Basic and Clinical Pharmacology of Varenicline

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TRDRP Webcast
September 20, 2012
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
Structure of Nicotinic ACh Receptors

acetylcholine

pore

ion

Picciotto M. Emerging neuronal nicotinic receptor targets. SRNT 9th Annual Meeting; February 2003; New Orleans, La.
NICOTINE

- DOPAMINE: Pleasure, Appetite Suppression
- NOREPINEPHRINE: Arousal, Appetite Suppression
- ACETYLCHOLINE: Arousal, Cognitive Enhancement
- GLUTAMATE: Learning, Memory Enhancement
- SEROTONIN: Mood Modulation, Appetite Suppression
- BETA-ENDORPHIN: Reduction of Anxiety and Tension
- GABA: Reduction of Anxiety and Tension
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

CIGARETTE SMOKING

NICOTINE ABSORPTION

AROUSAL MOOD MODULATION PLEASURE

CRAVING FOR NICOTINE TO SELF-MEDICATE WITHDRAWAL SYMPTOMS

DRUG ABSTINENCE PRODUCES WITHDRAWAL SYMPTOMS

TOLERANCE AND PHYSICAL DEPENDENCE
Basic Pharmacology of Varenicline
Receptor Pharmacology

- Potent partial agonist at $\alpha4\beta2^*$ and $\alpha6\beta2^*$ 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

- **Smoking No Partial Ag**: Nicotine
  - Response: 100%
  - Potential to relieve craving and withdrawal when quitting

- **No Smoking Partial Ag**: Partial Ag
  - Potential to block reinforcing effects when smoking

- **Smoking + Partial Ag**: Part Ag
  - Dual action of a partial agonist

$\alpha_{4}\beta_{2}$ nAChR Agonist

Nicotine
Nicotine, Varenicline and Brain Dopamine Release

![Graph showing the effect of nicotine and varenicline on dopamine release.](image-url)
Varenicline Actions on Other Receptors

$\alpha_7$ homomeric – full agonist
$\alpha_3\beta_4$ – weak agonist
5-HT$_3$ (serotonin) – full agonist
# Varenicline Binding Affinity to Nicotinic Receptors

<table>
<thead>
<tr>
<th>nAChr</th>
<th>Ki or IC50 (nM)</th>
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<tbody>
<tr>
<td>α4β2</td>
<td>0.4</td>
</tr>
<tr>
<td>α3β4</td>
<td>86</td>
</tr>
<tr>
<td>α7</td>
<td>125</td>
</tr>
<tr>
<td>α6*</td>
<td>111</td>
</tr>
</tbody>
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Clinical Pharmacology of Varenicline
Pharmacokinetics

• Half-life ~ 24 hours
• Cmax 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

Brandon, Psychopharm 2011
Varenicline antagonizes nicotine-induced high

Sofuoglu, Psychopharm 2009
7-Day Point-Prevalence of Abstinence: Open-Label Treatment Phase

Varenicline 12 Weeks Open-label

Week

Responders (%)

0 1 2 3 4 5 6 7 8 9 10 11 12

0 10 20 30 40 50 60 70 80 90

64.1
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 α3β4 receptors
• Central: activation of α3β4 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 α7 nAChR-schizophrenia
• Presistent activation of α4β2 – depression
• Activation of α3β4-anxiety
Varenicline Cardiovascular Concerns

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

• A3β4 receptors in peripheral ganglia - release catecholamines, activate platelets.
• α3β4 and α7 - may influence heart rate, blood pressure homeostasis.
• Varenicline levels predicted to be too low to activate α3β4 and α7 nAChRs
• No adverse CV effects in preclinical animal studies
Varenicline antagonizes nicotine-induced increase in heart rate

Sofuoglu, Psychopharm 2009
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-HT$_3$ and $\alpha_3\beta_4$ receptors.
Conclusions (cont.)

- Neuropsychiatric side effects speculated to be mediated by actions on α7, α4β2 and/or α3β4 receptors, but evidence is inconclusive.

- Cardiovascular side effects speculated to be mediated by actions on α3β4 and/or α7 receptors, but no evidence to support CV effects in experimental animal or human studies.