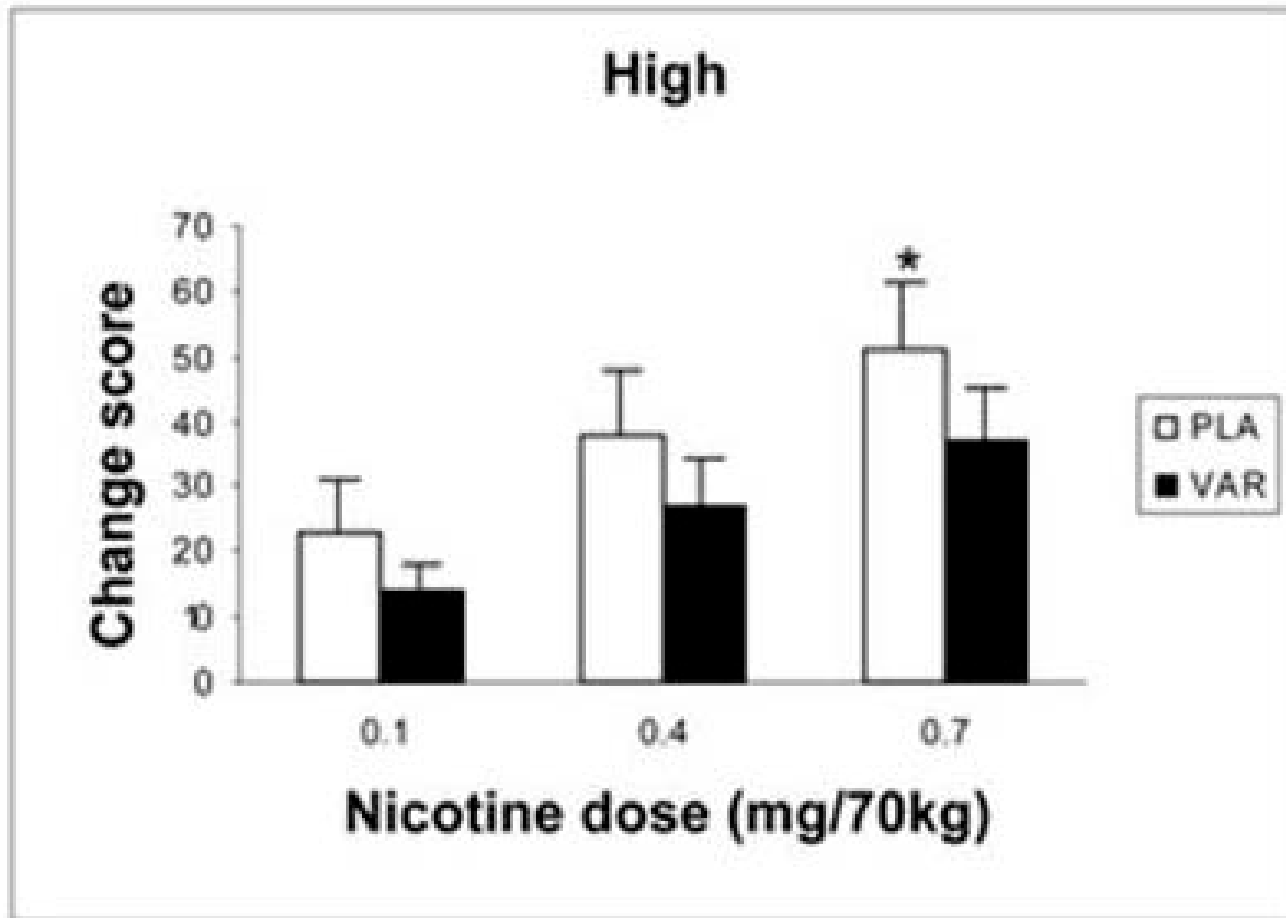
Pharmacokinetics

- Half-life ~ 24 hours
- C_{max} within 4 hours
- Steady State reached after 4 days
- No effect of food on concentrations
- 93% of recovered drug in urine unchanged, 99% renal clearance
- No inhibition of P450 enzymes

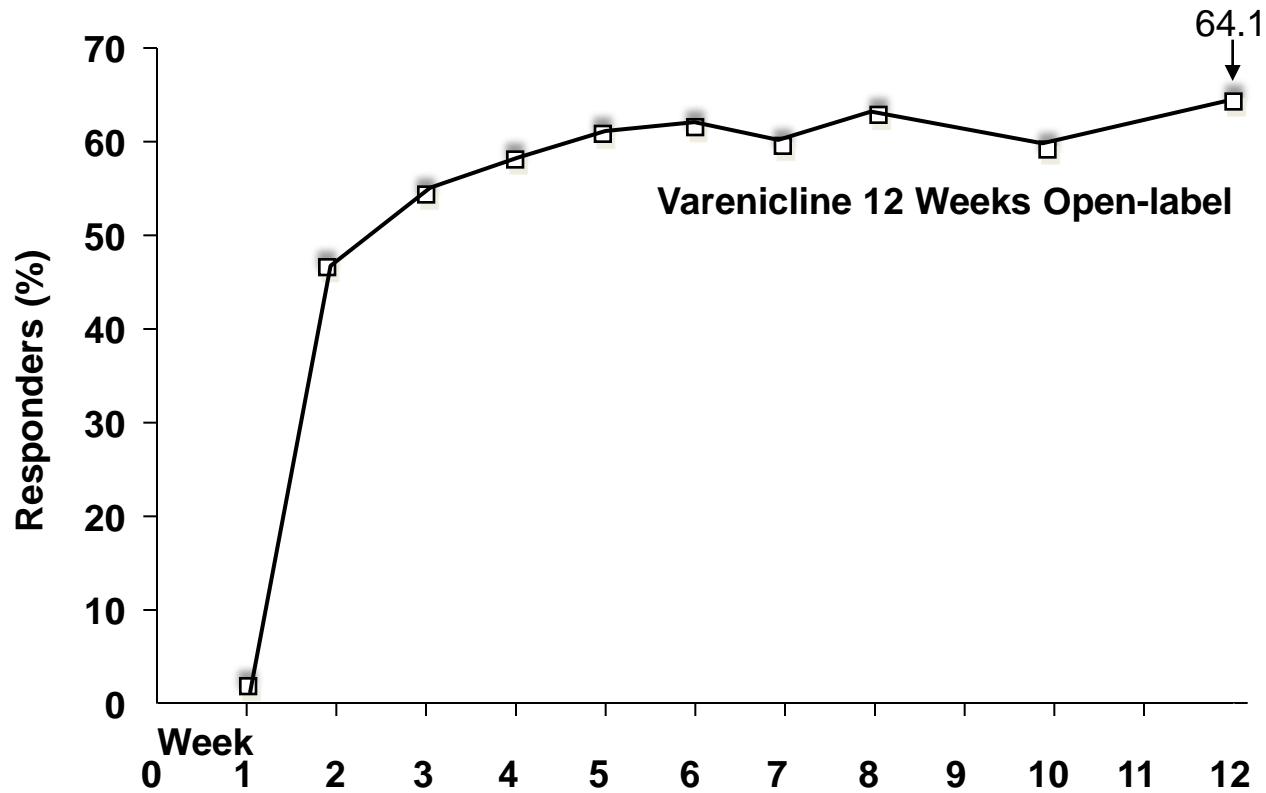
Varenicline effects during cigarette abstinence



Varenicline antagonizes nicotine-induced high



7-Day Point-Prevalence of Abstinence: Open-Label Treatment Phase



Varenicline Pharmacology & Safety Concerns

Varenicline Safety Issue

Most common side effects

- **Nausea (40%)**
- **Abnormal dreams (23%)**
- **Insomnia (19%)**

10% discontinue treatment due to adverse drug effect

Varenicline and Nausea

- May involve both central and peripheral mechanisms
- Afferent stimulation in GI tract:
 - 5-HT₃ and /or α 3 β 4 receptors
- Central: activation of α 3 β 4 receptors
- Tolerance usually develops

Varenicline Psychiatric and Neurological Safety Concerns

Reports of agitation, violent behavior, depressed mood, suicidal ideation and behavior, worsening of pre-existing psychiatric illness, seizures.

Possible Neuropsychiatric Toxicity Mechanisms

- Functional down regulation of $\alpha 7$ nAChR-schizophrenia
- Persistent activation of $\alpha 4\beta 2$ – depression
- Activation of $\alpha 3\beta 4$ -anxiety

Varenicline Cardiovascular Concerns

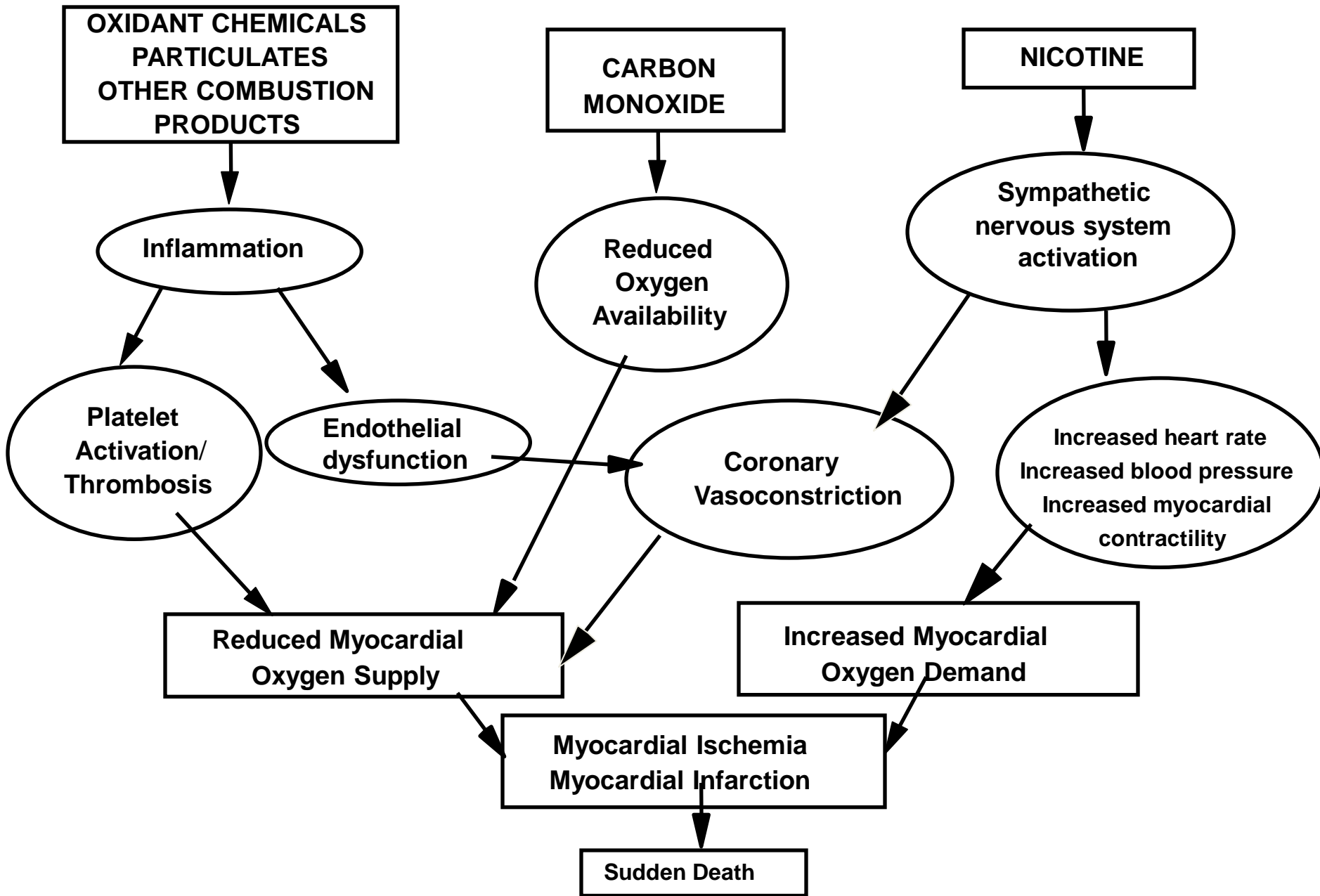
Reports of myocardial infarction,
heart rhythm disturbances,
sudden loss of consciousness

FDA Drug Safety Communication

Chantix (varenicline)

July 22, 2011

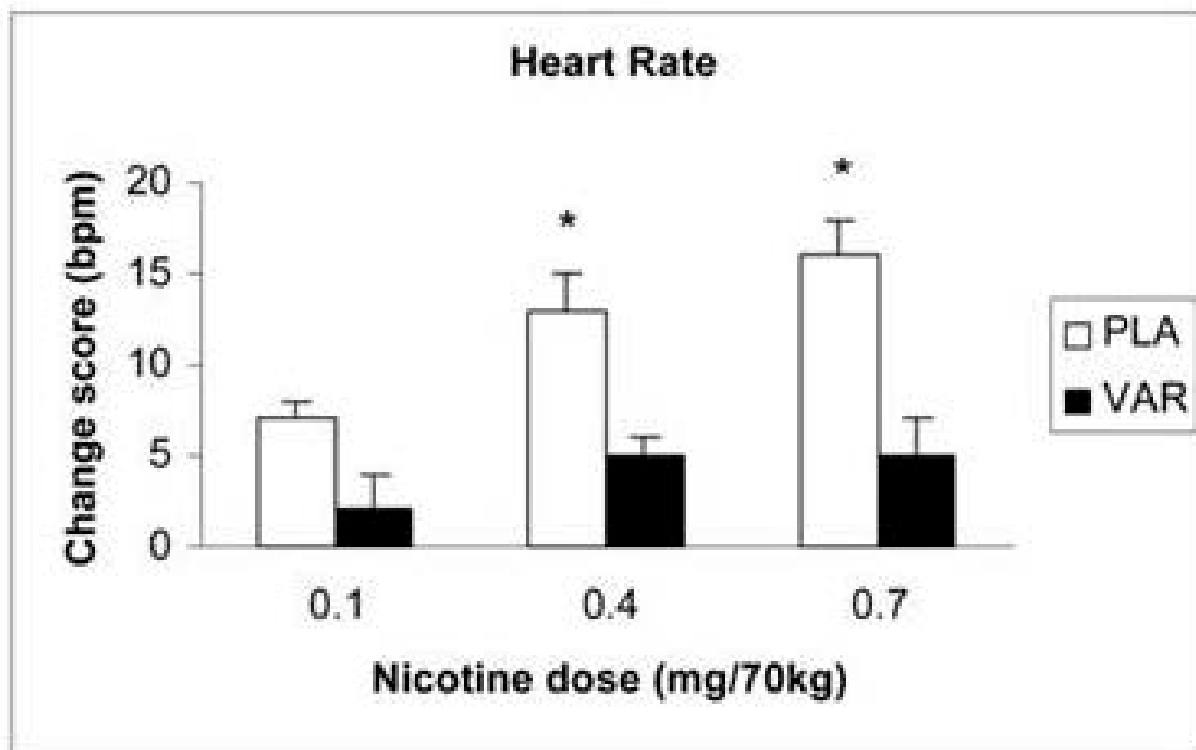
“Chantix may be associated with a small increased risk of certain CV events in patients who have CV disease...benefits should be weighed against potential risks in smokers with CV disease.”



Varenicline Cardiovascular Pharmacology

- $\alpha_3\beta_4$ receptors in peripheral ganglia - release catecholamines, activate platelets.
- $\alpha_3\beta_4$ and α_7 - may influence heart rate, blood pressure homeostasis.
- Varenicline levels predicted to be too low to activate $\alpha_3\beta_4$ and α_7 nAChRs
- No adverse CV effects in preclinical animal studies

Varenicline antagonizes nicotine-induced increase in heart rate



Conclusions

- Varenicline is a partial agonist that is highly but not entirely specific for $\alpha 4\beta 2$ nicotinic receptors.
- Nausea is likely mediated by stimulation in GI tract of 5-HT₃ and $\alpha 3\beta 4$ receptors.

Conclusions (cont.)

- Neuropsychiatric side effects speculated to be mediated by actions on $\alpha 7$, $\alpha 4\beta 2$ and/or $\alpha 3\beta 4$ receptors, but evidence is inconclusive.
- Cardiovascular side effects speculated to be mediated by actions on $\alpha 3\beta 4$ and/or $\alpha 7$ receptors, but no evidence to support CV effects in experimental animal or human studies.