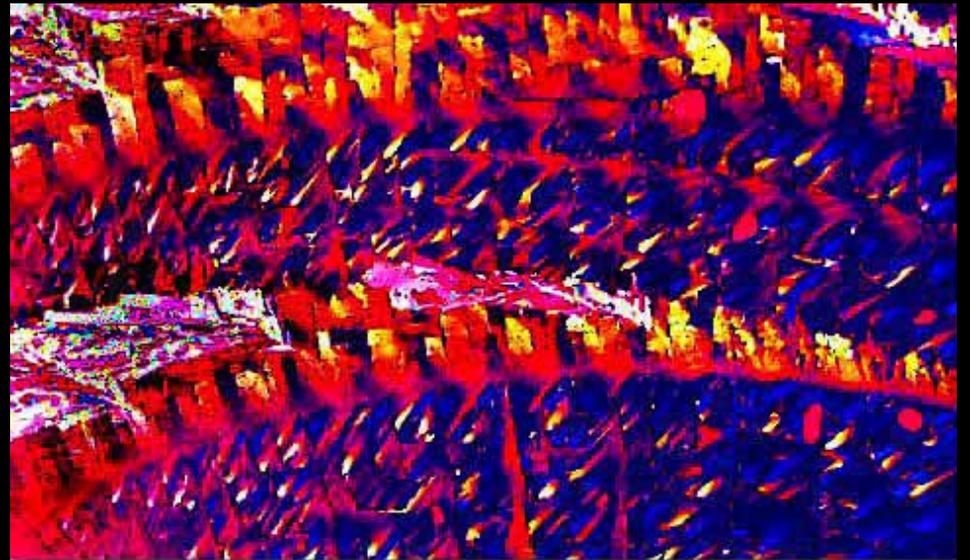


# *Nicotine/Tobacco*



# *Tobacco Overview*

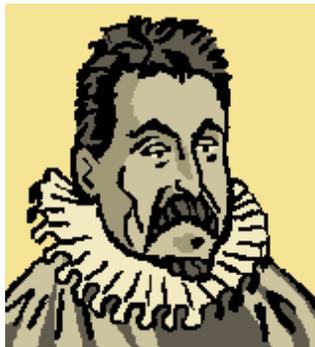
- Leaves of *Nicotiana tobacum* cured and (usually) smoked
- Indigenous to North America
- Smoked by natives for medicinal, ceremonial purposes (~1 B.C.)  
(enhancing fertility, predicting weather, conducting war councils, enabling vision quests, making peace)



# *Tobacco History*

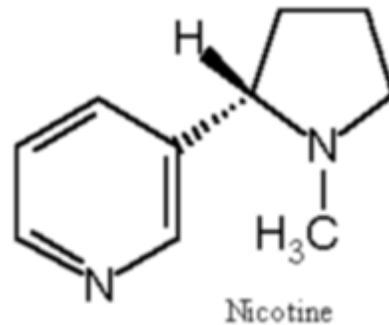


- Jean Nicot de Villemain introduces tobacco to France, promotes importation and cultivation (1556)
- Chewed recreationally, used for ailments (e.g. headaches, colds) in Europe (1500s)
- Tobacco becomes major cash crop of American colonies, spurring demand for slave labor (1600s)

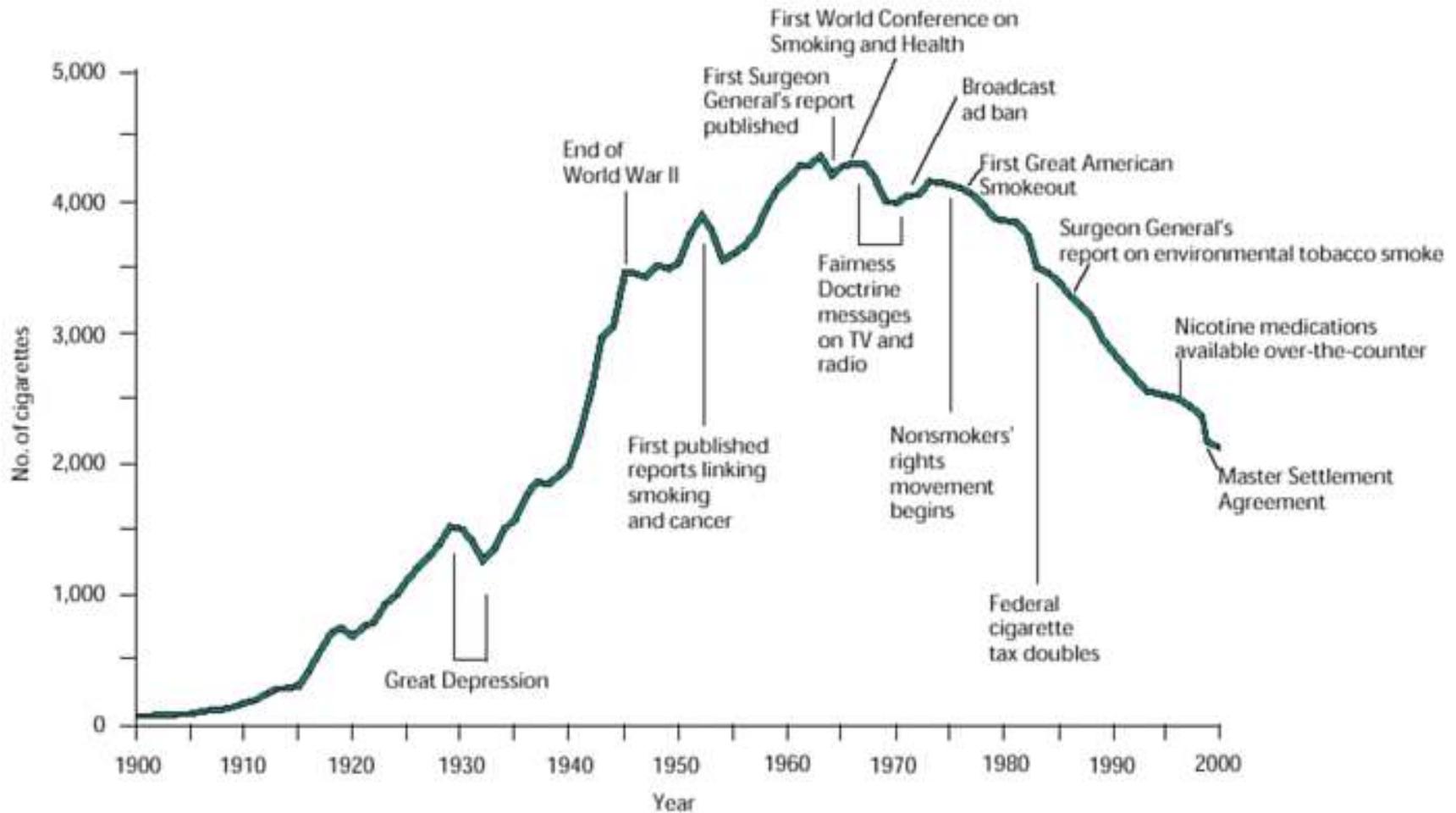


# *Nicotine*

- Nicotine is an alkaloid found naturally in tobacco plants, tomatoes, potatoes, eggplant and green peppers
- Nicotine isolated (1828)



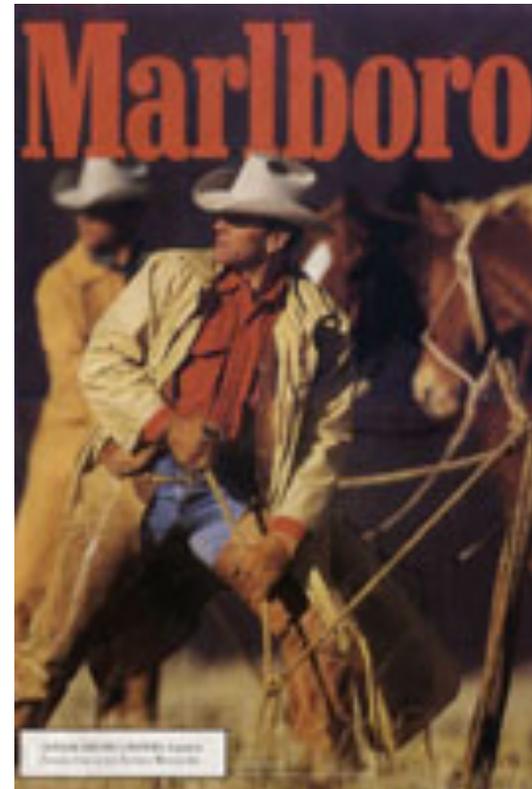
## Adult per Capita Cigarette Yearly Consumption and Major Smoking and Health Events, United States, 1900–1999



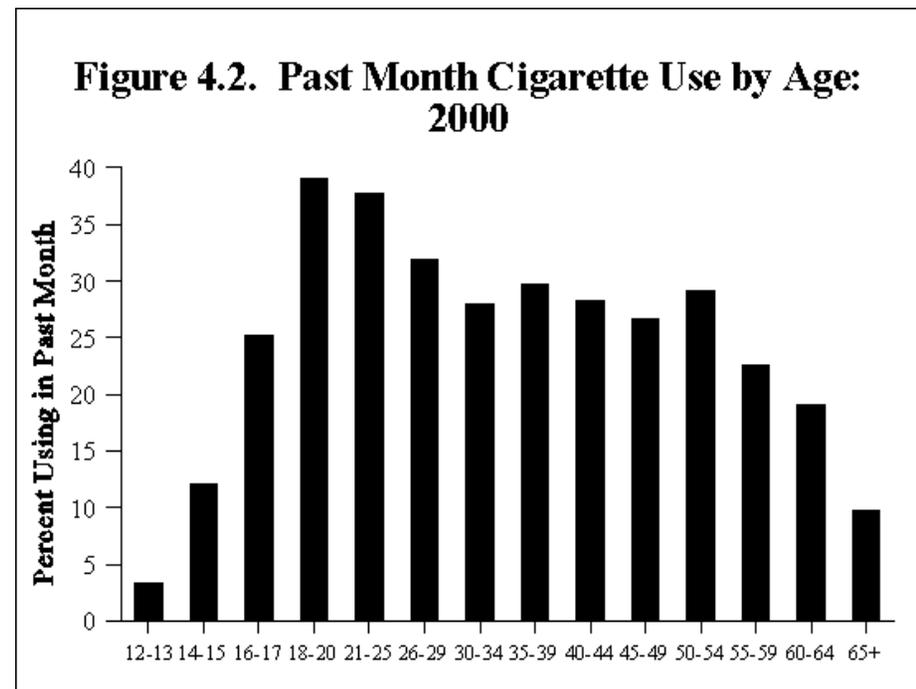
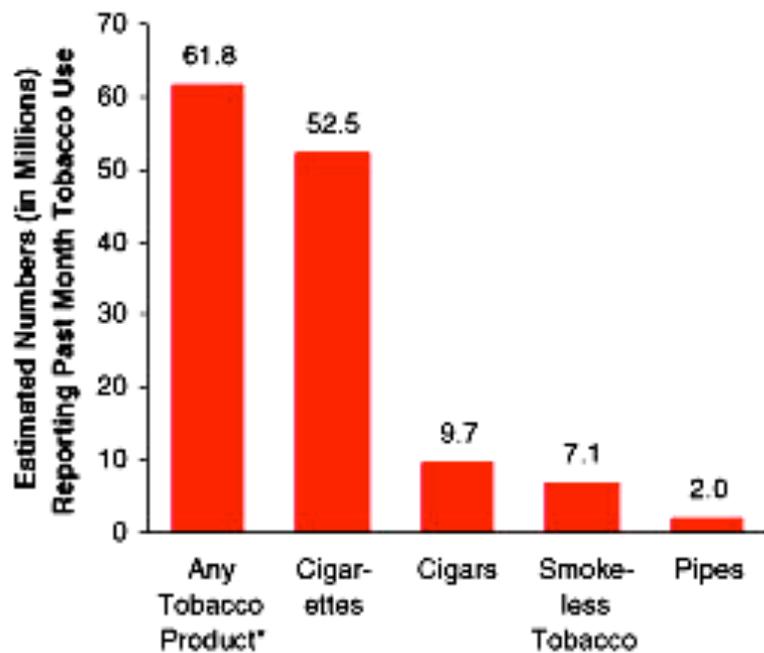
Sources: Centers for Disease Control and Prevention. Tobacco use—United States, 1900–1999. *Morbidity and Mortality Weekly Report* 1999;48(43):986; Department of Agriculture, Economic Research Service, Marketing and Trade Economics Division, Specialty Crops Branch, unpublished data; Department of Agriculture. *Agricultural Outlook*. Washington (DC): Department of Agriculture, Economic Research Service, 2001. USDA Publication No. ERS-AO-278.

# Determinants of Tobacco Use

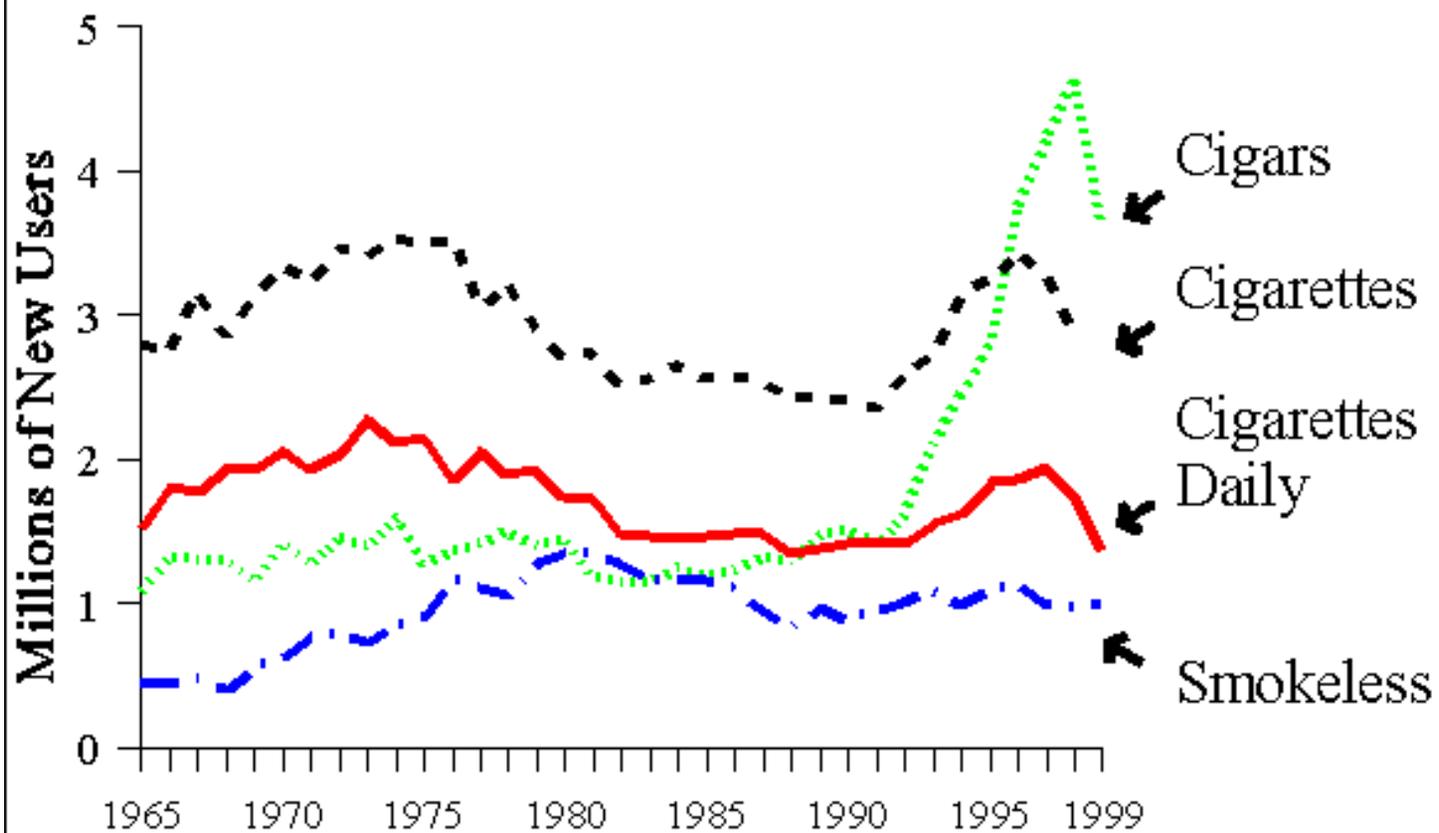
- Socioeconomic status
- Cultural characteristics
- Biological elements
- Stress
- Advertising (for and against)
- Price of tobacco products
- Peer pressure



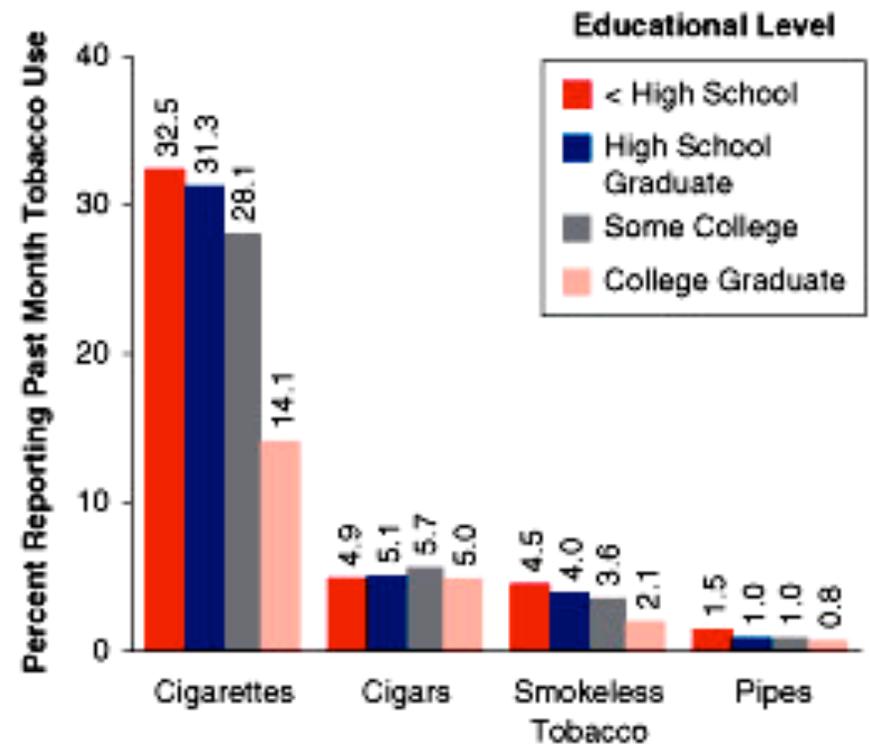
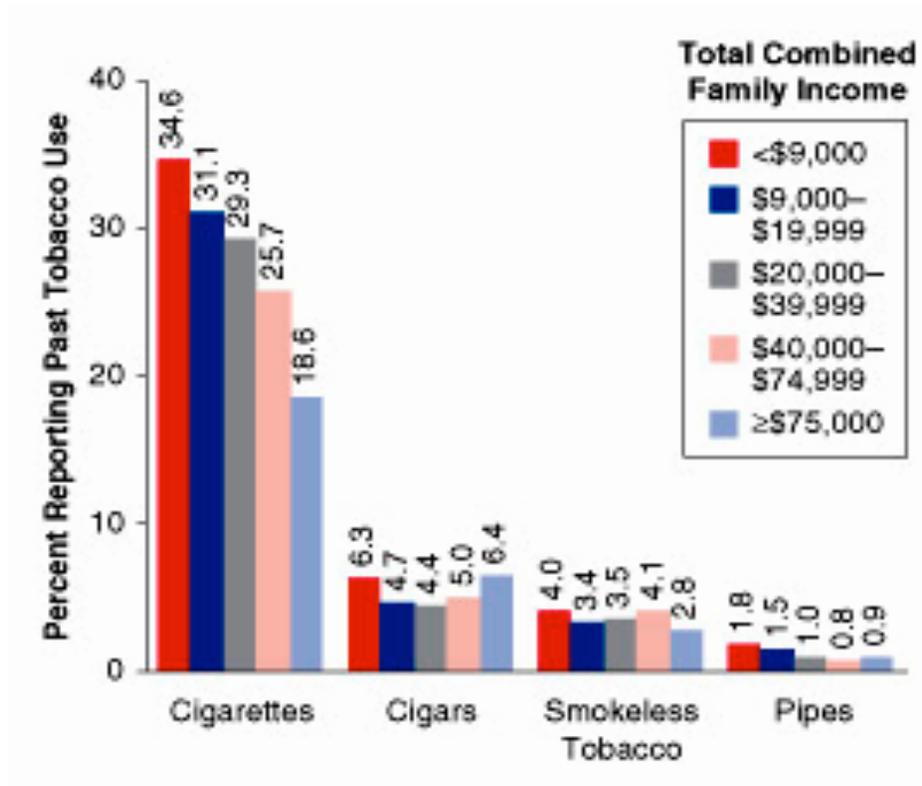
*Estimated Numbers (in Millions) of Persons Aged 18 or Older Reporting Past Month Tobacco Use: 2000*



**Figure 5.3. Annual Numbers of New Tobacco Users: 1965-1999**



# Income/Education and Tobacco Use



# Advertising

- TV and Radio Ads illegal (1971)
- Magazine Ads
- Outdoor Ads
- In-store promotions
  - Tobacco accounts for 26.5% total sales of convenience stores
- Sponsorships



# Targeted Advertising

- Exploit Ethnic Holidays
  - Hispanic Heritage Month
  - Black History Month
- Ethnic Groups
  - Rio / Dorado
  - American Spirit
  - Mild Seven
  - Uptown
- Children
  - Joe Camel is cool



Hispanics

American Indians

Asians

African Americans



**WILLIE THE PENGUIN SAYS:**

When you sniffle,  
Cough, kerchoo!  
You'll find Kools  
The smoke for you!



Smoke Kools - for that clean -  
K O O L taste in your mouth!

# We make Virginia Slims especially for women because they are biologically superior to men.

That's right, again: Women are more resistant to starvation, fatigue, exposure, shock, and illness than men are.

Women have two "X" chromosomes in their sex cells, while men have only one "X" chromosome and a "Y" chromosome... which some experts consider to be the inferior chromosome.

They are also less inclined than men to congenital baldness, Alzheimer of the eyes, improperly developed sweat glands, color blindness of

the red-green type, dry blindness, defective hair follicles, defective iris, defective tooth enamel, double eyelashes, skin cysts,

shortightedness, night-blindness, nystagmus, retinal detachment, and white occipital lobe of hair.

In view of these and other facts, the makers of Virginia Slims feel it highly inappropriate that women continue to use the fat, stubby cigarettes designed for mere men.



**Virginia Slims.**

*Slimmer than the fat cigarettes men smoke. With a Virginia Slims for women like*

**You've come a long way, baby.**



*In 1908, Drinky Fischer decided to smoke a cigarette while checking on her safety deposit box.*

*The bank decided to make an early withdrawal.*



**VIRGINIA SLIMS**



**You've come a long way, baby.**

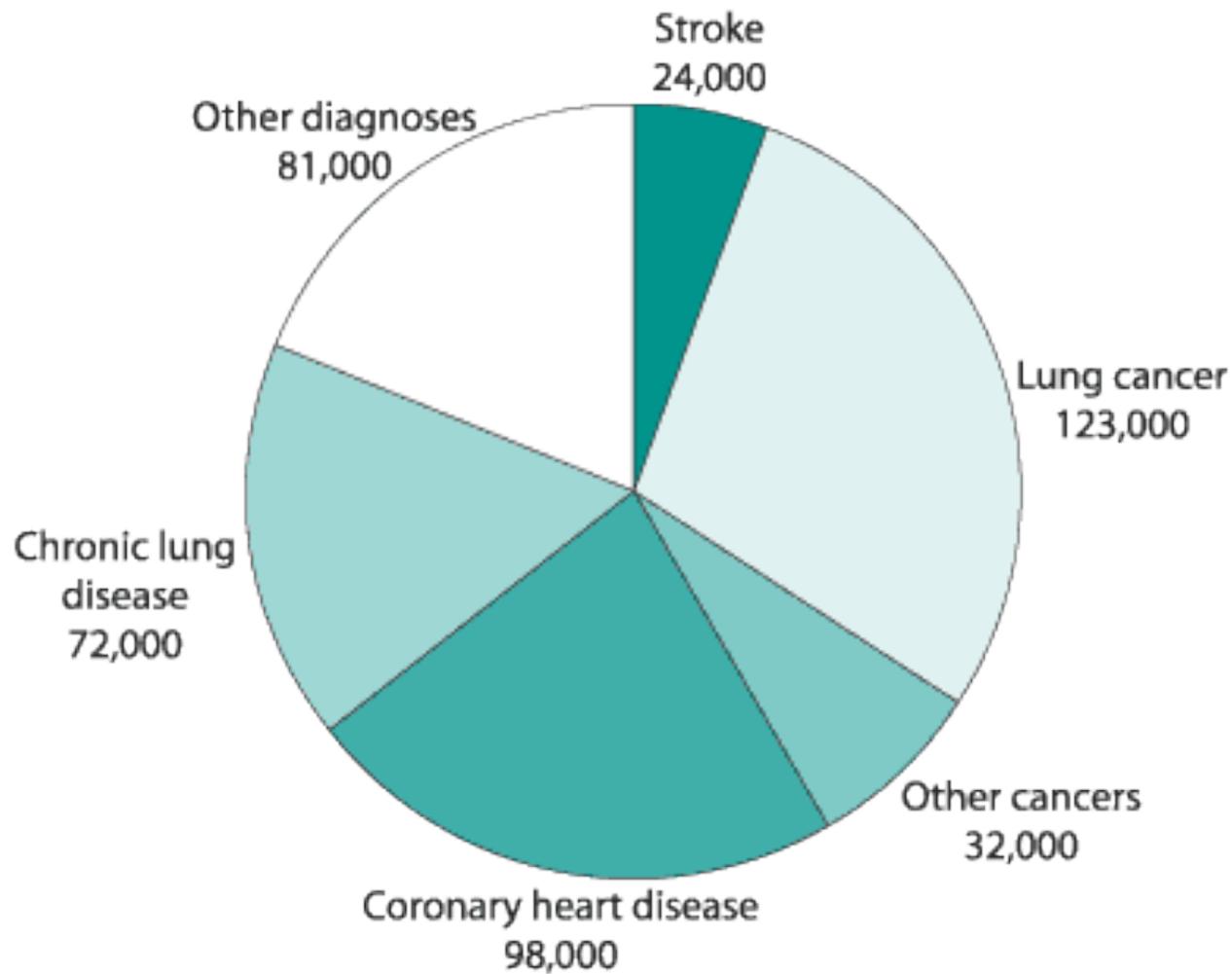
8 mg "tar," 0.8 mg nicotine av. per cigarette, FTC Report Feb. '95

**SURGEON GENERAL'S WARNING: Smoking By Pregnant Women May Result in Fetal Injury, Premature Birth, And Low Birth Weight.**

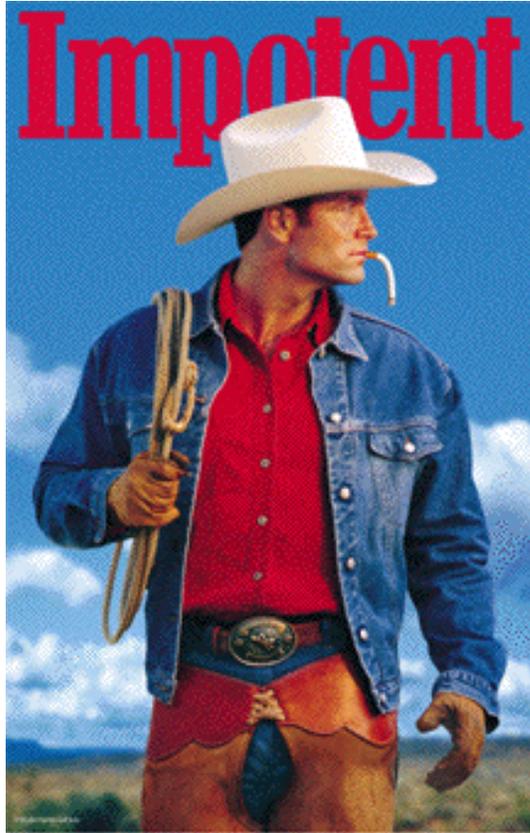
© Philip Morris Inc. 1995



# *Death by Cigarette 1990-1994*



# Anti-Smoking Ad Campaigns



**WARNING: SMOKING CAUSES IMPOTENCE**

Scare tactics



**WARNING:  
CIGARETTES  
CAUSE MOUTH  
DISEASES**

Cigarette smoke causes cancer, tooth loss and can cause gum disease.

Health Canada



THE SURGEON GENERAL WARNS THAT SMOKING IS A FREQUENT CAUSE OF WASTED POTENTIAL AND FATAL REGRET.

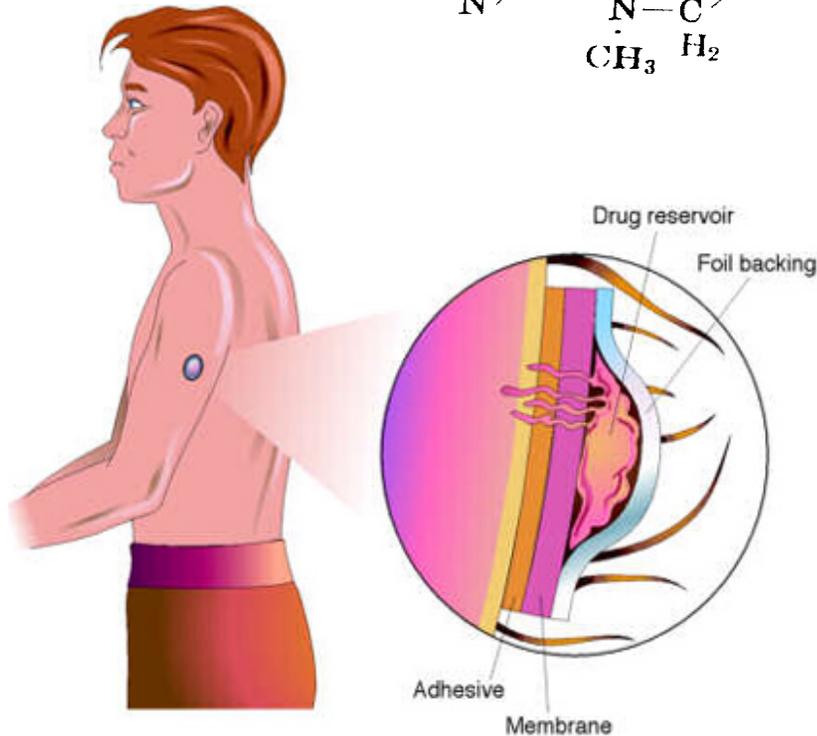
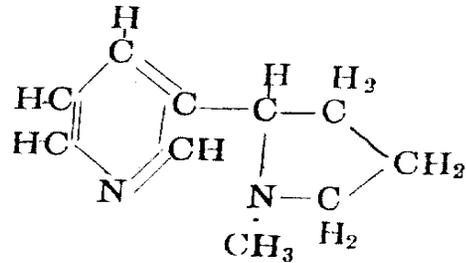
A photograph showing the silhouettes of two cowboys on horseback, walking away from the viewer towards a bright, orange sunset. The cowboys are wearing hats and riding gear. The scene is set in an open field with wooden fences visible on either side. The overall mood is nostalgic and somber.

**I miss my lung, Bob.**

California Department Of Health Services.  
Funded By The Tobacco Tax Initiative.

© 1998 California Department of Health Services

# Pharmacokinetics



- Readily absorbed from all over the body, including
  - Lungs (smoked)
  - Mucosa (cigar, chewing tobacco, gum, nasal spray)
  - Skin (patch)
  - Gastrointestinal tract (uncommon)

# *Pharmacokinetics*

- Absorption
  - The most common way to get nicotine into your bloodstream is through inhalation
  - Your lungs are lined by millions of alveoli, which are the tiny air sacs where gas exchange occurs
    - These alveoli provide an enormous surface area, 90 times greater than that of your skin, and thus provide ample access for nicotine and other compounds
  - Nicotine taken in by cigarette or cigar smoking takes only 10-15 seconds to reach the brain but has a direct effect on the body for only ~30 minutes

# *Pharmacokinetics*

- Nicotine in smoke peaks in brain very rapidly, despite relatively slow increase in blood concentration
- A typical cigarette contains 20 mg of nicotine
- ~2.5 mg of nicotine is absorbed
- Half-life: ~ 2 hours
- 80-90% metabolized in liver

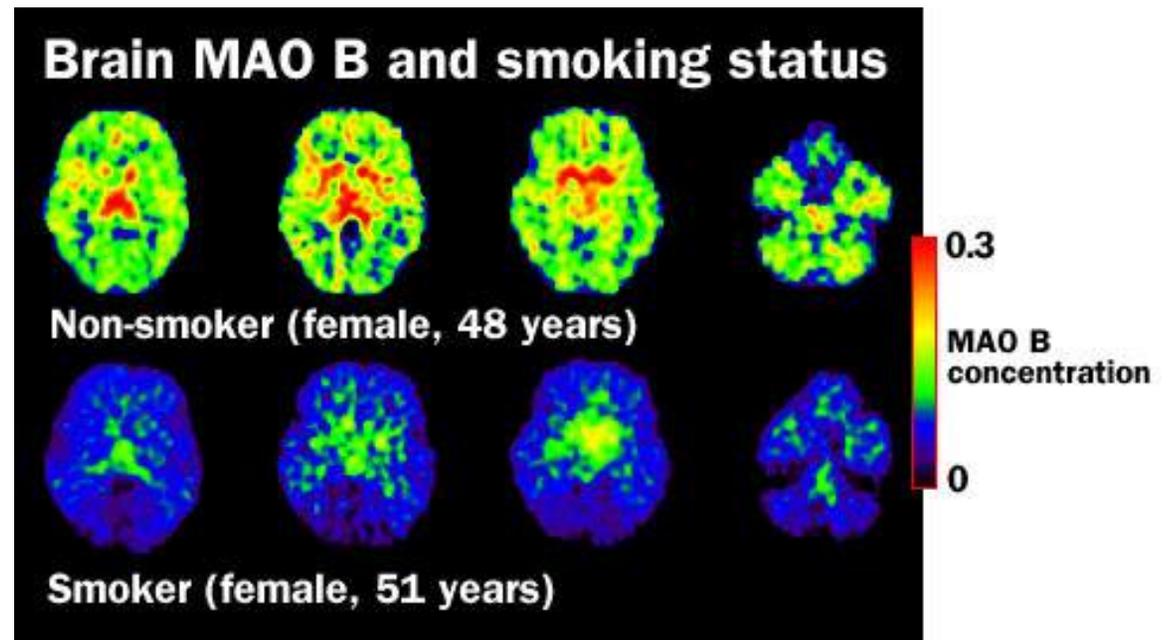
# *Pharmacokinetics*

- Metabolism & Elimination
  - About 80 percent of nicotine is broken down to cotinine by enzymes in your liver (e.g., CYP2A6)
  - Nicotine is also metabolized in your lungs to cotinine and nicotine-N-oxide
  - Cotinine and the remaining nicotine is filtered from the blood by your kidneys and excreted in the urine



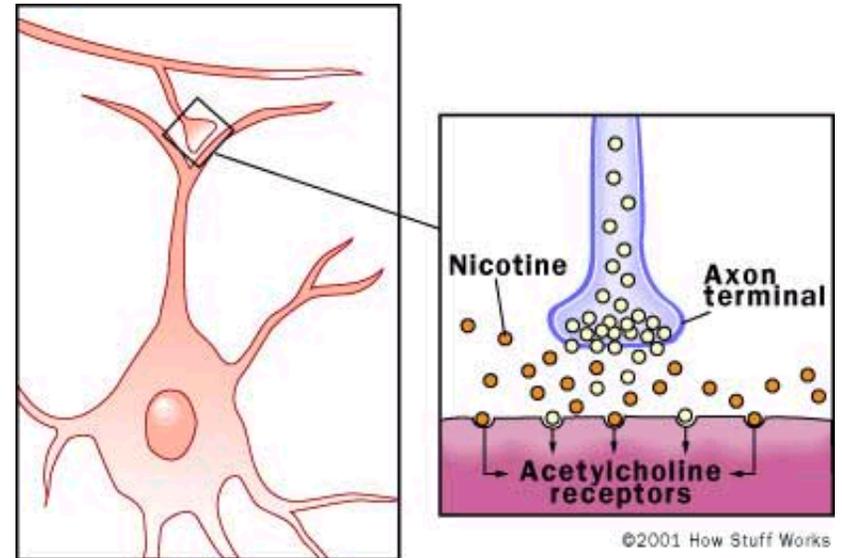
# *Smoking and MAO levels*

Something in cigarette smoke seems to slow the breakdown of dopamine by affecting MAO levels



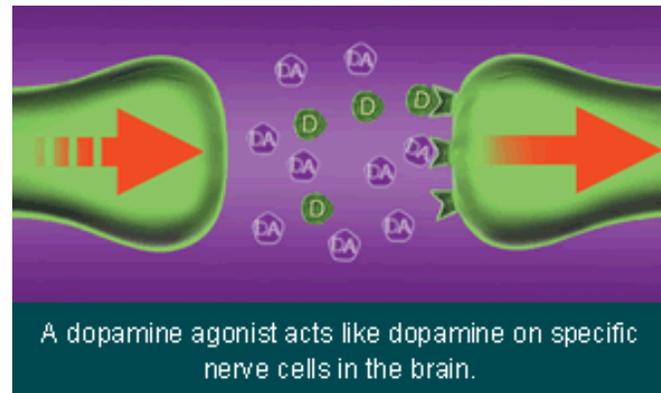
# Pharmacodynamics

- Nicotine is a direct agonist for nicotinic ACh receptors
- Nicotine initially causes a rapid release of adrenaline, the "fight-or-flight" hormone

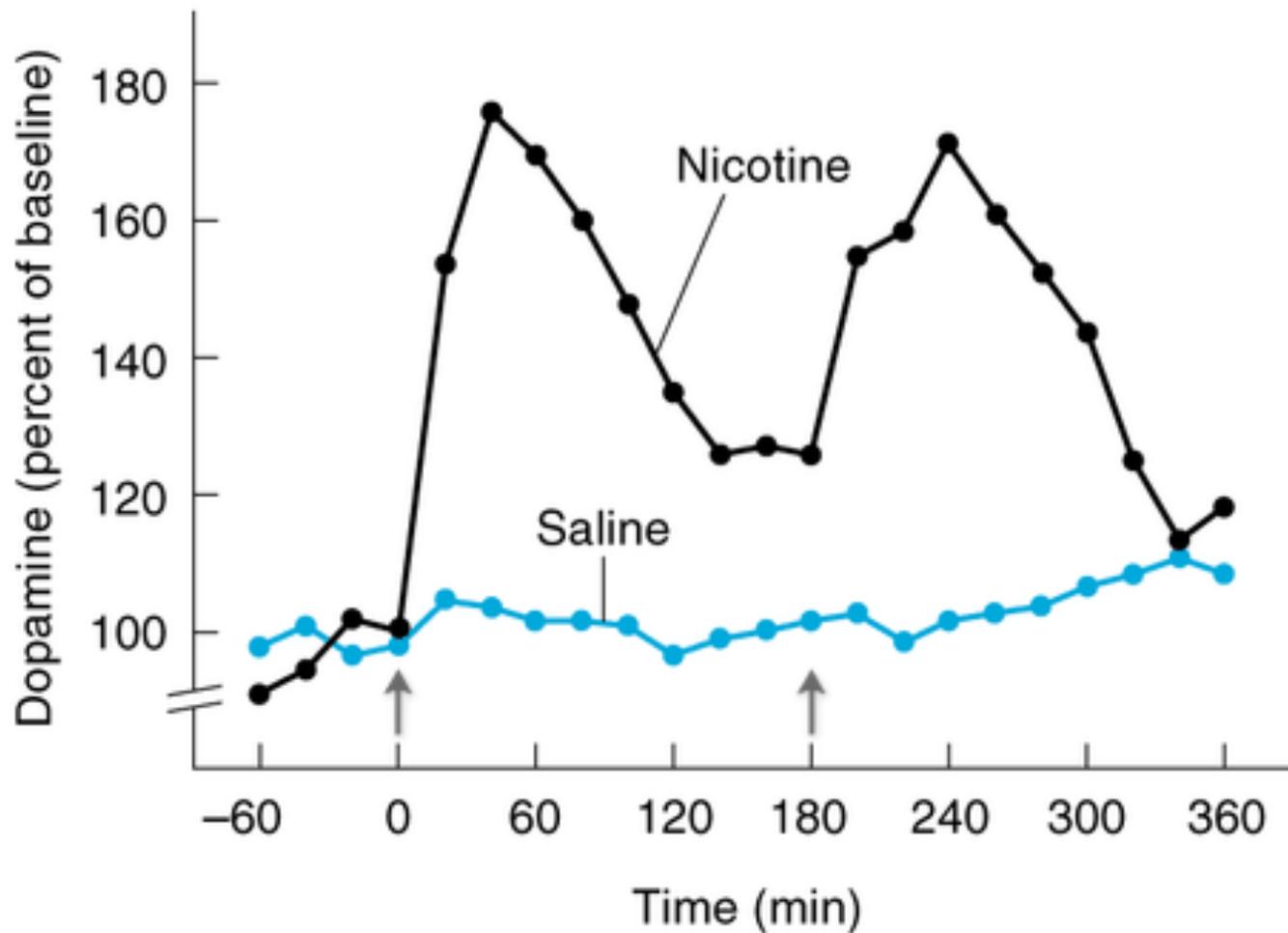


# Pharmacodynamics

- nAChRs found in limbic system (e.g. striatum, hippocampus, accumbens), midbrain (e.g. VTA, substantia nigra), various cortical areas (frontal lobe)
- nAChRs both postsynaptic and presynaptic, facilitating ACh, DA, 5-HT and Glu action
- Nicotine also increases release of various neurohormones
- Has powerful effects on peripheral nervous system, heart, and other organs



► Changes in Dopamine Concentration in the Nucleus Accumbens



Source: Adapted from Damsma, G., Day, J., and Fibiger, H.C. *European Journal of Pharmacology*, 1989, 168, 363-368.

# *Acute Effects*

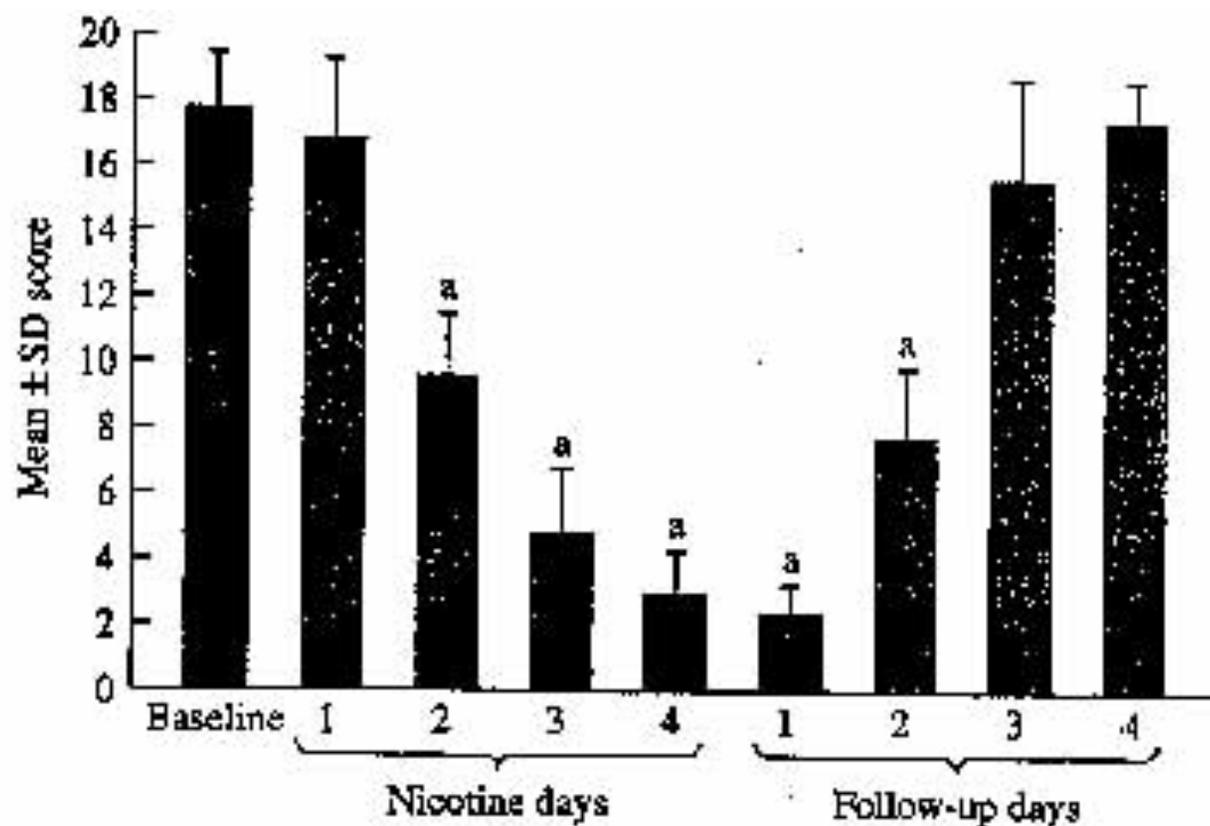
- Classic stimulant effects of arousal (e.g. increased heart rate and blood pressure, alertness, appetite suppression)
- Carbon monoxide (in smoked form) reduces oxygen transport to heart and other organs
- Vasoconstriction
- Can have calming (anxiolytic) effects in some individuals
- Mild euphoria (relief?)
- Cognitive enhancements
- Antidepressant effects

**WARNING:** There is no safe tobacco product - including cigarettes, cigars, pipes, and spit tobacco; mentholated, "low tar," "naturally grown" or "additive free" - can cause cancer and other adverse health effects.

# Positive Effects

- Alzheimer's Disease
  - The first neurons lost to Alzheimers are cholinergic neurons
  - Patients showed increased capacity for learning verbal material when exposed to nicotine
- Symptoms reduced in
  - ADHD
  - Tourette's Syndrome
    - Nicotine patches that slowly deliver nicotine were used
- Glutamate
  - Increases learning and memory
  - Enhances connections between sets of neurons

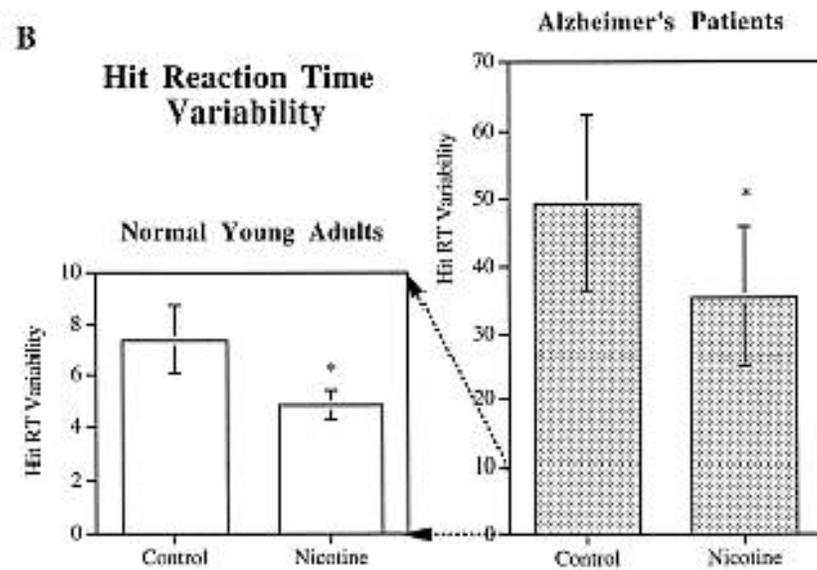
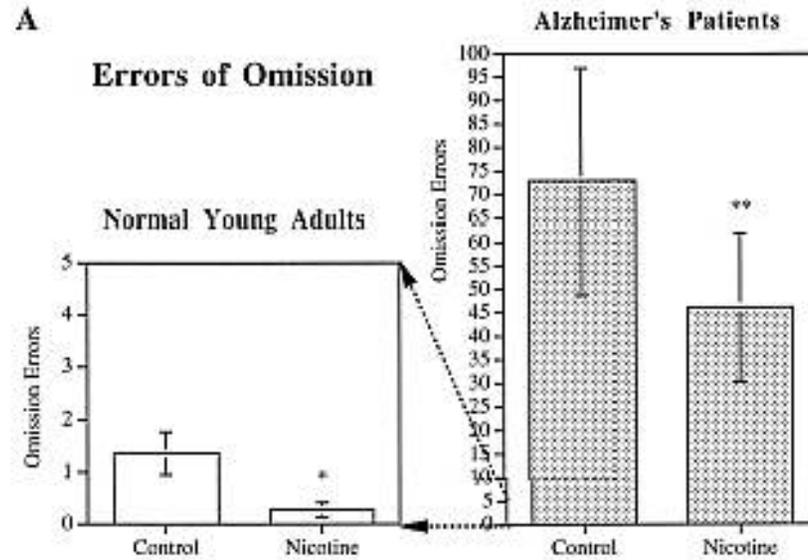




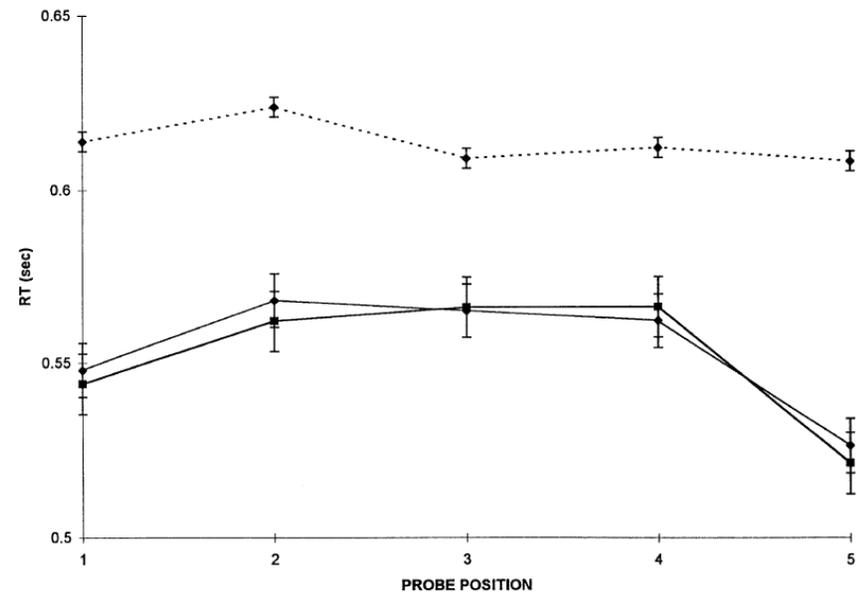
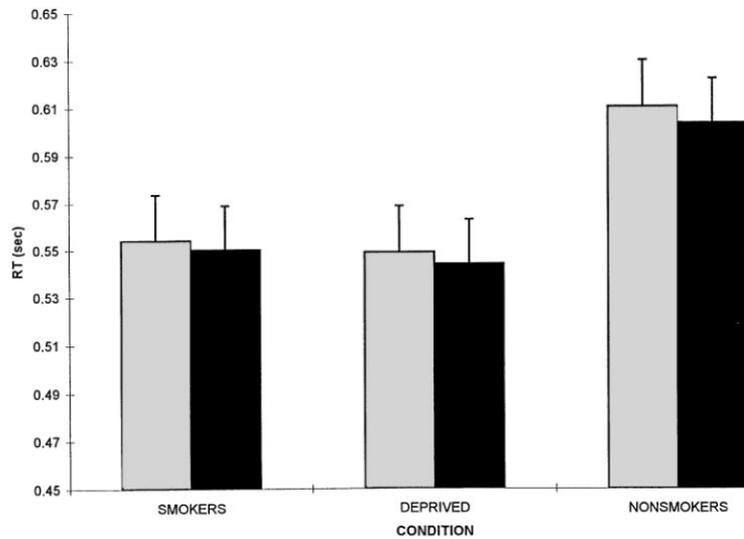
**FIGURE 8.6** Hamilton rating scale for depression ratings of 10 depressed patients before, during, and after administration of nicotine patches. A significant reduction was observed on the second day of nicotine patches and continued until the second follow-up day. [From Salin-Pascual et al.<sup>34</sup>]

# *Cognitive Enhancements?*

- Working memory (e.g. N-back)
- Visual Perception (e.g. Critical Flicker Fusion)
- Visual Attention (e.g. reaction time)
- Motor function (e.g. reaction time)
- P300 (increased amplitude, decreased latency)??

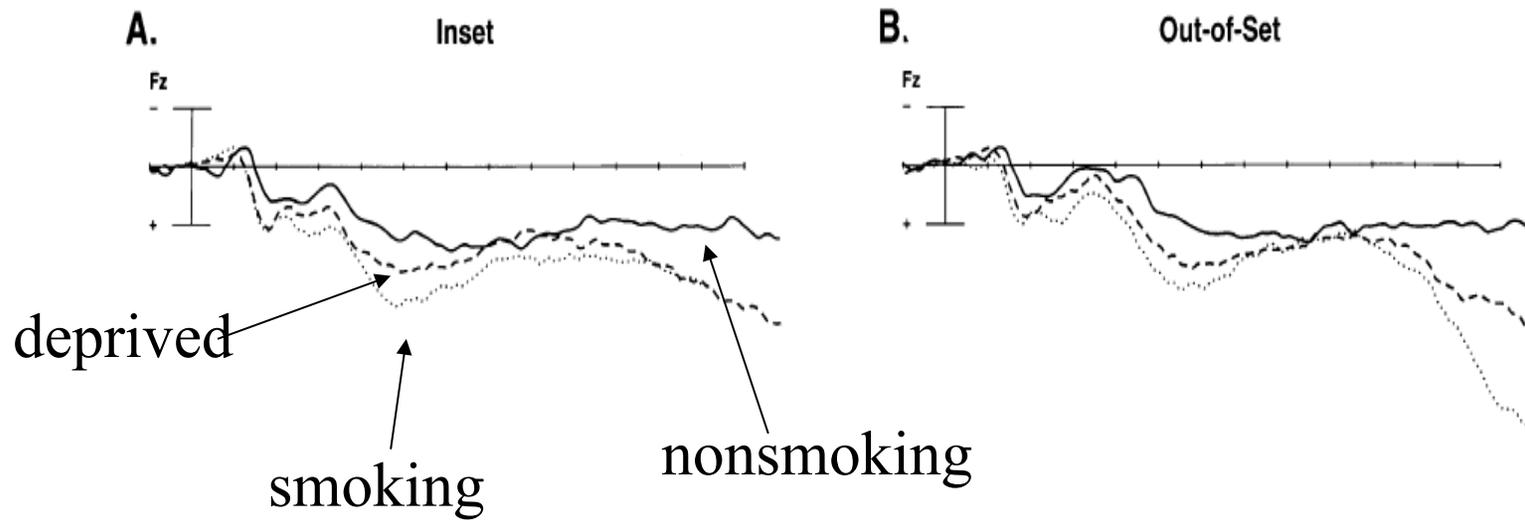


# *Cognitive Enhancements*



Enhanced primacy and recency effects

# *Effects on ERPs*



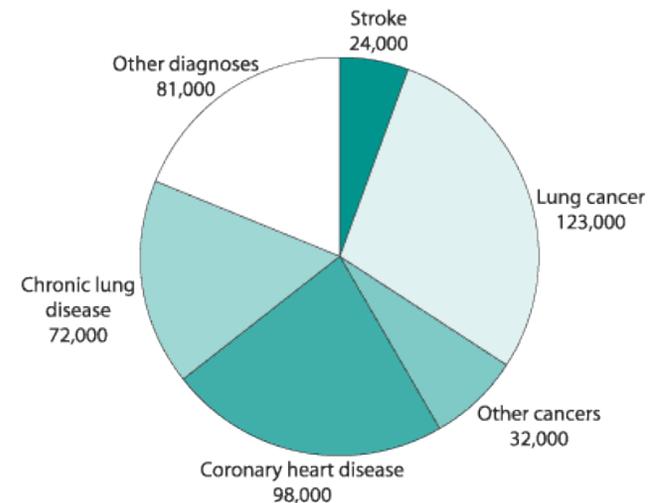
# Chronic Effects: CANCER

- Tobacco use accounts for one-third of all cancers

– **Cancers** relating to tobacco include:

- Mouth
- Pharynx
- Larynx
- Esophagus
- Stomach
- Lung
- Cervix
- Kidney
- Bladder
- Throat
- Pancreas

- Cigarette smoking has been linked to about 90 percent of all lung cancer cases
- 430,000 annual deaths are attributed to cigarette smoking



# More Chronic Effects

- Emphysema
  - Chronic bronchitis
  - Stroke
  - Vascular disease
  - Aneurysm
  - Esophageal reflux
  - Heart Disease
    - It is estimated that nearly one-fifth of deaths from heart disease are attributable to smoking
- \* Many of these are actually caused by other chemicals in cigarette smoke or in smokeless tobacco products



Environmental tobacco smoke (ETS) exposure has been linked also with sudden infant death syndrome

# Addiction

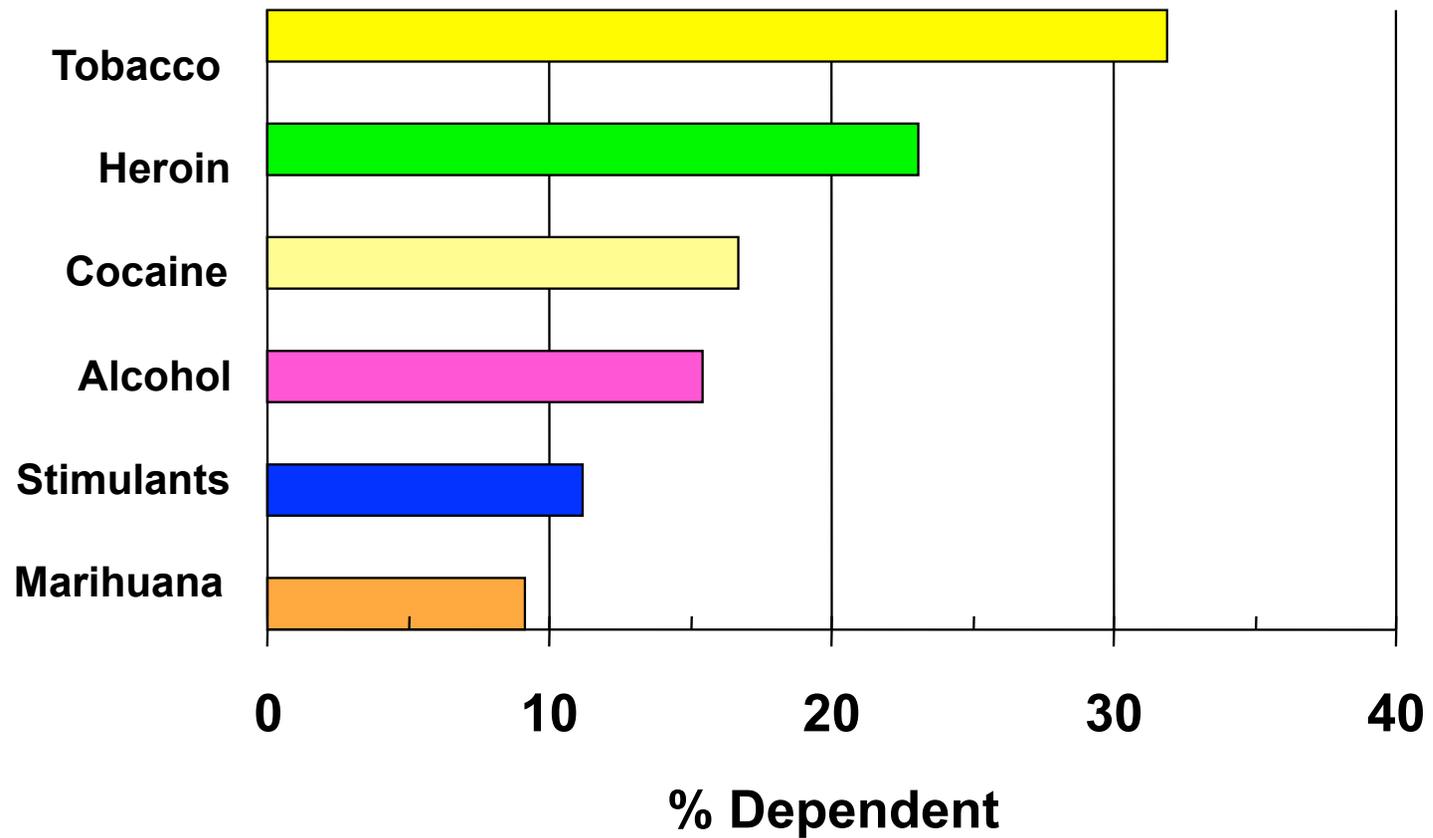
- Nicotine meets both the psychological and physiological measures of addiction
  - **Psychological** - People who are addicted to something will use it compulsively, without regard for its negative effects on their health or their life
  - **Physiological** - anything that turns on the reward pathway in the brain is addictive. Because stimulating this neural circuitry makes you feel so good, you will continue to do it again and again to get those feelings back

Recent studies suggest those excitatory amino acid systems and, in particular, *N-methyl-D-aspartate (NMDA) receptors*, may have an important role in this phenomenon.

Nicotine is as addictive as heroin



# *Drug Dependence Among Ever-Users*



# *Tolerance & Withdrawal*

- Mild tolerance to behavioral and cardiovascular effects
- Upregulation of receptors has been interpreted as a compensation to desensitization of nicotinic acetylcholine receptors (nAChRs), and this prolonged desensitization has been proposed as the mechanism of chronic tolerance to nicotine
- Withdrawal may start after as little as one hour, may last for as long as several months, can include:
  - Craving
  - Irritability
  - Anxiety
  - Dysphoria
  - Anger
  - Difficulty concentrating
  - Restlessness
  - Impatience
  - Increased appetite, weight gain
  - Insomnia

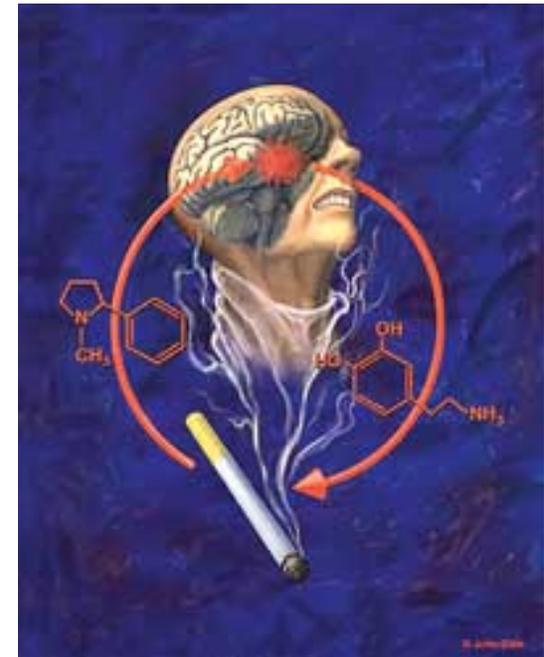
# *Treatment options*

- **Behavior modification**
- Nicotine lozenges
- Nicotine gum
- Nicotine patches
- Nicotine inhaler
- Nicotine nasal spray
- Bupropion SR



# Challenges of Quitting

- Smokers seeking treatment for other drug problems often find it harder to quit smoking than other drugs
- Quitters often increase caffeine intake (blood levels increased for up to 6 months) — symptoms of nicotine withdrawal and caffeine toxicity similar enough that reported withdrawal symptoms may reflect mixture of the two
- Among self-quitters considered strongly motivated to quit, 60-65% relapse in 1<sup>st</sup> month after cessation
- Conditioned cues considered important elements for maintenance and relapse



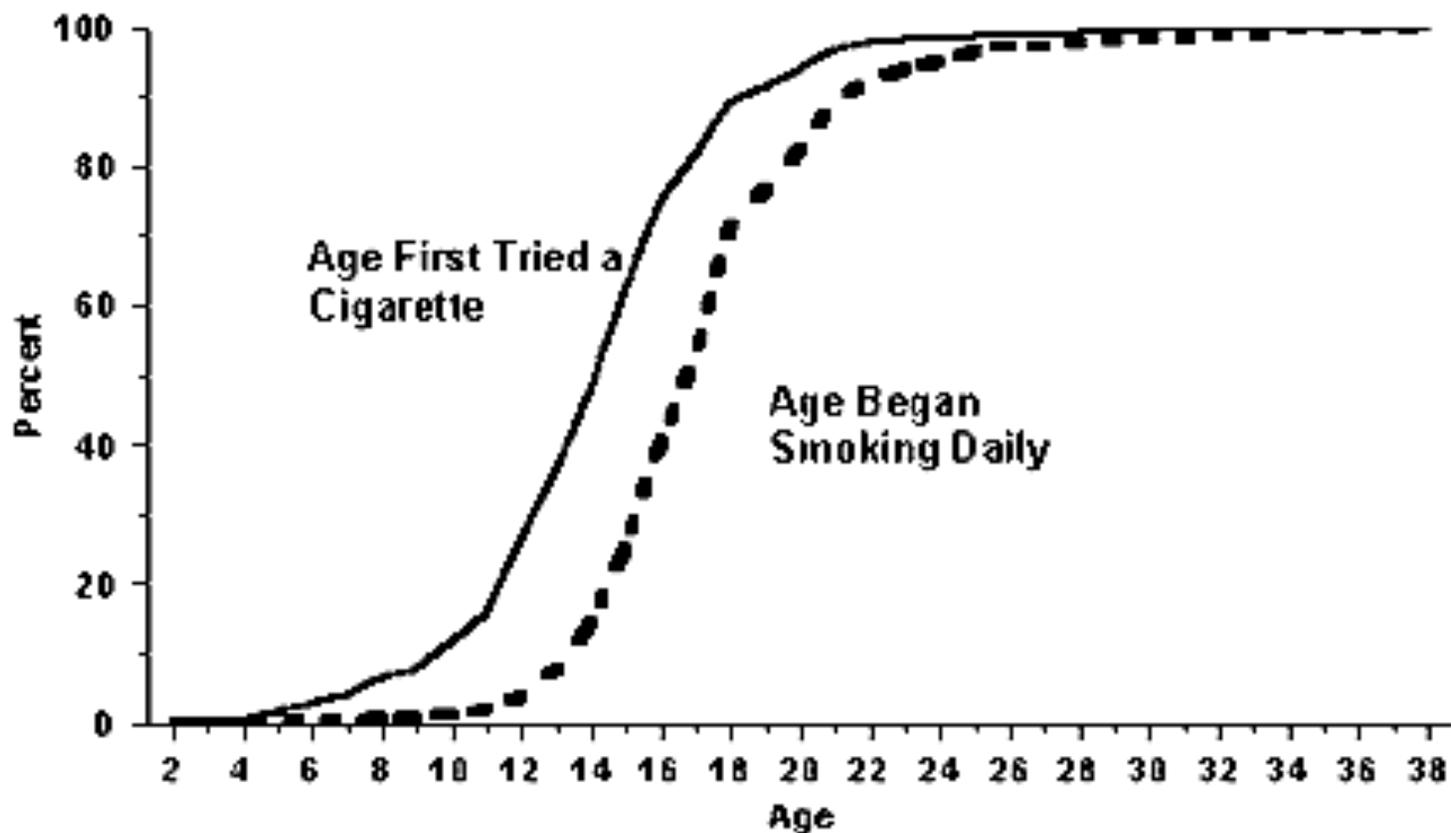
# *What's new?*

- Rimonabant (Acomplia; Zimulti)
  - Cannabinoid Receptor (CB1) Antagonist
  - Weight loss, tobacco cessation
  - Phase III clinical trials

Acomplia was officially withdrawn by the European Medicines Agency (EMA) in January 2009 due to the risks of dangerous psychological side effects, including increased suicide risks.

- E-cigarettes

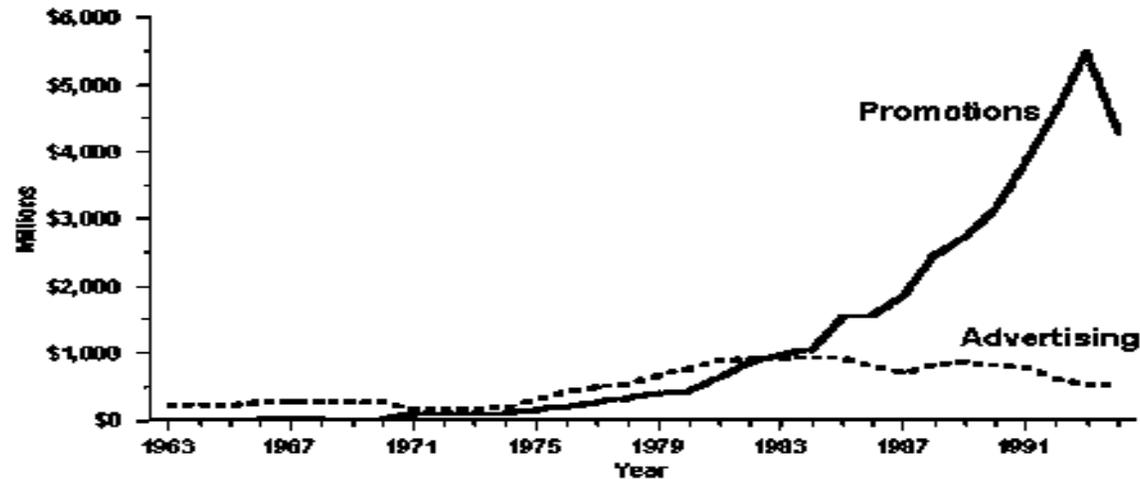
*Cumulative Age of Initiation of Cigarette Smoking\**  
—United States, 1991



Source: National Household Survey on Drug Abuse

\*Among persons 30-39 years old who have ever smoked daily

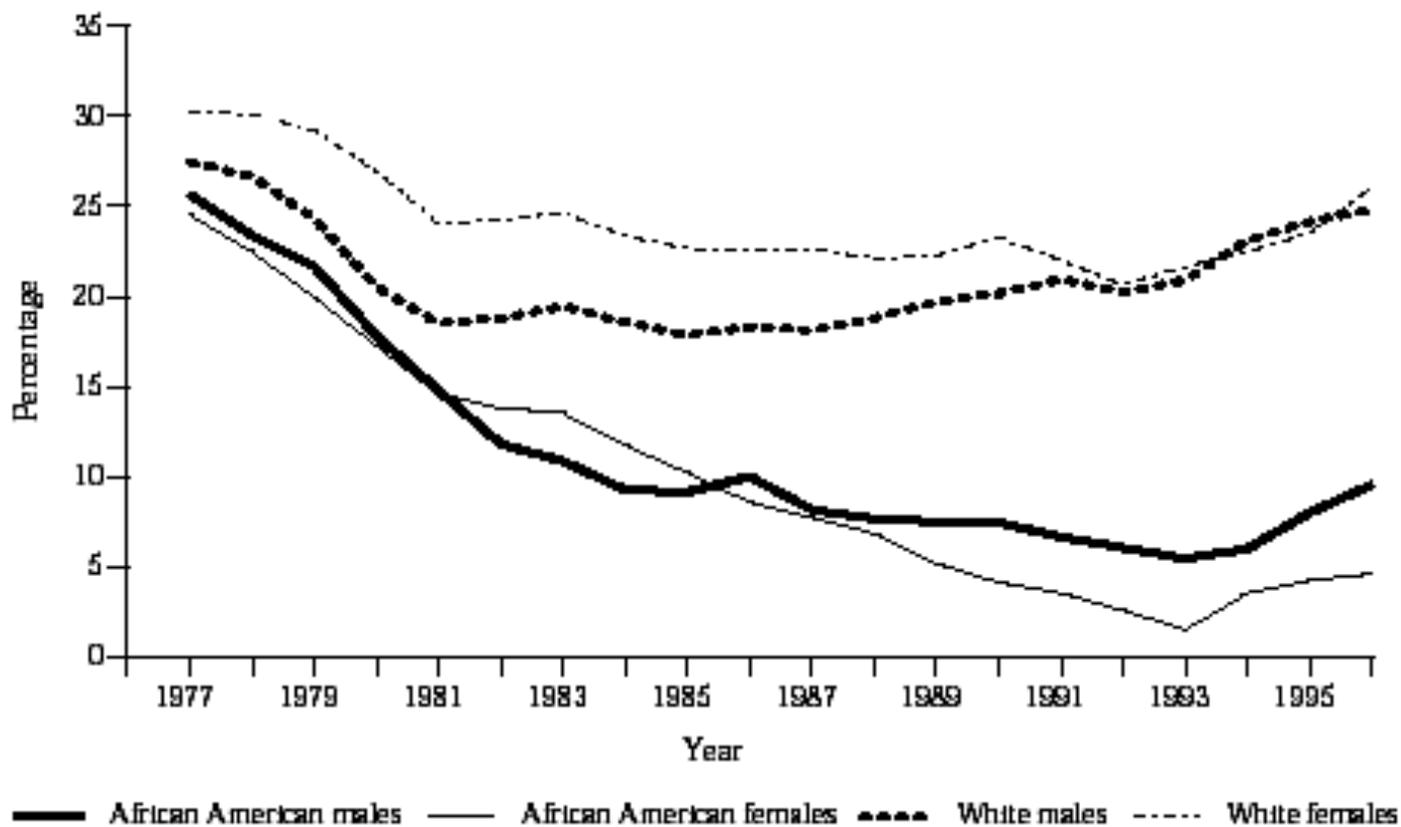
# Advertising vs. Promotions



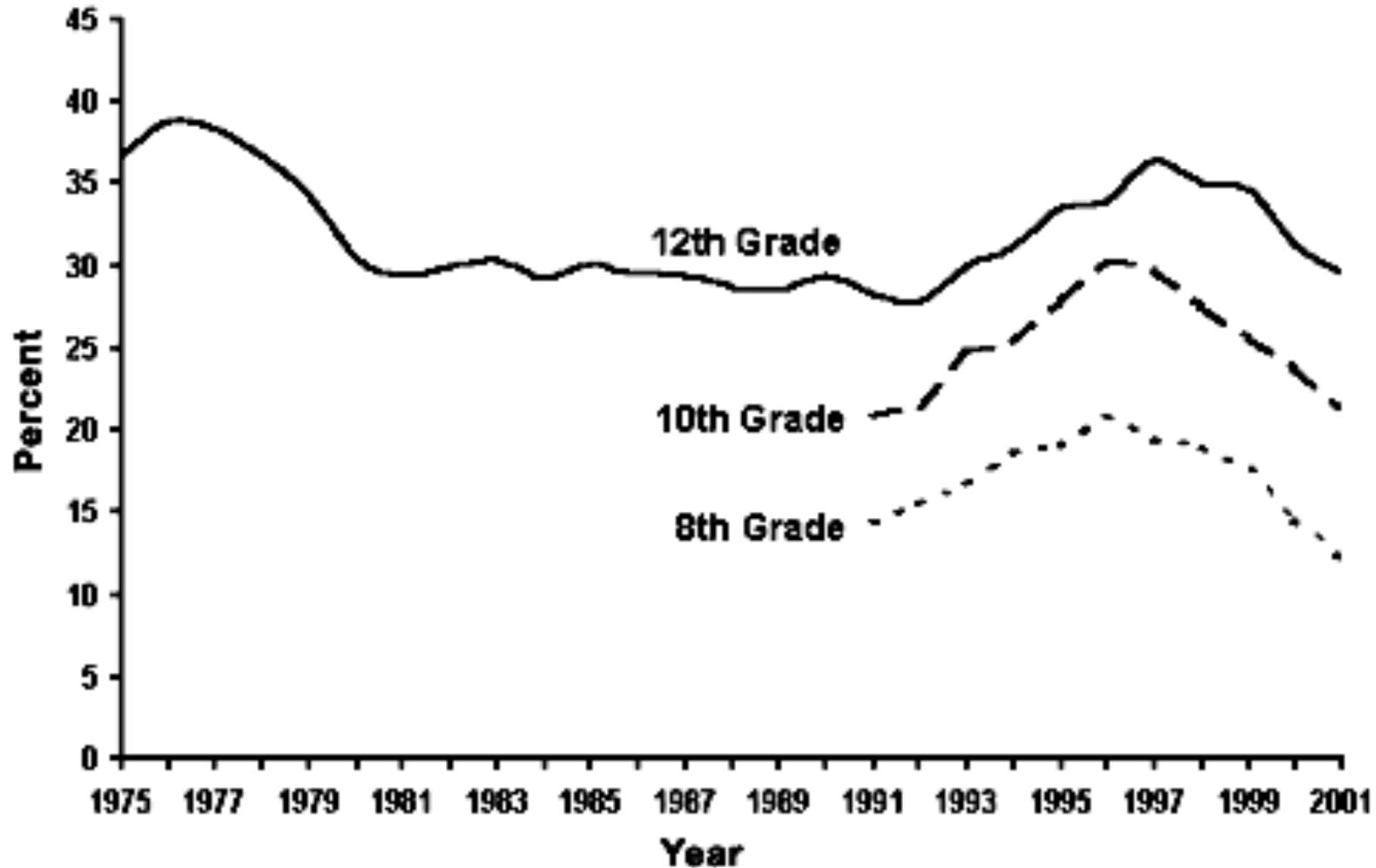
**Advertising:** newspaper, magazine, outdoor, transit expenditures, television and radio (before 1971).

**Promotions:** point-of-sale, promotional allowances, sampling distribution, direct mail, public entertainment, endorsement, and testimonial expenditures

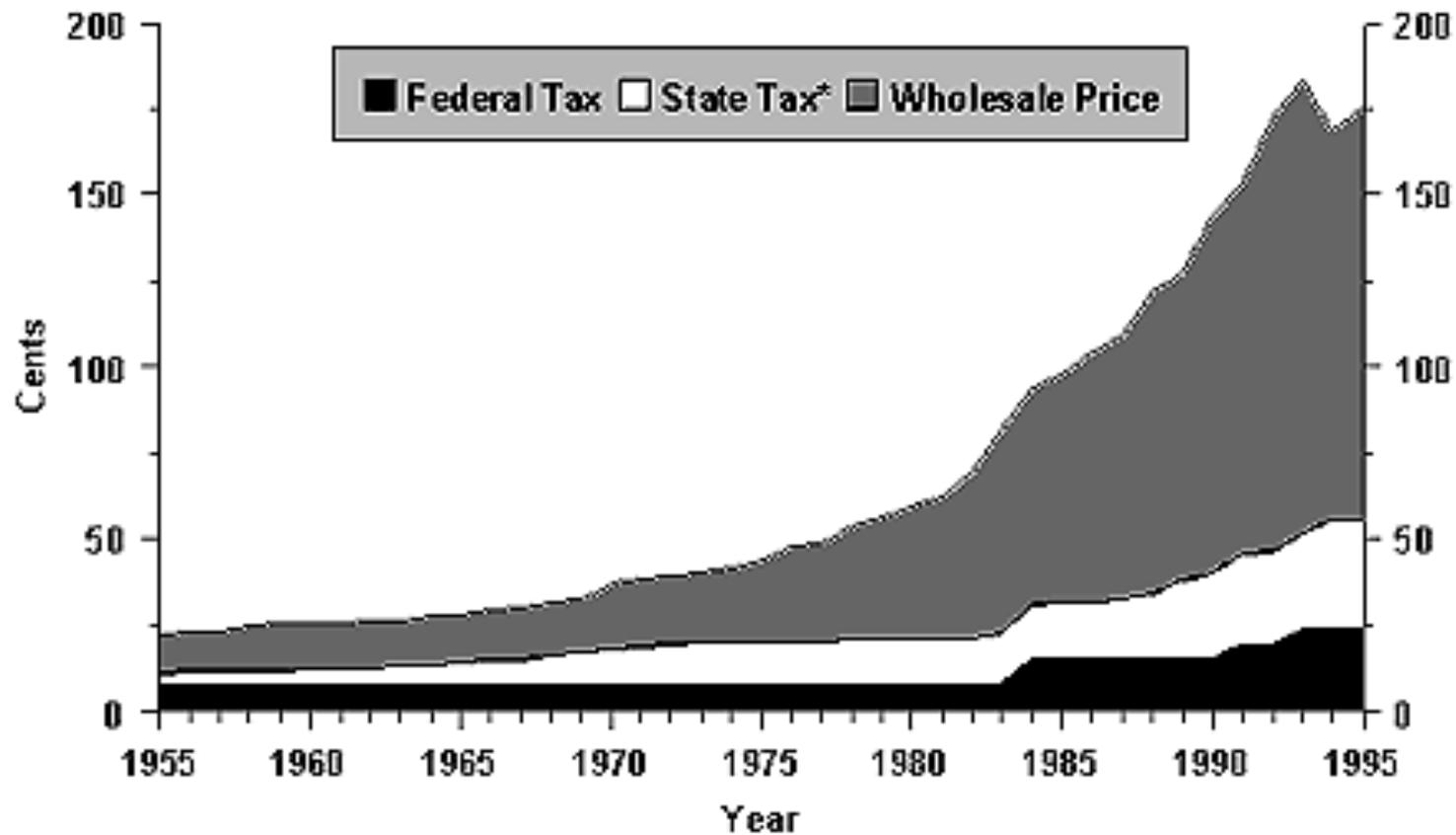
*Trends in daily smoking\* among African American and white high school seniors, by gender*



*Trends in Current\* Cigarette Smoking by Grade in School—United States, 1975-2001*

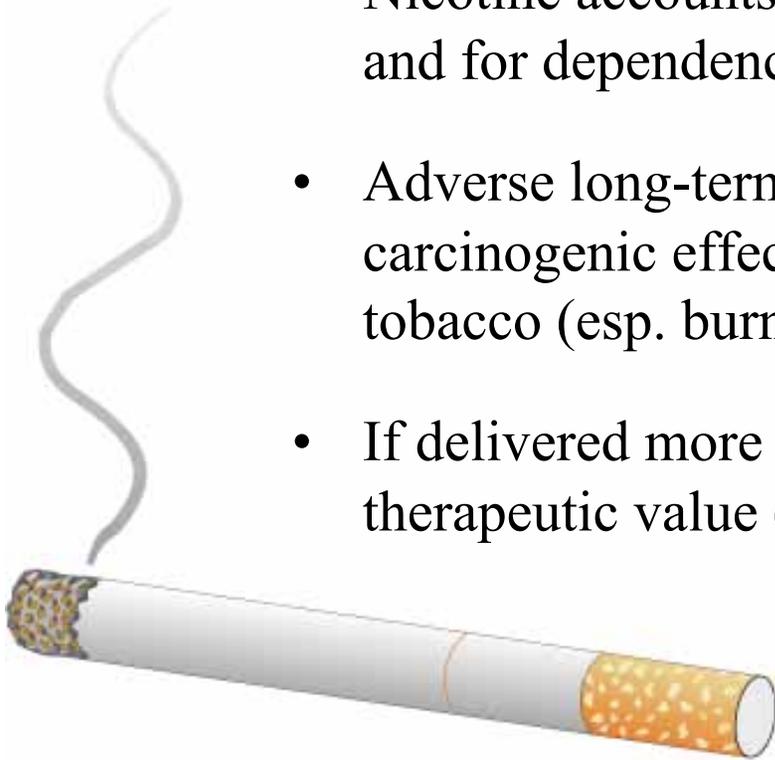


# Economics: Price and Tax



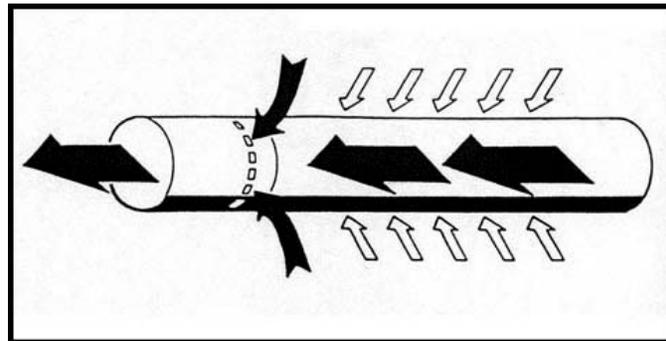
# *Cigarette = Dirty Needle?*

- Nicotine is only 1 of ~ 4000 compounds released by burning a cigarette
- Nicotine accounts for acute pharmacological effects and for dependence, but...
- Adverse long-term cardiovascular, pulmonary, and carcinogenic effects related to other compounds in tobacco (esp. burned).
- If delivered more safely, nicotine may have potential therapeutic value (e.g. Alzheimer's disease).

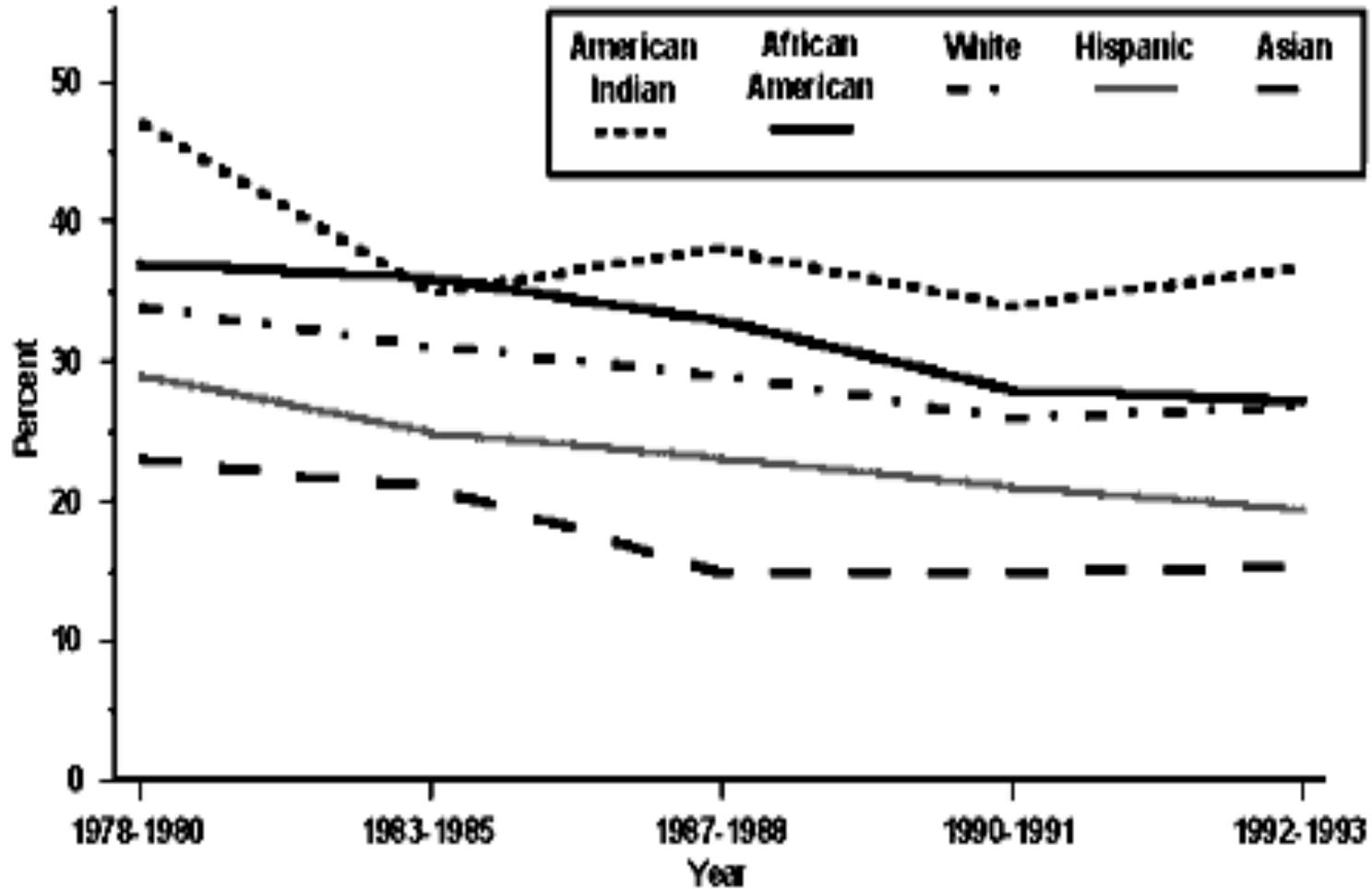


## *or The Perfect Delivery Device?*

- Rapid onset/offset of effects
- Additives facilitate nicotine effects, widen air passages, reduce smoke visibility/odor
- Personal control of dosing
- Provides comforting habit/ritual
- Air vents and smoking style regulate amount delivered

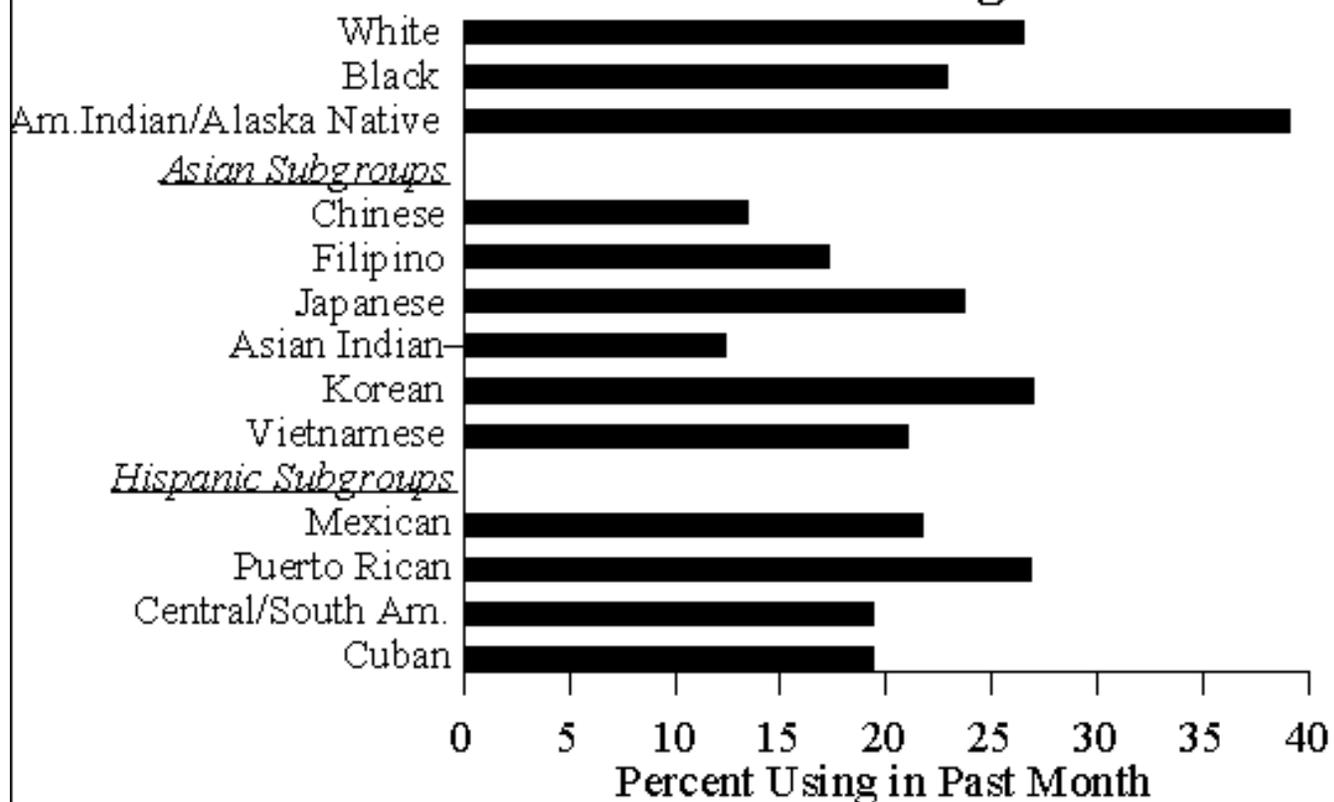


# Who Uses Tobacco: Ethnic Breakdown

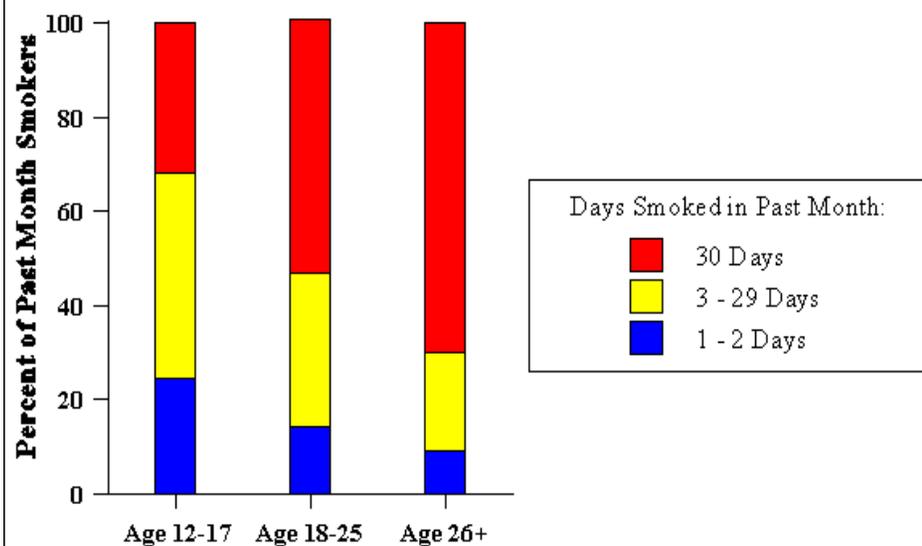




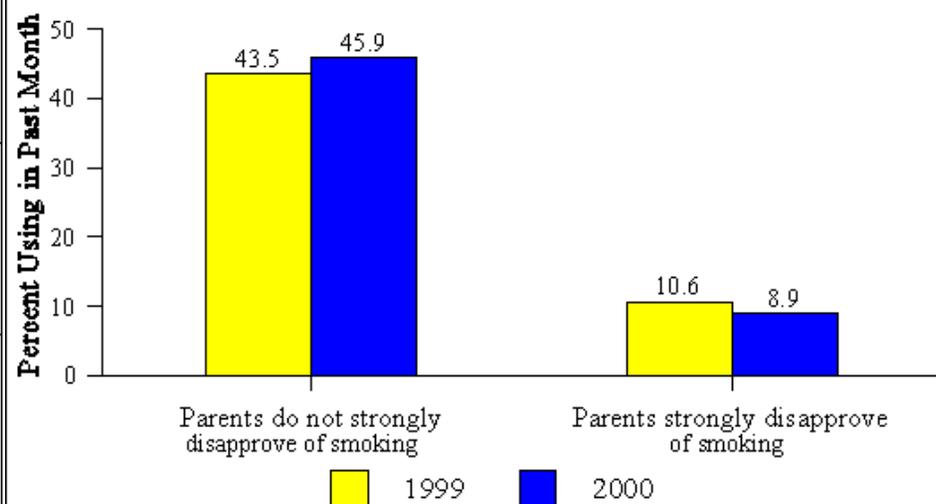
**Figure 4.5. Past Month Cigarette Use Among Persons Aged 12 and Older, by Race/Ethnicity: 1999-2000 Annual Average**



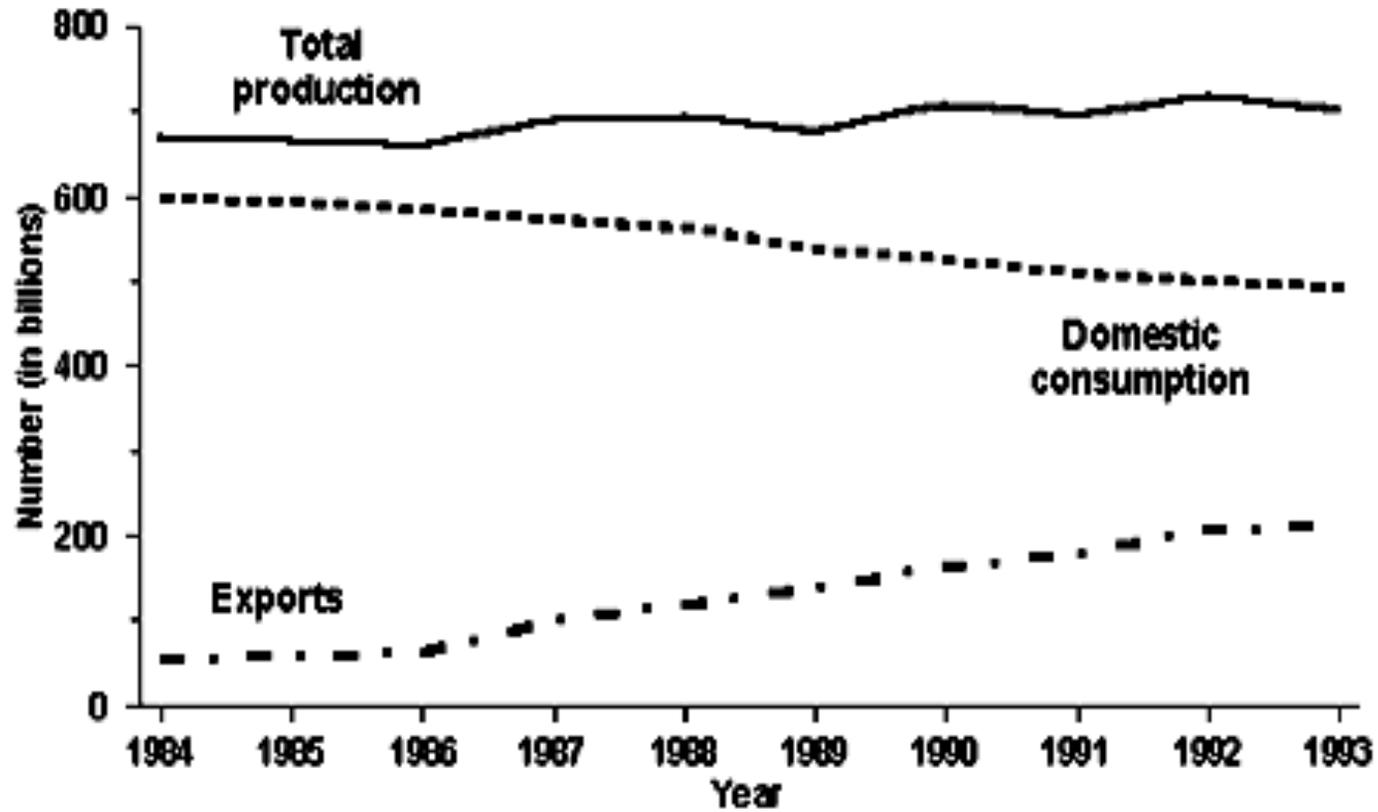
**Figure 4.6. Frequency of Cigarette Use Among Current Smokers, by Age: 2000**



**Figure 6.5. Past Month Cigarette Use Among Youths Aged 12 to 17, by Perceived Parental Attitudes About Smoking: 1999 and 2000**



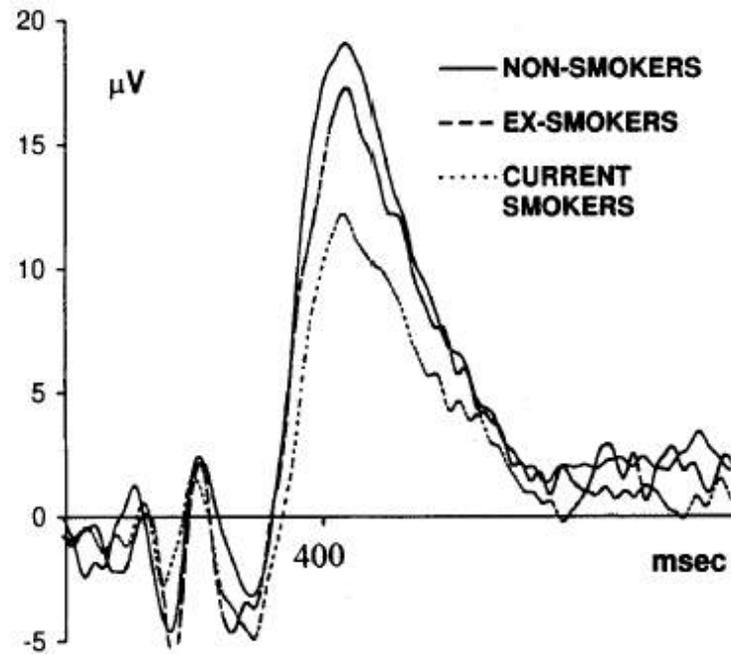
# Domestic vs. Foreign Use



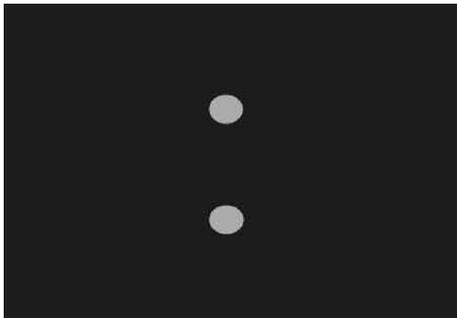
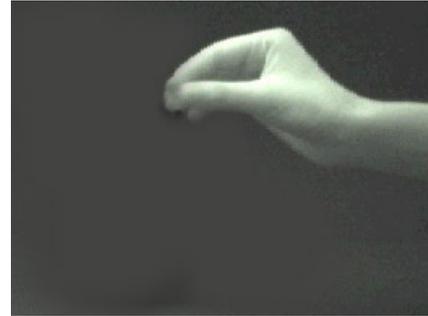
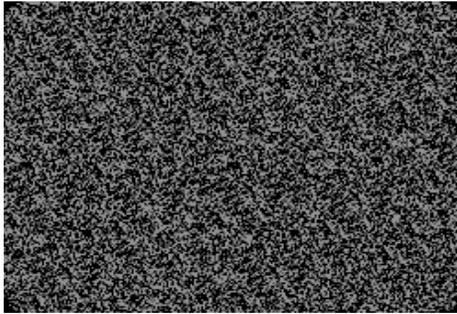
Source: USDA 1993

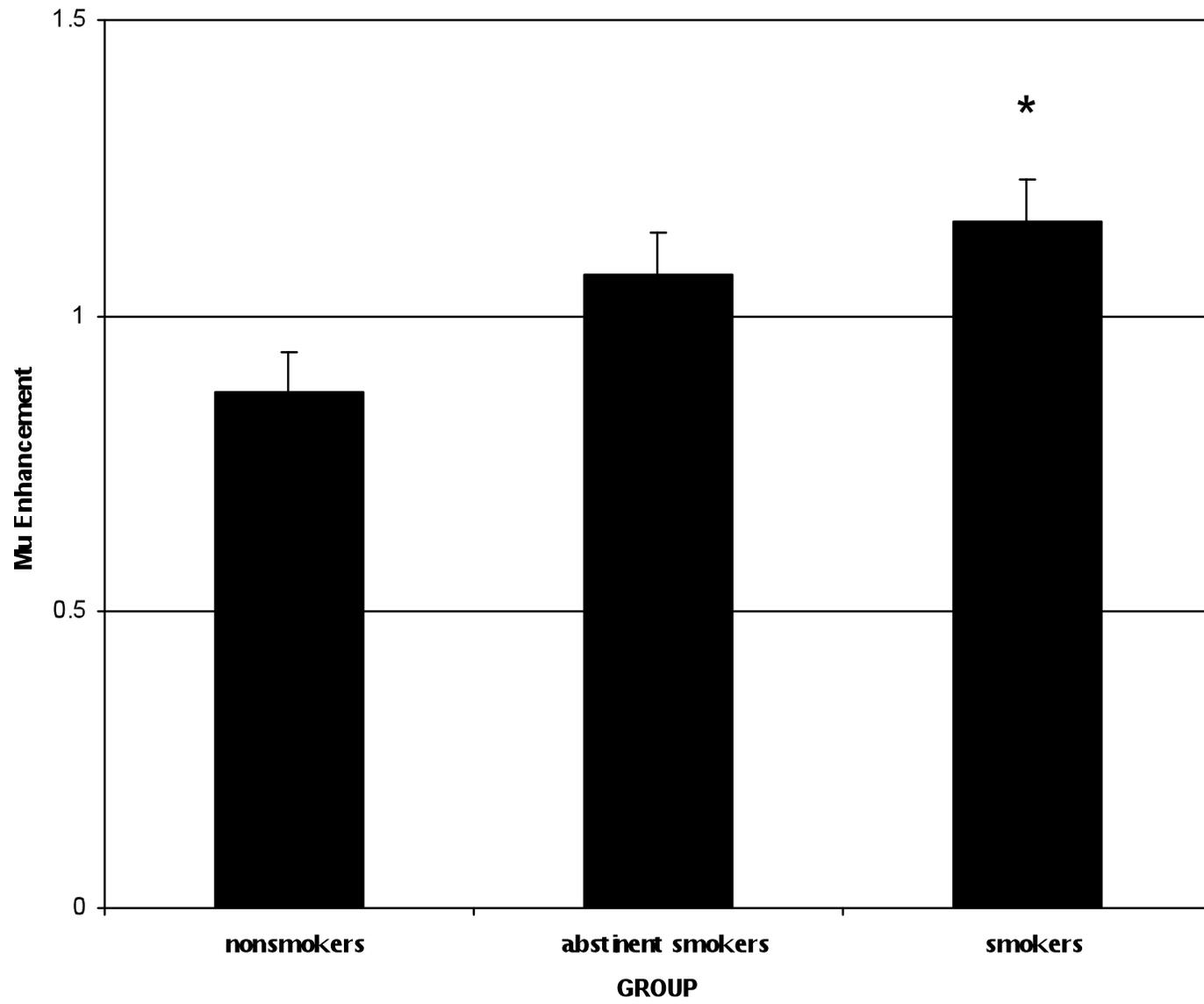
## *Or not?*

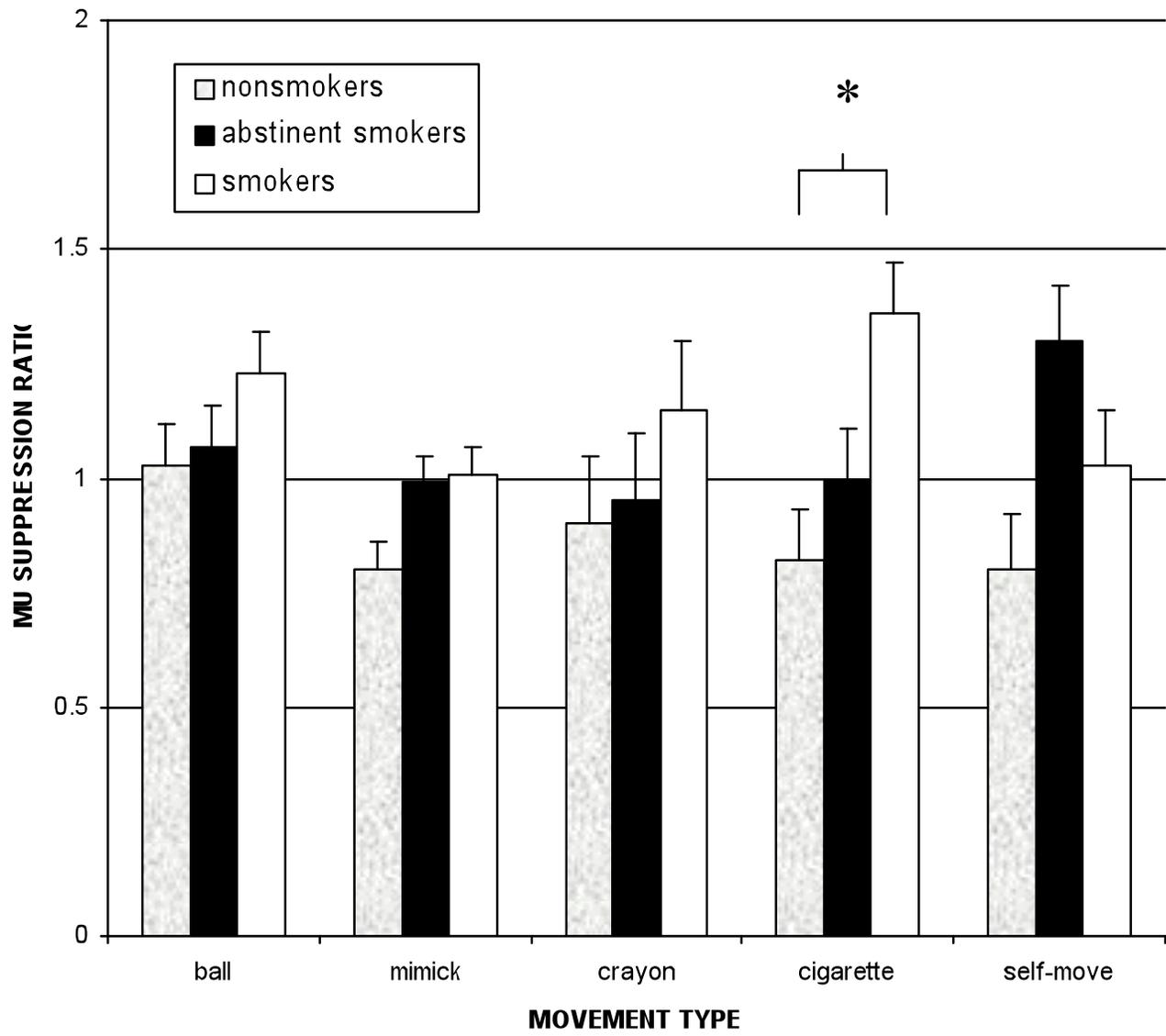
- Benefits = reversal of withdrawal?
- Highly variable dosing with smoking
- Inconsistent results when nonsmokers used as controls (except for motor effects)
- Smokers generally have smaller P300 than ex-smokers and never-smokers (Anokhin et al., 2000)



**Fig. 1** Grand average ERP waveforms elicited by the visual target stimulus at the mid-parietal ( $Pz$ ) location. These waveforms are based on a portion of the data from the Missouri COGA laboratory (71 never-smokers, 35 current smokers, and 27 ex-smokers) and are representative of data obtained from all contributing laboratories

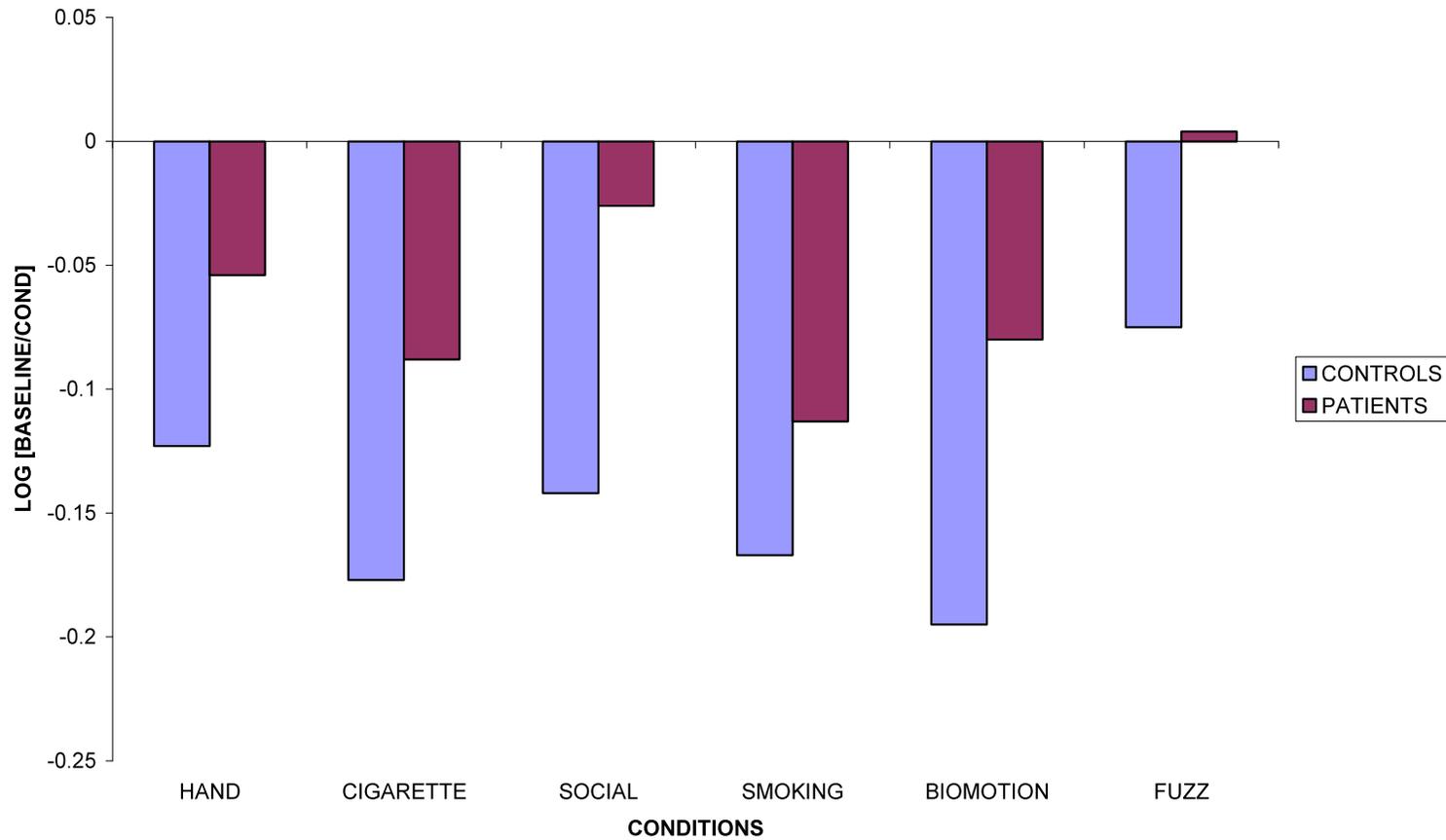






# *Schizophrenia and Smoking*

MU SUPPRESSION OVER SENSORIMOTOR CORTEX  
FOR FIRST EPISODE PATIENTS vs CONTROLS



# *Treatments for Nicotine Dependence*

- MAO inhibitors
- Noted that a constituent in cigarette smoke is an MAO ( A and B) inhibitor- Fowler et al PNAS (1996) and Fowler et al Nature (1996)
- Suggests that MAO inhibition may assist smokers in quitting

# *Treatments for Nicotine Dependence*

- Inhibition of nicotine metabolism
- Based on observations of differences in nicotine metabolism ( CYP 2A6) and risk of dependence formation – Pianezza et al Nature (1998)
- Clinical study with Methoxsalen ( CYP2A6 inhibitor ) reduced CO and smoking – Sellers et al CPT (2000)