

# **Nicotine: A Drug of Abuse**

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# Lecture Outline

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- Prevalence, economic and medical impact of cigarette smoking in the US
- Pharmacology and neurobiology of nicotine
- Clinical assessment and treatment of nicotine dependence
- Treatments for smoking and relative efficacy
  - Non-pharmacologic treatments
  - Pharmacologic treatments
- Role of the physician in smoking cessation
- Are there populations that are particularly affected by smoking?

# Question 1

The percentage of Americans who smoke is approximately:

A. 36%

B. 17%

C. 25%

D. 41%

## Question 2

For each pack of cigarettes sold in the US, the cost to the US in medical care and lost productivity is :

- A. \$7.18
- B. \$ 9.30
- C. \$ 4.45
- d. \$2.89

# Question 3

## K-type

- Variables which contribute to nicotine addiction include:
  - 1. Pulmonary absorption area is large
  - 2. Brain delivery within seconds
  - 3. Individual vulnerability
  - 4. Avoidance of withdrawal
  - 5. All of the above

## Question 4

- The highest quit rates for non-drug treatment of nicotine are from
- A. Frequent contact with provider
- B. Cognitive -behavior treatment
- C. Brief counseling/advice
- D. No treatment

## Question 5

- The highest quit rates for smoking cessation were associated with:
  - A. Nicotine patch
  - B. Bupropion
  - C. Combined nicotine patch and bupropion
  - D. Placebo

## Question 6

- The strongest motivation for smoking cessation comes from:
  - A. Peer pressure
  - B. Health concerns
  - C. Physician
  - D. Significant other
  - E. Desired lifestyle change



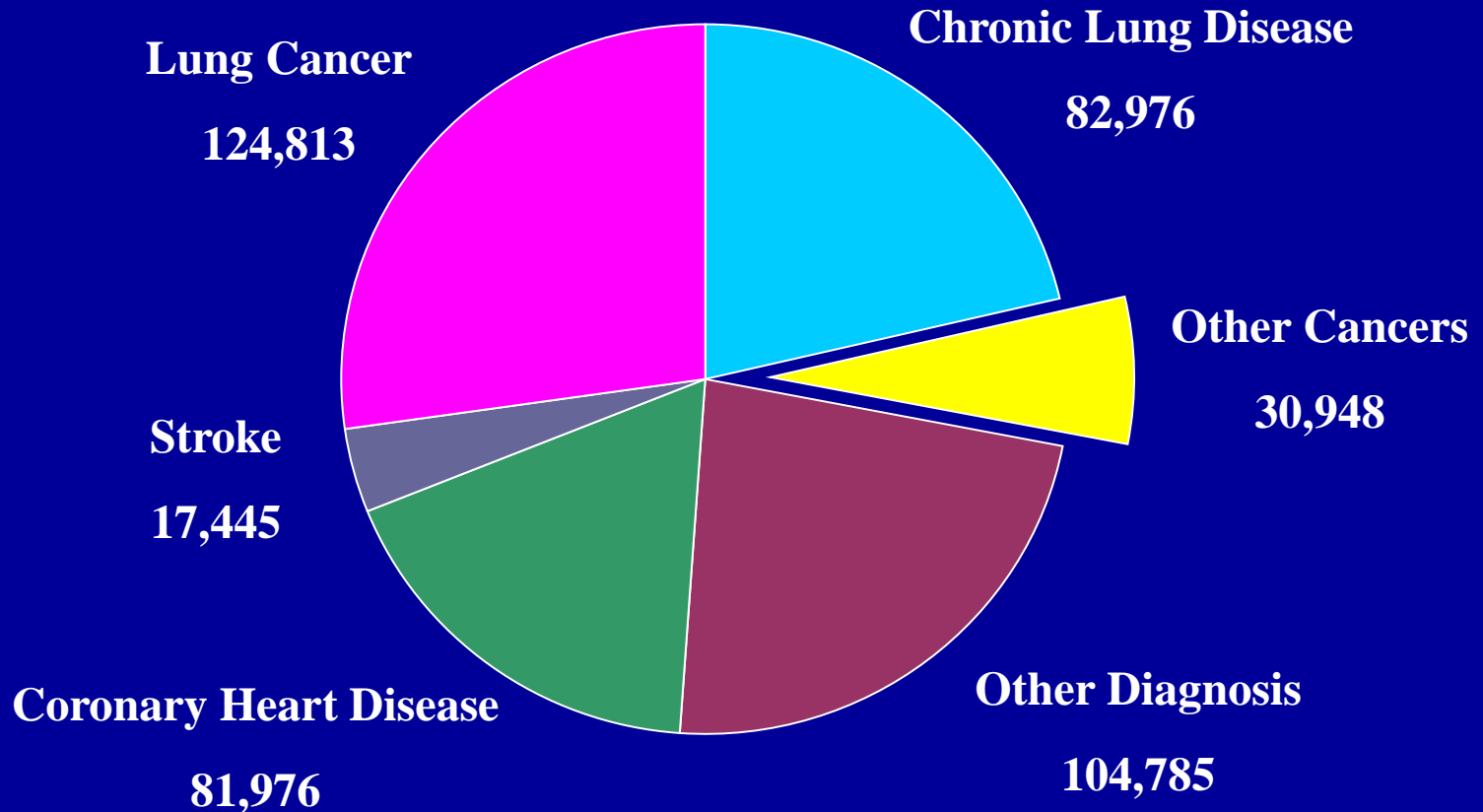
**How prevalent is cigarette smoking  
and what is the medical and  
economic impact of smoking?**

# **Cigarette Smoking is a Major Public Health Problem**



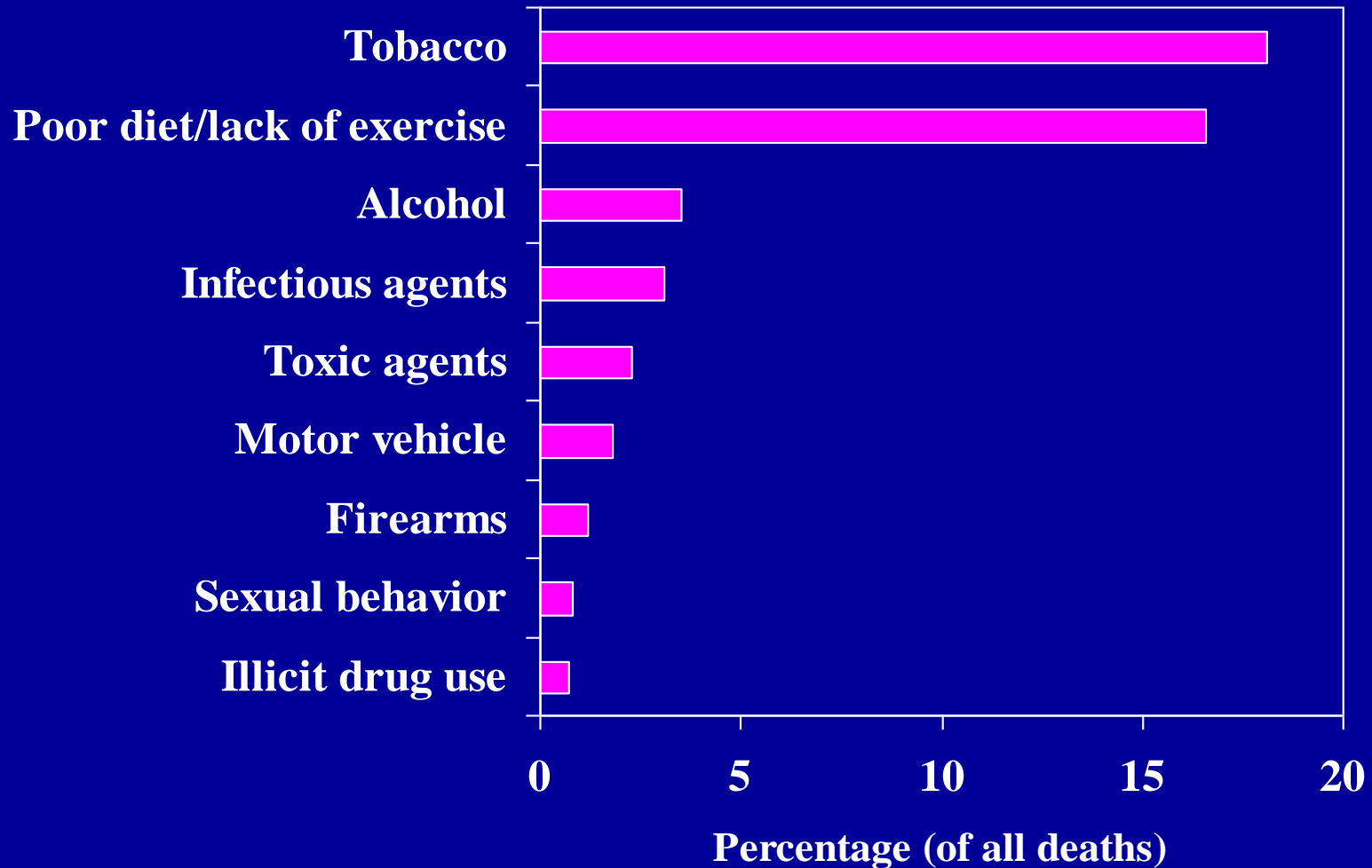
- **Each day, over 2200 high school students in the U.S. start smoking regularly**
- **Almost 1 in 4 Americans smoke cigarettes**
- **Each year, over 400,000 individuals die from smoking-related illness**

# 442,398 U.S. DEATHS ATTRIBUTABLE EACH YEAR TO CIGARETTE SMOKING



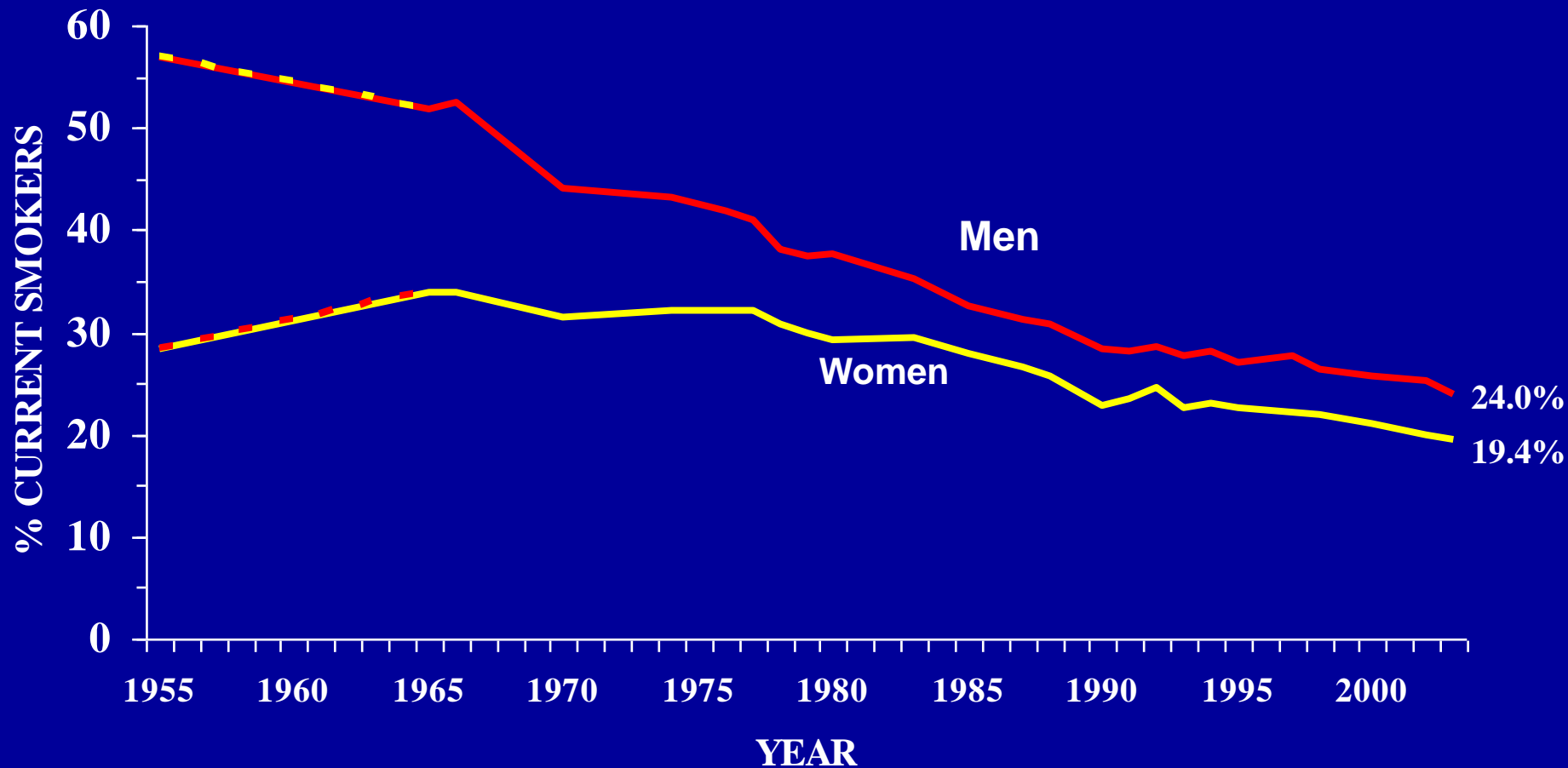
Annual smoking-attributable mortality, years of potential life lost, and economic costs, 1995-1999 Source: CDC, MMWR, 2002; 51; 300-3

# ACTUAL CAUSES OF DEATH, U.S., 2000



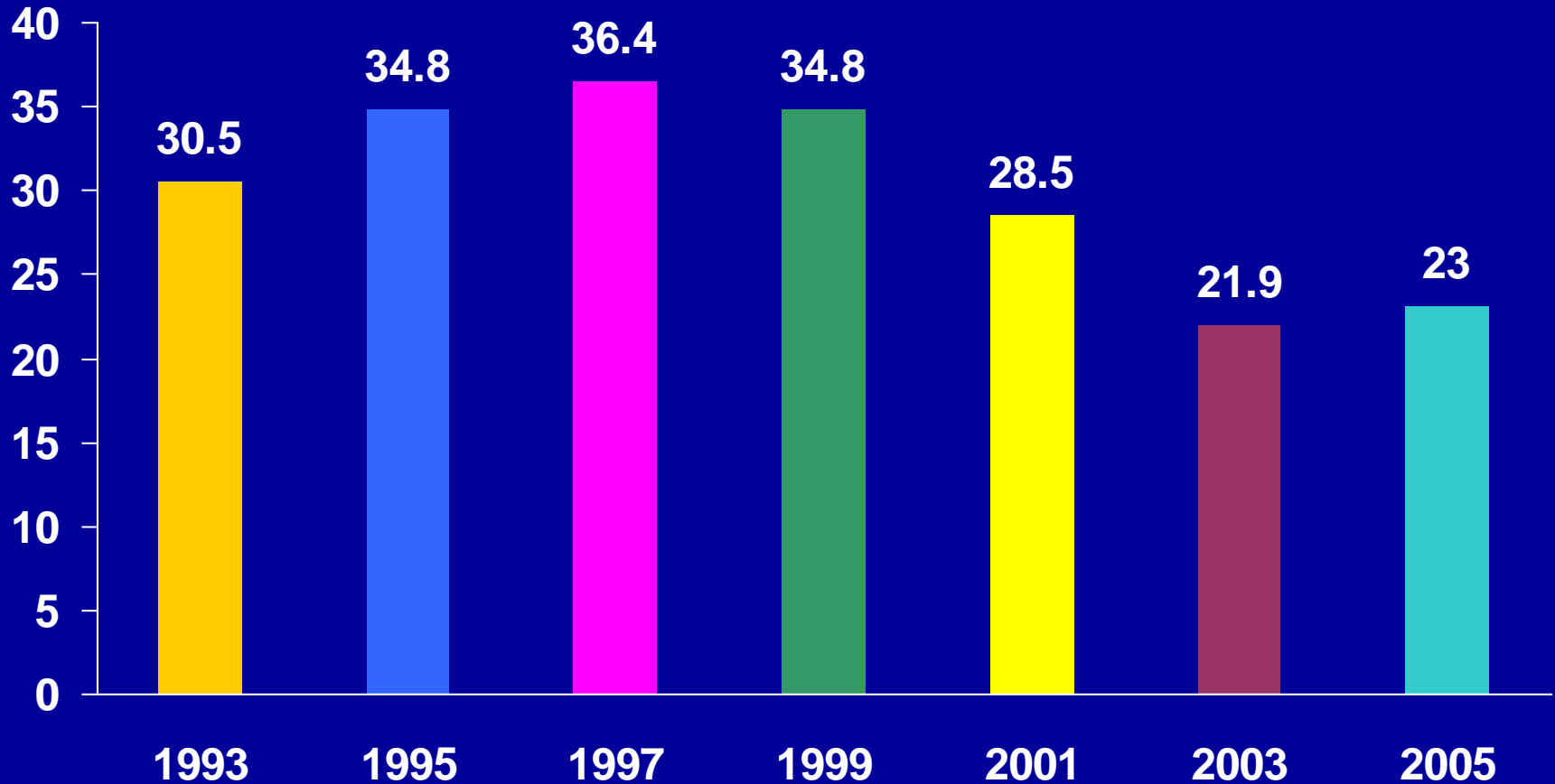
Source: Mokdad et al., JAMA 2004

# Trends in cigarette smoking among adults, by sex - United States, 1955-2003



Source: 1955 Current Population Survey; 1965-2003 National Health Interview Surveys

# Percentage of High School Students Who Reported Current Cigarette Smoking



Source: CDC, Youth Risk Behavior Surveillance United States 2005, MMWR, 2006

# Adverse Medical Consequences

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- Respiratory disease (e.g., COPD) \*Pulmonology
- Cardiovascular disease (e.g., CHD) \*Cardiology
- Cancers (e.g., lung, colon, bladder, kidney) \*Oncology
- Osteoporosis \*Orthopedics
- Infertility, Pregnancy, Postpartum problems \*OB/GYN
- Lowers medication blood levels \*Psychiatry, others
- Prolonged wound healing \*Surgery, Infectious Disease
- Vision problems (e.g. macular degeneration, cataracts)  
\*Ophthalmology

# Economic Burden to Society

- \$75 billion a year in smoking-related direct medical care costs.
- \$82 billion a year in productivity losses
- Combined, the medical care costs and productivity losses represent a cost to society of \$157 billion a year.
- Each pack of cigarettes sold in the US costs the nation an estimated \$7.18 in medical care costs and lost productivity.



# Economic Burden to an Average Smoker

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- The average smoker spends ~ \$2,500/year on cigarettes.
- It is estimated that an individual who smokes more than 20 cigarettes a day will pay up to \$19,000 extra in medical expenses in the course of a lifetime<sup>1</sup>.

1.) Hodgson, T.A., The Milbank Quarterly, 1992; 70(1); 81-125

**Why do people smoke?**

# Reasons for Smoking

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- Pleasurable
- Mood and Stress Management
- Weight and Appetite Control
- Aids Concentration
- Bottom Line: most smokers are dependent on the nicotine in cigarettes.

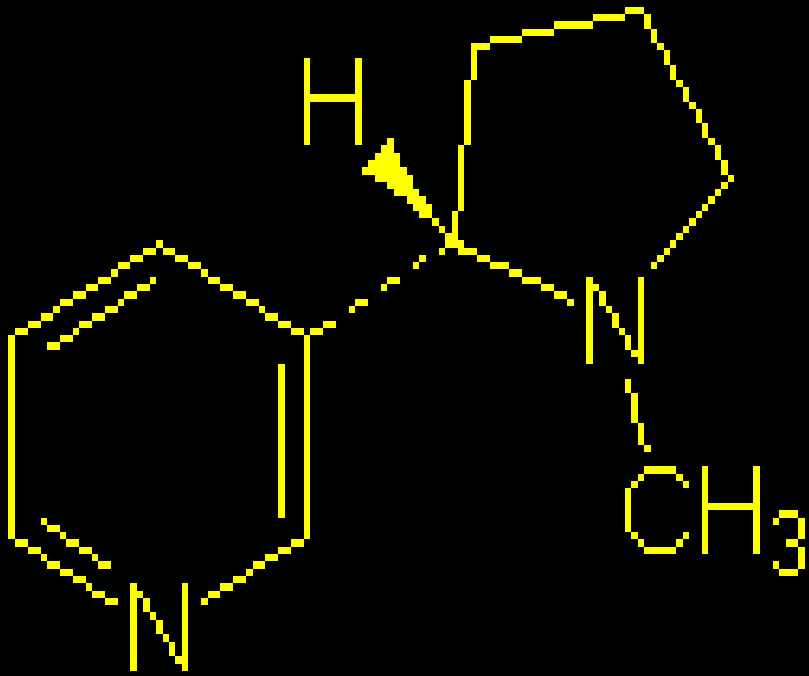
**What is the general pharmacology  
and neurobiology of nicotine?**

# Psychopharmacology of Nicotine

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- Nicotine is the major pharmacologically active alkaloid in tobacco.
- Pharmacologically, nicotine is as addictive as heroin and cocaine.
- Tobacco differs from other drugs of abuse since a greater percentage of those who try it become daily users than those who try other drugs of abuse.

# General Pharmacology of Nicotine



There are two rings in the structure of nicotine, a pyridine and pyrrolidine ring.

# Delivery & Absorption of Nicotine

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- Nicotine is distilled from burning tobacco and is carried on “tar” droplets and in the vapor phase.
- 90% of the nicotine is absorbed in the mainstream cigarette smoke.
- The lungs present an enormous surface area for the inhaled smoke.
- Absorption into the pulmonary circulation results in the rapid delivery of nicotine to the arterial system and from there to the brain.

# Absorption of Nicotine

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- Nicotine reaches the brain in seconds, contributing to its reinforcing and addictive nature.
- The nicotine intake from a single cigarette averages 1 mg (.37 - 1.56).



# Metabolism of Nicotine

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- 70% of nicotine is cleared from the blood during each pass through the liver.
- 85% - 90% of nicotine is metabolized in the liver and the majority on the first pass through the liver before it enters into the systemic circulation.
- The half-life of nicotine in the blood is ~ 120 minutes.
- 5% - 10% of nicotine is excreted via urine, unchanged (range 2% - 35%).

# Pharmacologic Properties

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- Nicotine is a powerful pharmacologic agent that changes cardiovascular, neural, endocrine, and skeletal muscle functions.
- Nicotine readily crosses biological membranes and acts upon specific receptors in the brain and periphery.
- Nicotine affects nearly all components of the neuroendocrine system.
- Nicotine has direct and indirect effects on several neurotransmitters.

# Nicotine Dependence

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- Tolerance – need more for larger effects, diminished effects with same amount
- Withdrawal symptoms - if longer interval between smoking or in past quit attempt(s).
- Repetitive use or loss of control over use.
- Use despite health hazards
- A great deal of time is spent smoking or trying to smoke

# Commonalities Between Nicotine Dependence and Other Drug Dependencies

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- Persistent use despite knowledge of harmful effects.
- Individual vulnerability to dependence.
- Deprivation increases drug seeking.
- Increasing the cost decreases intake.
- Paired stimuli or conditioned factors can increase drug use.
- Self-administration is controlled by dose.
- Remission from and relapse to drug use.
- Useful effects of drug administration.

# Nicotine and the Brain

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- Nicotine stimulates release of dopamine from nucleus accumbens (brain reward center)
- Dopamine enhances feelings of reward and pleasure
- Nicotine increases serotonin levels, mostly in the amygdala (brain emotional response center)
- Serotonin can relieve depression and anxiety

# Nicotine and the Brain

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- Initial experience with smoking causes nausea, dizziness, and/or coughing in some individuals
- Initial experience with smoking causes pleasurable experiences in others (e.g., head rush, buzz, dizziness).
- Tolerance to the aversive effects develops quickly with repeated smoking.

# Nicotine and the Brain

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- Beginning smokers smoke to receive the dopamine release in the reward center that gives them a “buzz.”
- As the habit progresses they seek this effect, but also strive to keep nicotine plasma levels high to avoid withdrawal symptoms.
- Thus, smoking is positively (pleasure) and negatively (avoidance of withdrawal) reinforced.

# Why do smokers want to quit?

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- Health concerns
- Social sanctions
- Pressure from significant others
- Costly habit
- Lifestyle change



“To cease smoking is the easiest thing I ever did; I ought to know because I’ve done it a thousand times.”

Mark Twain

**What are the available treatments  
for smoking and which tend to be  
more effective?**

# Smoking Cessation Treatment Options

- Non-Pharmacologic

- self-help materials
- behavioral therapy
- brief advice from a health care provider

- Pharmacologic

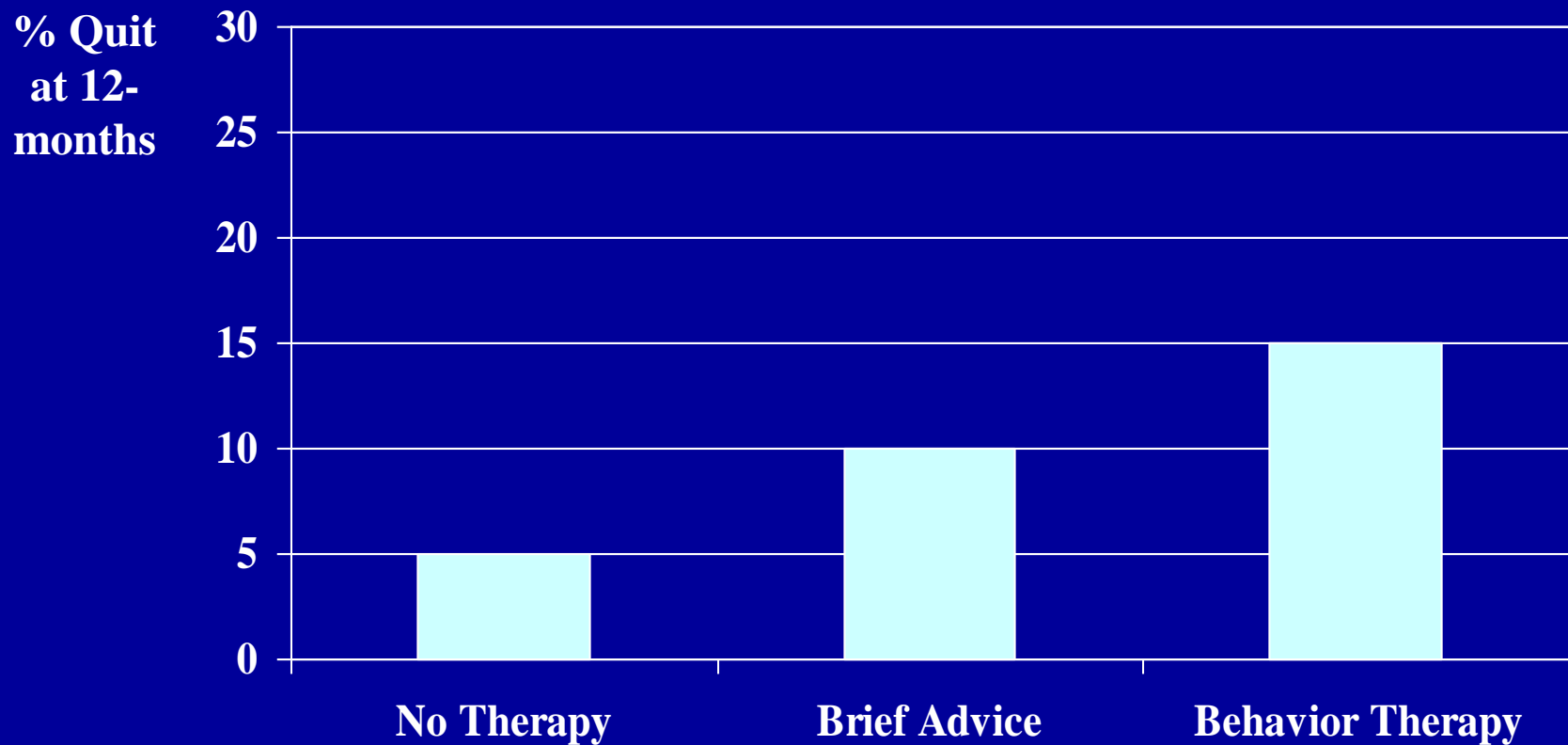
- nicotine gum
- nicotine nasal spray
- transdermal nicotine patch
- nicotine inhaler
- nicotine lozenge
- bupropion/zyban
- new non-nicotine meds

# Non-Pharmacologic Treatments

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- Quit rates range from 4% - 22%
- Multi- versus single component interventions produce higher quit rates
- Dose response relation between the intensity of counseling and its effectiveness.
- Treatments involving person-to-person contact (individual, group, or telephone) are consistently effective and their effectiveness increases with treatment intensity (e.g., minutes of contact).

# Effectiveness of Non-Pharmacologic Treatments



# Non-Pharmacologic Treatments – Physician Advice

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- Brief physician counseling is one of the strongest messages to motivate smokers to quit<sup>1</sup>.
- While formal smoking cessation programs have higher cessation rates, few smokers attend these programs while 70% of smokers see a physician annually<sup>2</sup>.

# Physician Advice

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- Given that 70% of smokers see a physician annually, physicians in the US could intervene with ~ 33 million of the nations 46 million adult smokers annually.
- If only half of US physicians delivered a brief quitting message to their patients who smoked and were successful with 1 in 10, this would yield 1.75 million new ex-smokers every year.
- This would more than double the national annual quit rate.

# Physician Advice

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- Half of patients report ever being told by a physician to quit smoking<sup>1</sup>.
- < 60% of physicians address smoking in the context of a smoking related illness or disease<sup>1</sup>.
- Physicians counseled patients on smoking on 21% - 37% of smoker's visits<sup>2</sup>.

1.) Source: Thordike et al., 1998; Goldstein et al., 1997; Gilpin et al., 1993; Frank et al., 1992; Anda et al., 1987 ; 2.) Source: Thorndike et al., 1998



# Physician Advice

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- Feeling unprepared or ineffective to help their patients change their smoking habit<sup>1</sup>.
- Lack of emphasis on skills to provide smoking cessation intervention in medical training<sup>2</sup>.
- Time and reimbursement barriers

1.) Source: Cantor et al., 1993; Cummings et al., 1989

2.) Source: Spangler et al., 2002; Ferry et al., 1999; Fiore et al., 1994; Fiore et al., 2000

# Physician Advice

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## Basic Steps:

- Advise cessation
- Inform of risks of smoking
- Provide self-help materials, a referral, and possibly pharmacotherapy
- Set agreement for cessation/reduction
- Request follow-up in-person or via telephone

# Physician Advice

- Ask about smoking. *Have you thought about stopping? Reasons for stopping?*
- Advise a quit attempt.
- Assess willingness and past experience with stopping smoking. *Would you like to make an attempt to quit smoking? When was the last time? Problems? What helped?*
- Assist with Treatment. *Referral? Possible problems or barriers to stopping? Solutions to help with these problems?*
- Assess appropriateness for pharmacotherapy. *Dependent? Past experience? Preference? Contra-indications?*
- Arrange to follow-up. Phone, In-person

# Quick Assessment of Nicotine Dependence

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- Smokes first cigarette within 30 minutes of awakening.
- Difficulty refraining from smoking in places where it is forbidden.
- The cigarette that they would hate most to give up is the first one in the morning.
- Smoke a pack a day or more.
- Smoke more frequently during the first hours after waking than the rest of the day.
- Smoke when ill, even when they are in bed most of the day.

# Physician Advice

*Ask* about smoking

*Advise* quit attempt

*Assess* willingness to quit

*Assist* with treatment

*Arrange* follow-up



## There is a Doctor in the House

*—and it took a minimum  
of '15,000 and 7 years'  
hard work and study  
to get him there!*

● Proudly he "hangs out his shingle," symbol of his right to engage in the practice of medicine and surgery. But to a doctor it is more than a right: it is a privilege—the privilege of serving mankind, of helping his fellow man to a longer, healthier, and happier life.



According to a recent nationwide survey:

**More Doctors  
Smoke Camels  
than any other cigarette**

E. J. Reardon Tobacco Company, Winston-Salem, N. C.

*When you invite mention THE TRAINED NURSE, March, 1946*

# Pharmacologic Treatments

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- Nicotine Gum
- Nicotine Patch
- Nicotine Spray
- Nicotine Inhaler
- Nicotine Lozenge
- Zyban (bupropion)
- Others: Including Varenicline

# Pharmacologic Treatments

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- Nicotine Gum

- Some adverse side-effects such as oral and gastric problems, jaw ache, under-dosing
- 2mg dose outperforms placebo at 6-month assessment (OR=1.66)
- 4mg dose more effective than 2mg, particularly among more dependent smokers
- tends not to be effective with brief advice

# Pharmacologic Treatments

- Transdermal Nicotine Patch

- Relatively few side effects, popular form of NRT
- 21mg/4 weeks, 14mg/2weeks, 7mg/2weeks
- Shown to double quit rates achieved by placebo at EOT
- Combined with physician advice, quit rates can reach 28% at 12-month follow-up <sup>1</sup>
- No conclusive evidence to show that the higher, 42 - 44 mg initial dose, produces higher quit rates than 21 - 22 mg dose <sup>2</sup>

<sup>1</sup> Hurt et al., JAMA, 1994; <sup>2</sup> Jorenby et al., JAMA, 1995



# Pharmacologic Treatments

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- Nicotine Nasal Spray (NS)
  - Faster delivery of nicotine (10-minutes) than patch (5-10 hours) and gum (30 mins)
  - Side effects (burning sensation, watery eyes) prevalent in first week of use
  - Used at least 8 times per day, but not more than 40
  - More than doubles quit rates achieved by placebo

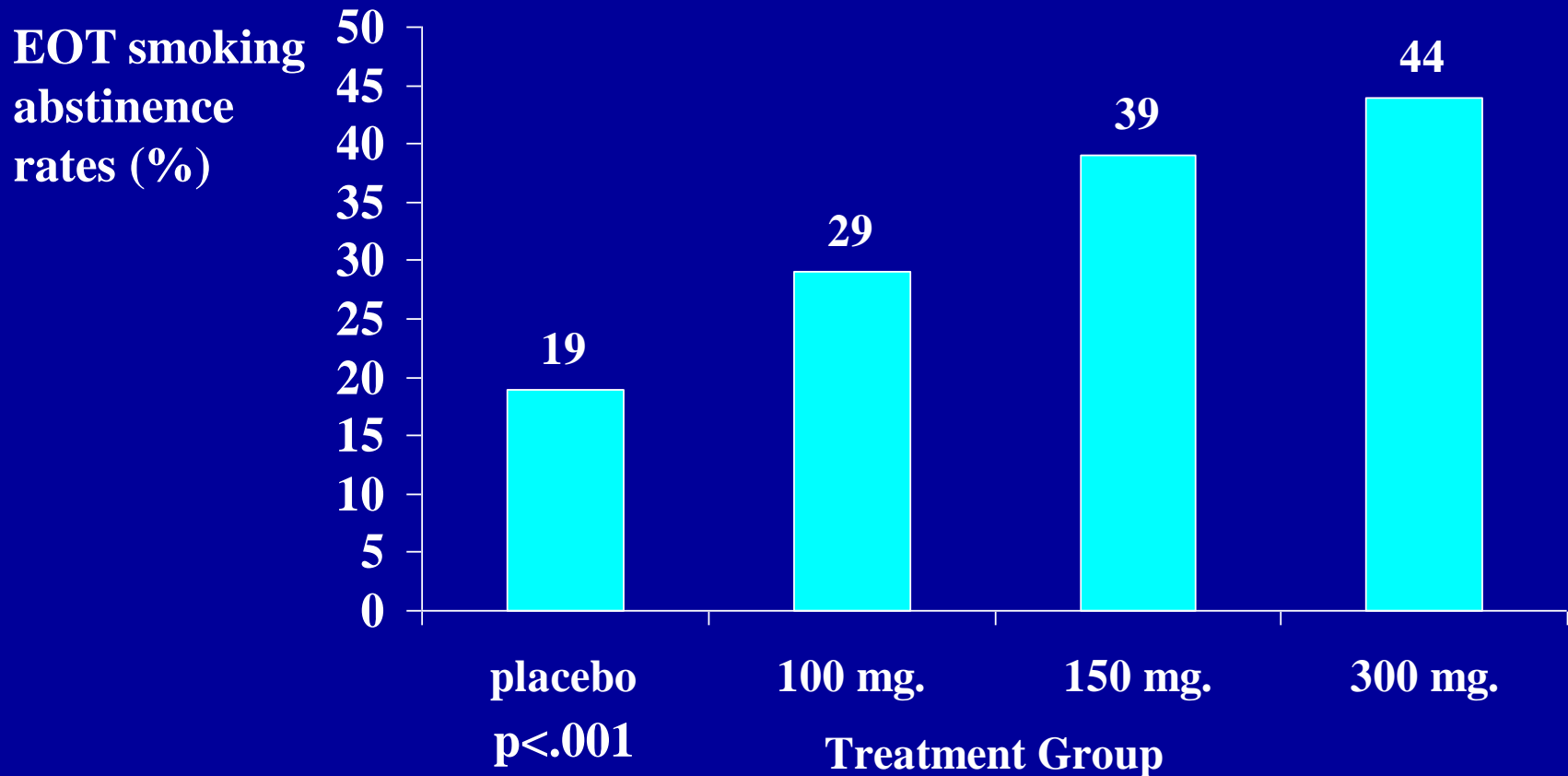
# Pharmacologic Treatments

- Bupropion

- Initiated 7-14 days before quit date and treatment duration is 7 – 12 weeks.
- 300mg dose shown to outperform patch and placebo at EOT and 1year follow up.
- Reported to reduce relapse rate, especially among African Americans, older smokers, and women.
- side effects (headache, insomnia, constipation, nervousness/restlessness, seizures) and contraindications (concurrent use of some meds, seizure disorder, past eating disorder, alcohol use).

# Randomized Trial of Bupropion for Smoking Cessation

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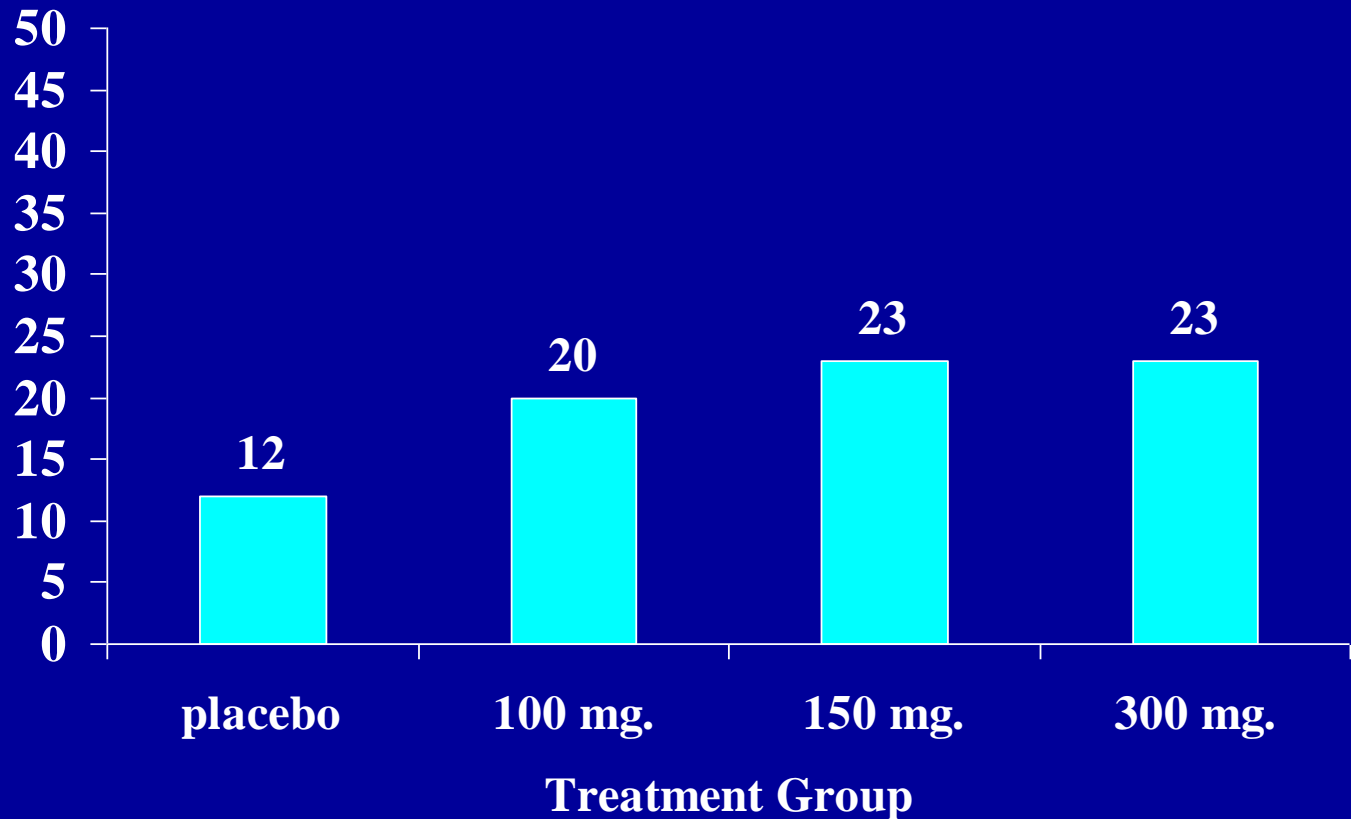


Hurt et al., NEJM, 1997

# Randomized Trial of Bupropion for Smoking Cessation

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12-month  
smoking  
abstinence  
rates (%)

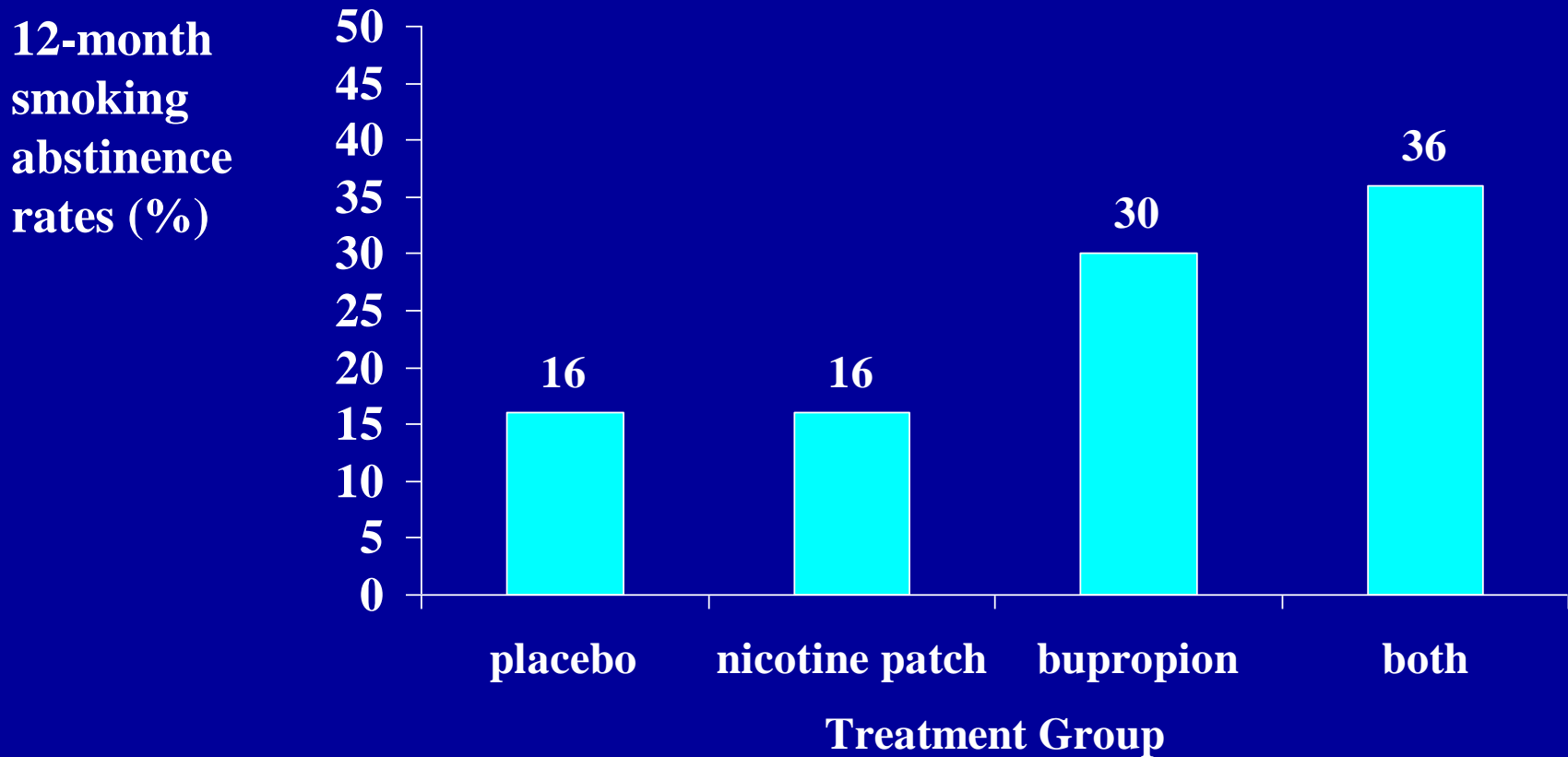


\* $p < .05$  for 150mg and 300 mg

Hurt et al., NEJM, 1997

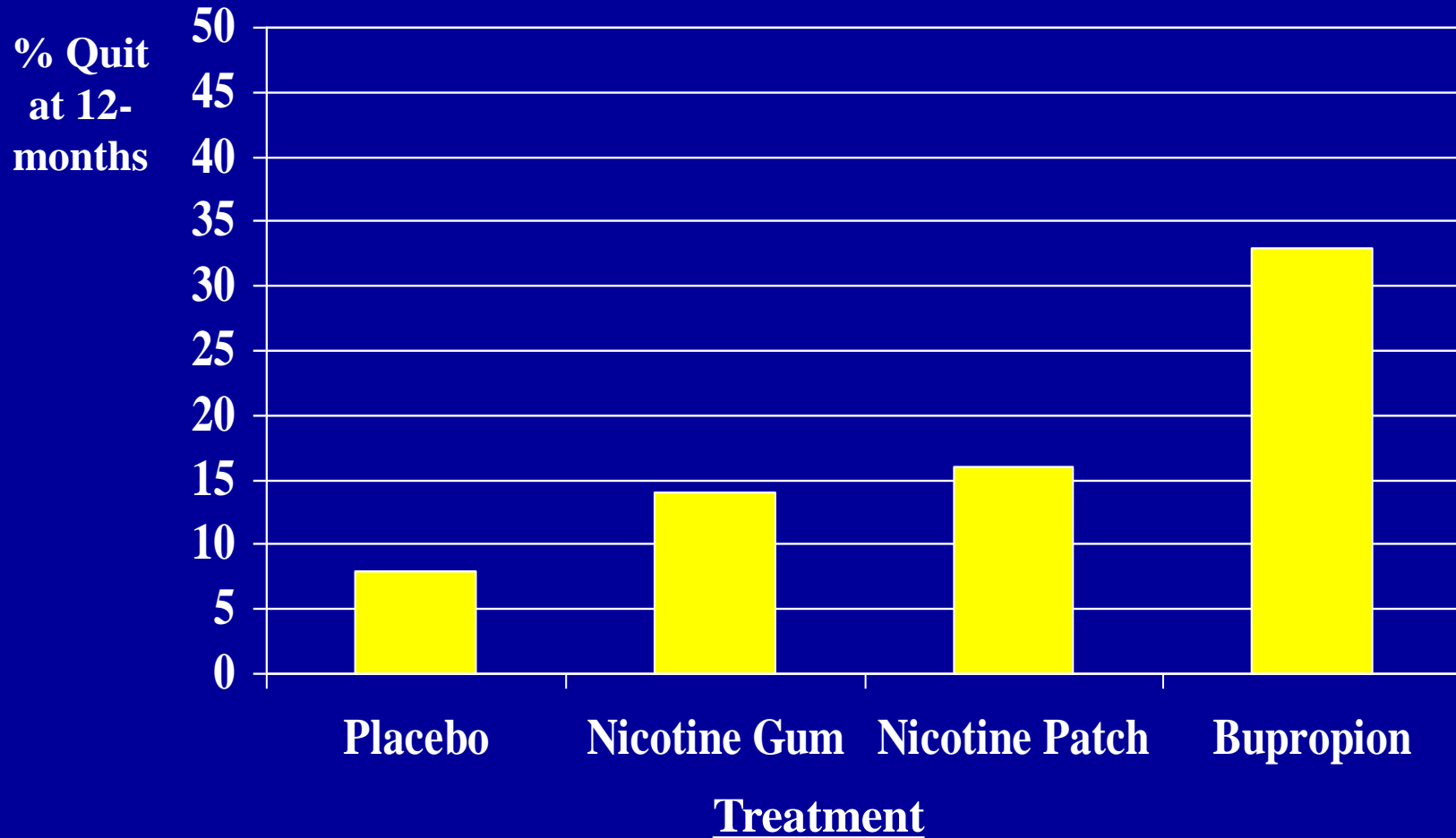
# Bupropion, Nicotine Patch, or Both for Smoking Cessation

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\* $p < .001$  for bupropion and both; combination therapy was not significantly more effective than bupropion alone (Jorenby et al., NEJM, 1999).

# Effectiveness of Pharmacologic Treatments



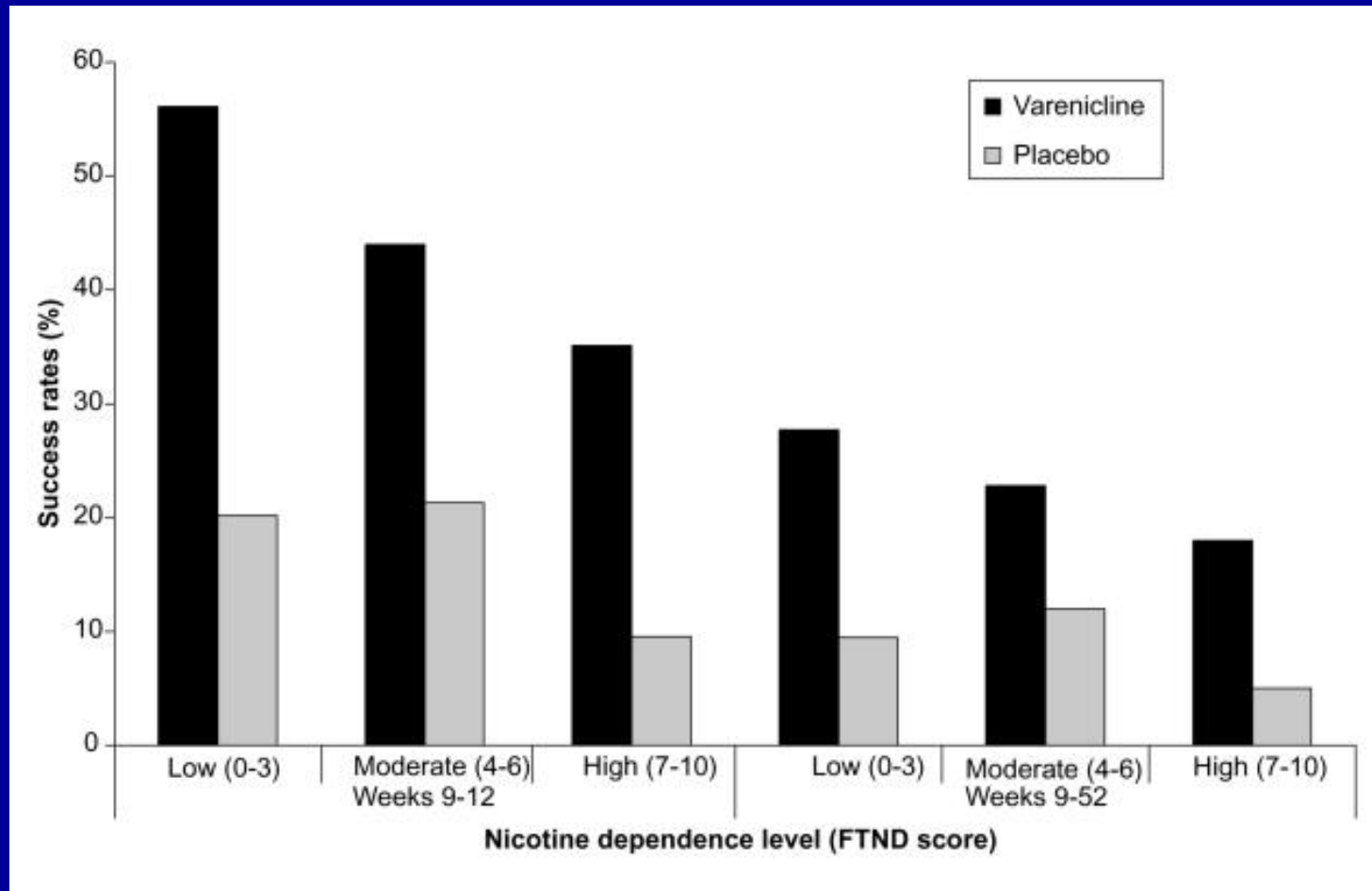
Jorenby et al., 1999. *NEJM*.

Hughes et al., 1999. *JAMA*

# Summary of Quit Rates by Tx Type

Treatment	Standard Dose and Duration	End of Treatment Abstinence Rates (%)	6-month Abstinence Rates (%)
Bupropion	300 mg for 8-10 wks	43-60	18-30
Nicotine gum	6-8 wks of 2 mg 6-8 wks of 4 mg	30-73 54-81	19-38 13-44
Transdermal nicotine	4-6 wks of 21 mg + 2 wks of 14 mg + 2 wks of 7 mg	15-62	10-54
Inhaler	≤16 cartridges/day for 12 wks	28-46	17-35
Nicotine spray	8-40 doses/day for 8 wks	43-66	24-44
Nicotine lozenge	9 lozenges/day for 6 wks followed by 6 wk taper	46-49	Not reported

# Varenicline for Smoking Cessation



Percentage of varenicline and placebo participants achieving continuous abstinence at Weeks 9–12 and Weeks 9–52 according to nicotine dependence level (low/med/high). Derived from data of [Nides et al \(2008\)](#). Fagerström K, Hughes J. (2008) Varenicline in the treatment of tobacco dependence. *Neuropsychiatr Dis Treat.* 4(2):353-63.



**Are there populations that are particularly affected by smoking?**

# Special Populations

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- Women
- Pregnant and postpartum women
- Psychiatric populations
- Adolescents

# Women Smokers

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- Women tend to smoke fewer cigarettes per day than men and score lower on measures of nicotine dependence.
- However, women have as much difficulty quitting as men.
- While women benefit from NRT relative to placebo, they may get less clinical benefit from most NRT products than do men.

# Nicotine Gum Success Rate

<b>Assessment</b>	<b><i>Men</i></b>	<b><i>Women</i></b>
12 months <sup>1</sup>	<b>29%</b>	<b>17%</b>
12 months <sup>2</sup>	<b>25%</b>	<b>18%</b>
12 months <sup>3</sup>	<b>29%</b>	<b>25%</b>
60 months <sup>4</sup>	<b>47%</b>	<b>42%</b>

1.) Source: Fagerstrom, Prev Med, 1984; 13; 517-27; 2.) Source: Killen, et al., J Consult Clin Psychol, 1990; 58; 85-92; 3.) Source: Bjornson, et al., Am J Pub Health, 1995; 85; 223-30; 4.) Source: Murray, et al., Addict Behav, 1997; 22; 281-6

# Nicotine Patch Success Rate

<b>Assessment</b>	<b>Men</b>	<b>Women</b>
6 months <sup>1</sup>	25%	18%
6 months <sup>2</sup>	31%	22%
6 months <sup>3</sup>	32%	15%

1.) Source: Gourlay et al., BMJ, 1994; 309; 842-6; 2.) Source: Swan et al., Addict, 1997; 92; 207-18; 3.) Source: Wetter et al., J Consult Clin Psychol, 1999; 67; 555-62

# Women Smokers

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- Women tend to smoke less for nicotine reinforcement and more for non-nicotine reinforcement (e.g., sensory effects of smoking, management of stress and negative affect, secondary social reinforcement).
- Initial studies have shown that women may benefit more from Zyban (bupropion), a drug originally marketed as an anti-depressant, such that women have cessation rates comparable to men.

# Pregnant and Postpartum Women

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- Smoking while pregnant can cause adverse health complications such as intrauterine growth retardation, low birth weight, congenital malformations, pre-mature births, and fetal mortality<sup>1</sup>.
- Approximately 20-30% of women continue to smoke for the duration of their pregnancy despite these risks<sup>1,2</sup>.

1.) Source: USDHHS, 2001

2.) Source: LeClere et al., 1997; Fingerhut et al., 1990; Husten et al., 1996

# Pregnant and Postpartum Women

- Up to 40% of pregnant women who smoke quit prior to starting prenatal care<sup>1</sup>.
- These women usually quit on their own, unaided.
- Others are referred to a variety of interventions with various success (cessation rates up to 30%)<sup>2</sup>.
- Interventions often do not take into account the unique needs of pregnant women, they tend to be highly dependent on nicotine, and NRT is not usually given to this population as the risk benefit profile is not clear.



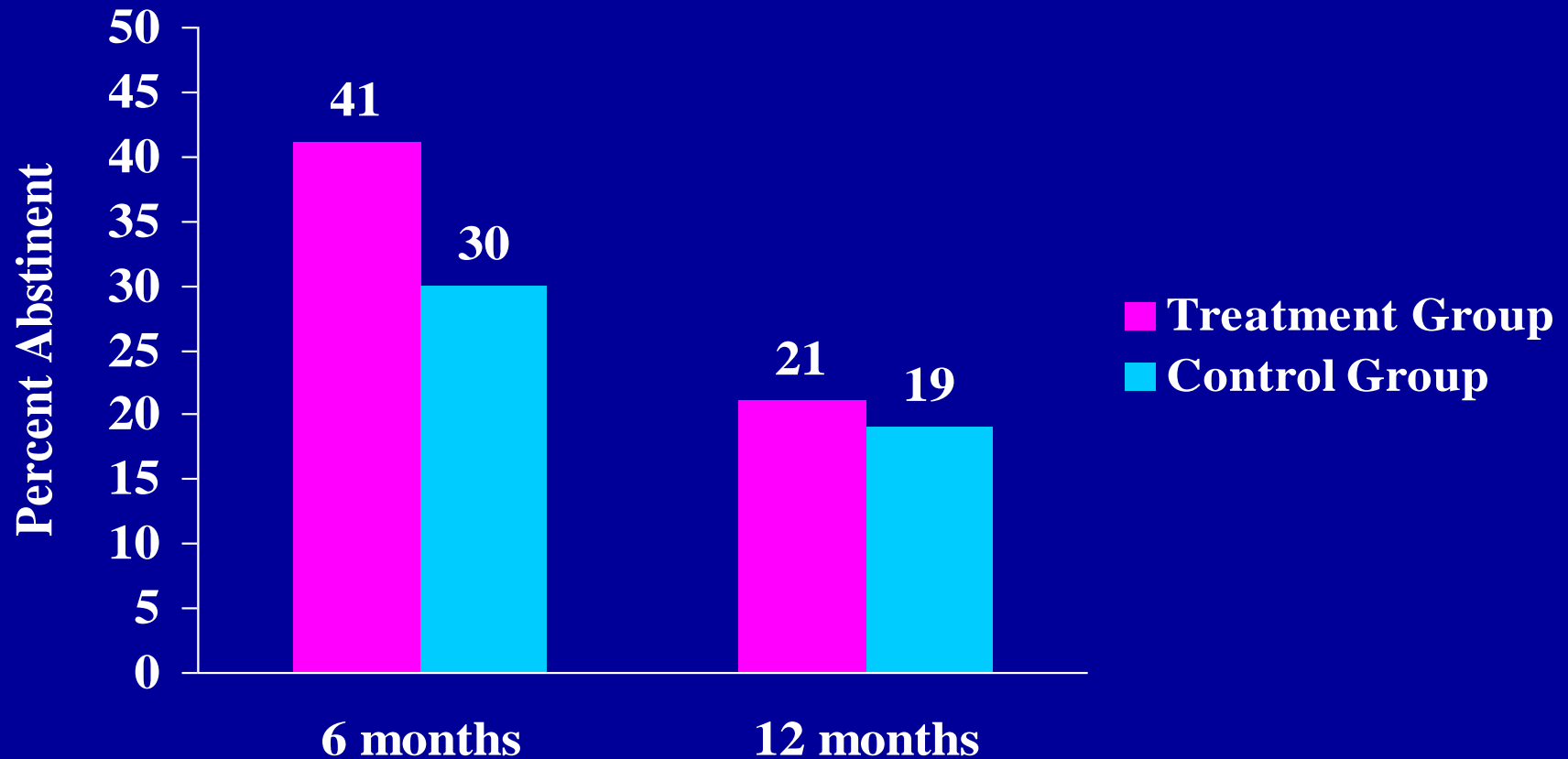
# Pregnant and Postpartum Women

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- Although as many as 40% of pregnant women who smoke quit prior to starting prenatal care<sup>1</sup>, 60-80% will relapse by 6-months postpartum<sup>1</sup>
- Thus, interventions in the post-partum time period have focused more on relapse prevention.
- Relapse prevention interventions have included minimal contact, brief advice, although there have been few more intensive tailored interventions.

1.) Source: DiClemente et al., 2000; McBride et al., 1990

# Smoking Status at 6 and 12 Months Postpartum



Source: Ratner et al., Addictive Behaviors, 2000

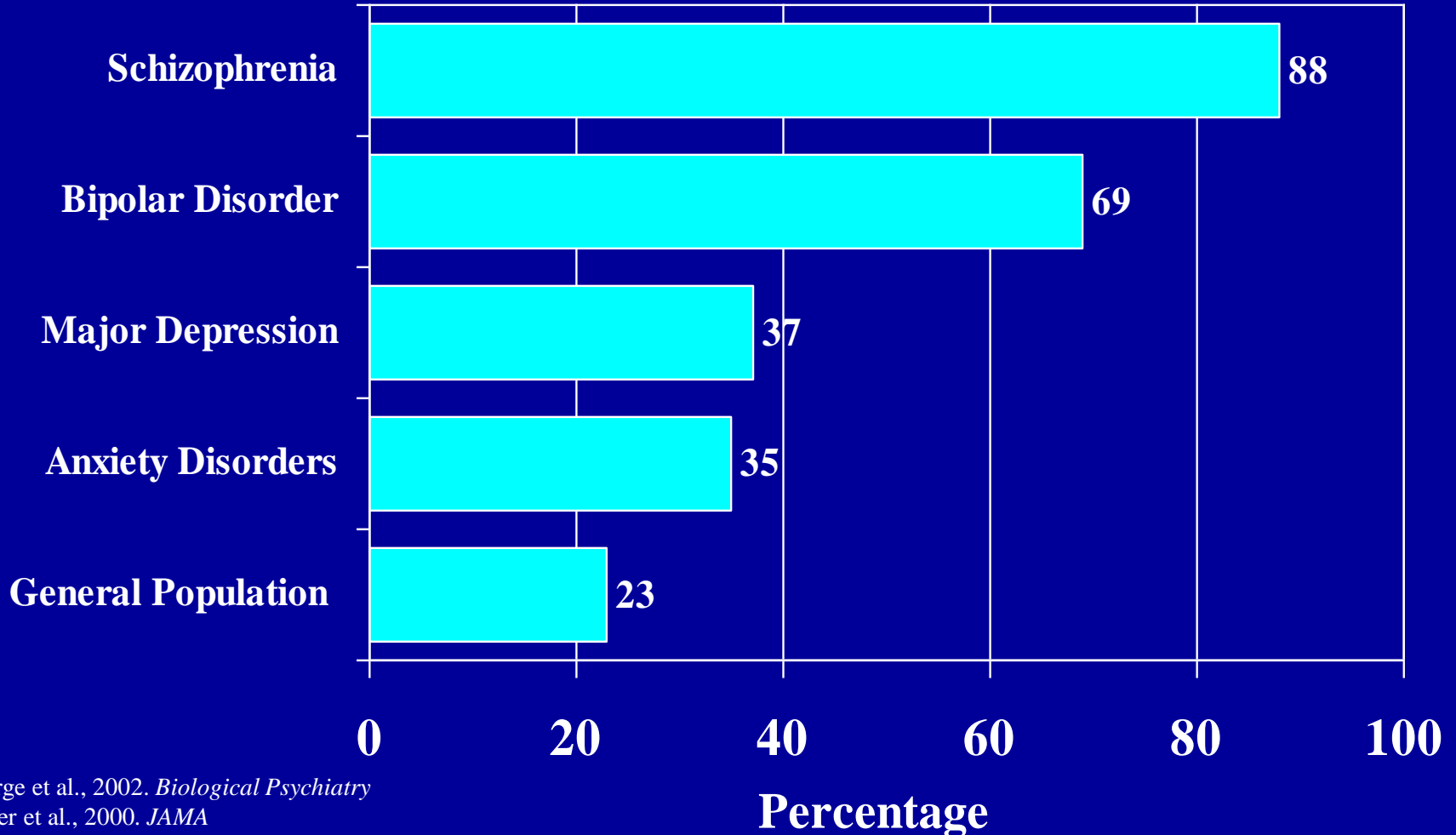
# Facts about Smoking and Psychiatric Illness

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- 44% of all cigarettes consumed are smoked by persons with psychiatric illness
  - e.g., ADHD is a specific, independent risk factor for tobacco use (Molina and Pelham 2003; Milberger et al. 1997)
- Persons with psychiatric illness are more likely to be heavy smokers (>20 cpd) and extract more nicotine from cigarettes
- Persons with psychiatric illness are 2 times more likely to develop cancer, heart disease and respiratory illness
- Among persons with psychiatric illness, those who smoke are 2.6 times more likely to commit suicide

# Prevalence of Current Smoking in Different Groups

## Population



George et al., 2002. *Biological Psychiatry*

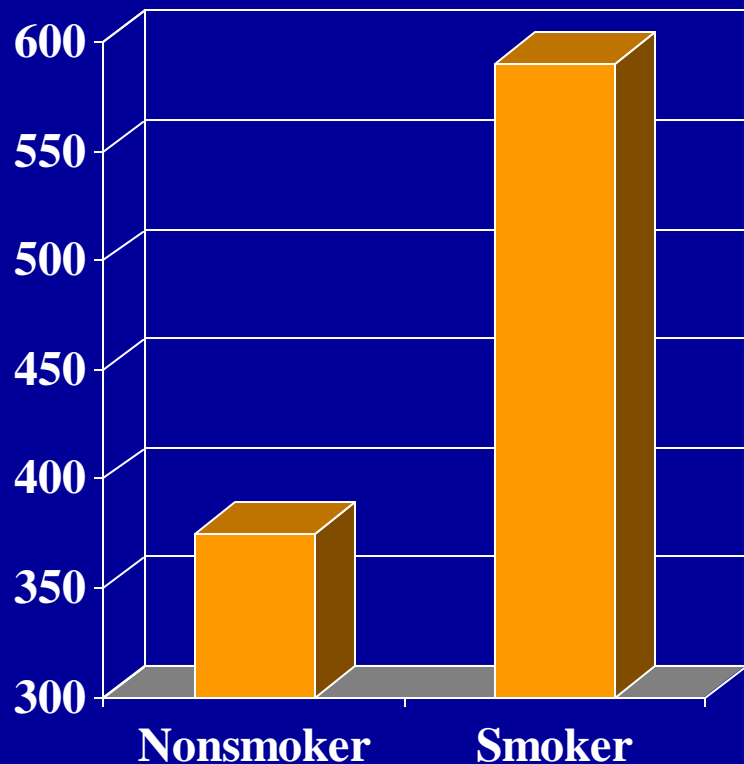
Lasser et al., 2000. *JAMA*

CDC, 2002 *MMWR*

Leonard et al., 2001. *Pharmacology, Biochemistry and Behavior*

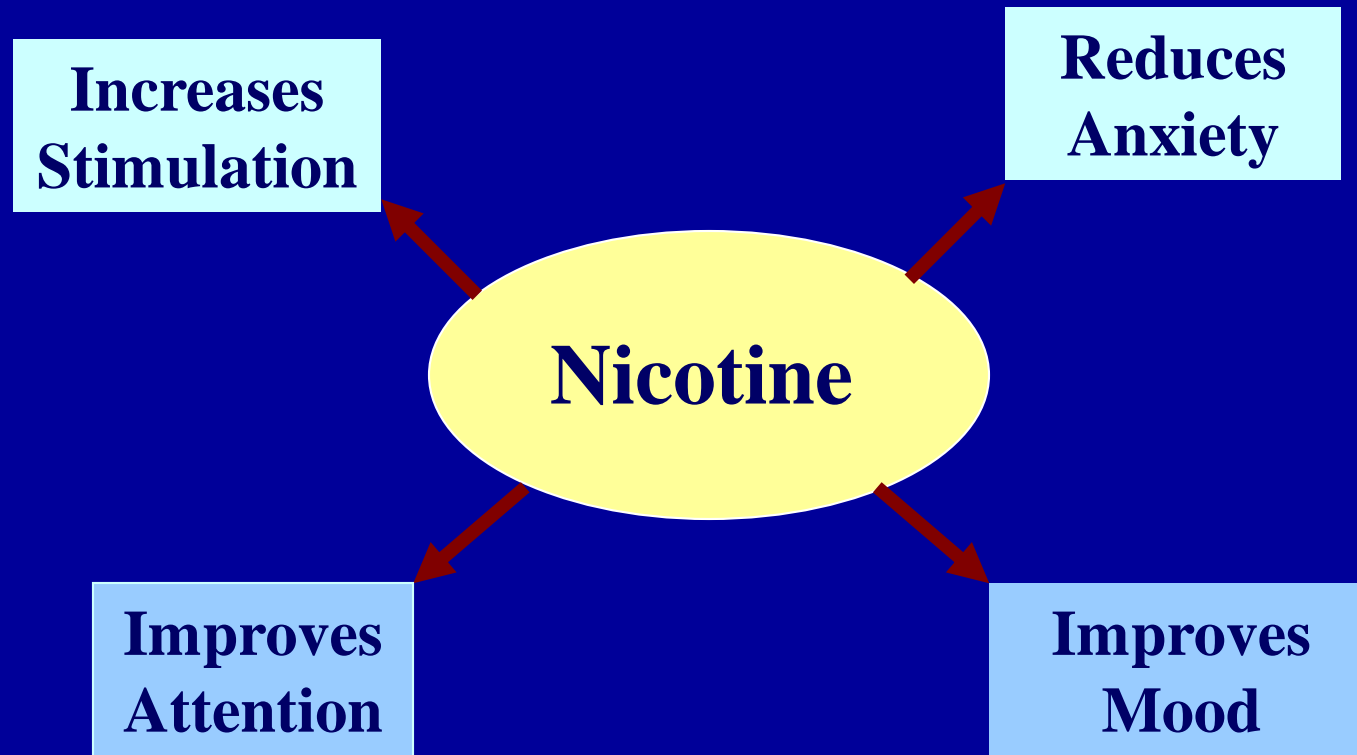
# Smoking May Alter the Effectiveness of Anti-psychotic Medications

Chlorpromazine (mg)



- Tobacco increases the activity of enzymes that breakdown medications
- Higher doses of medication may be required to manage symptoms
- Stabilizing blood levels of medication is more difficult

# Persons with Psychiatric Illness May Use Nicotine to Self-Medicate Their Symptoms

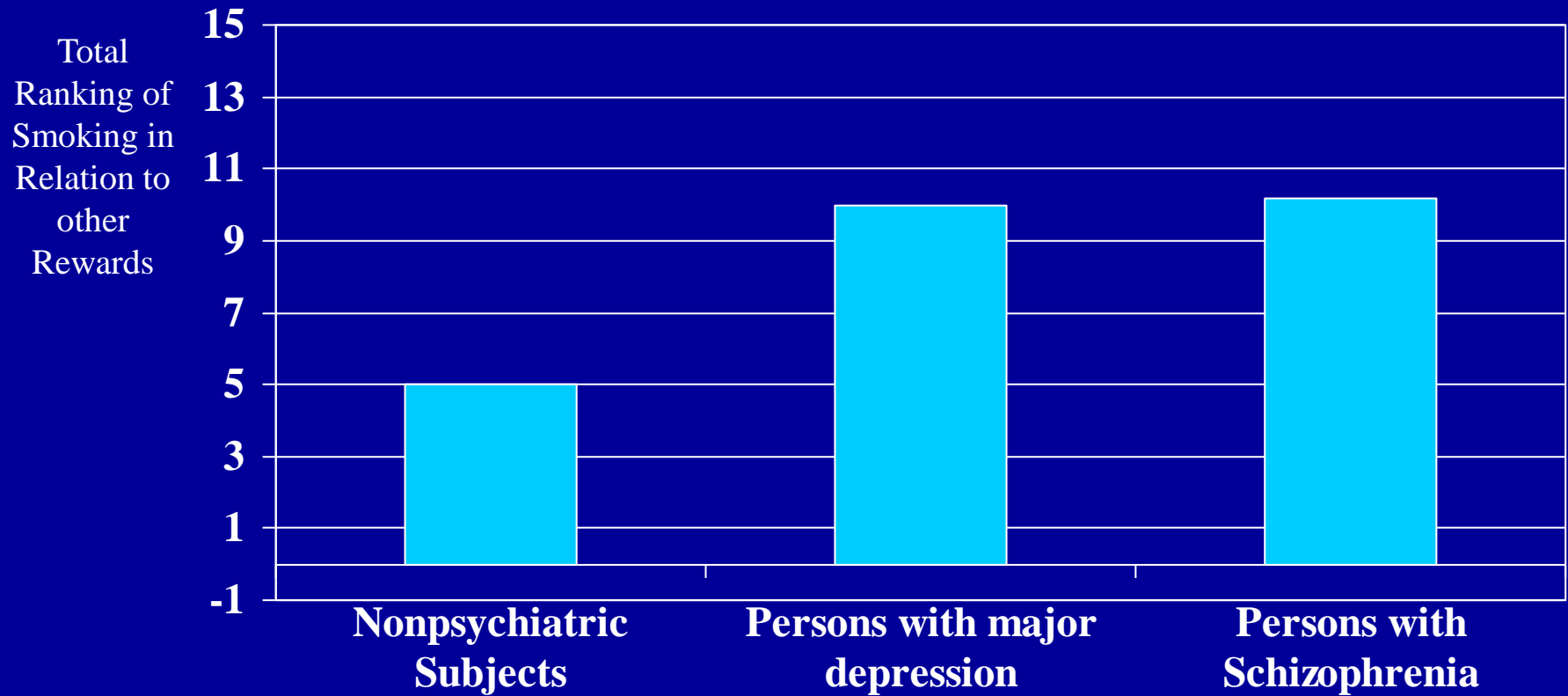


# **Social/Environmental Factors Promoting Smoking in Persons with Psychiatric Disorders**

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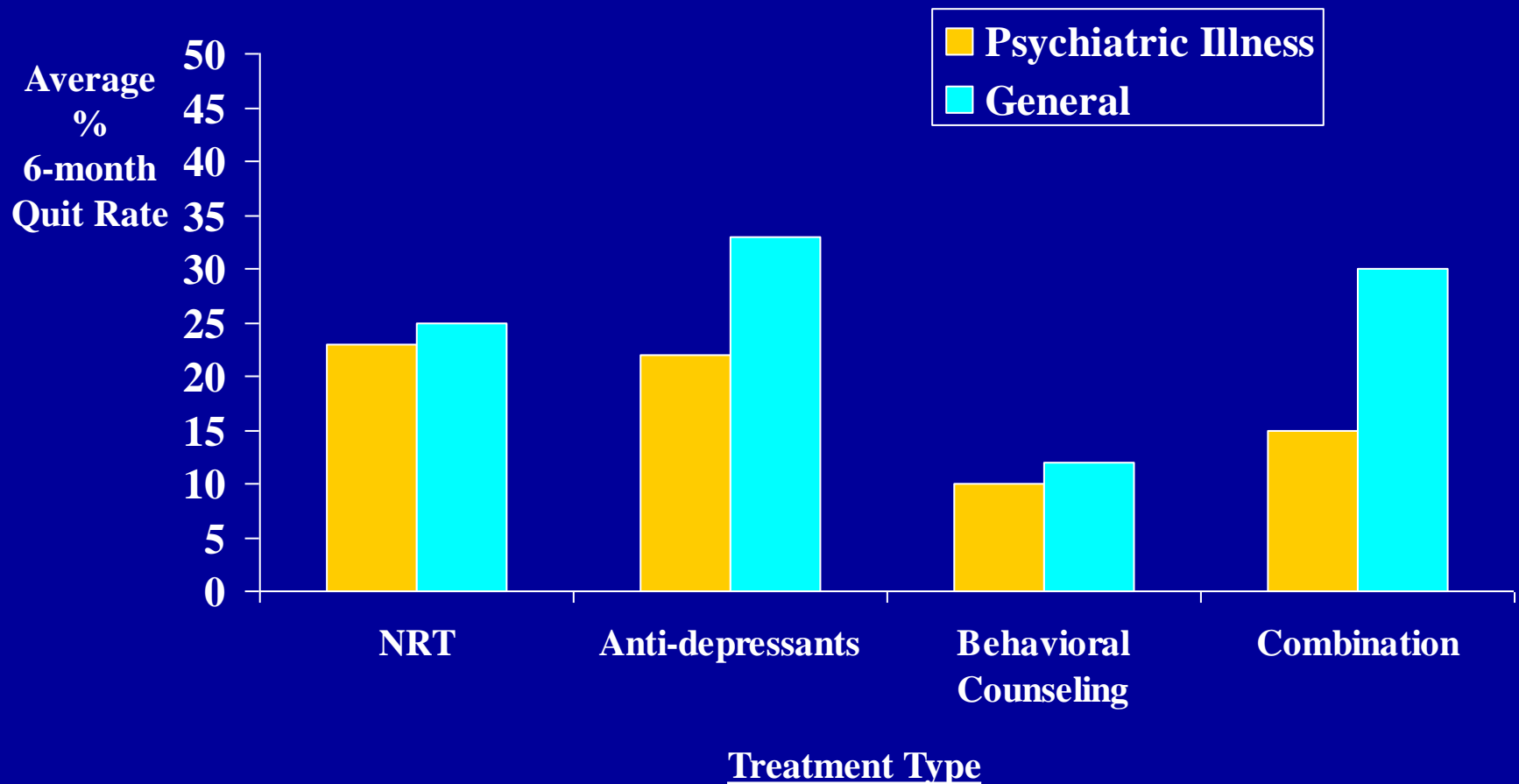
- Exposure to other smokers in residential or outpatient programs
- Boredom and/or loneliness
- Need for reward in an environment lacking reinforcers

# Persons with Psychiatric Illness Choose Nicotine Over Most Other Pleasurable Activities





# Effectiveness of Smoking Cessation Treatments



# Promising New Treatments for Smoking Cessation

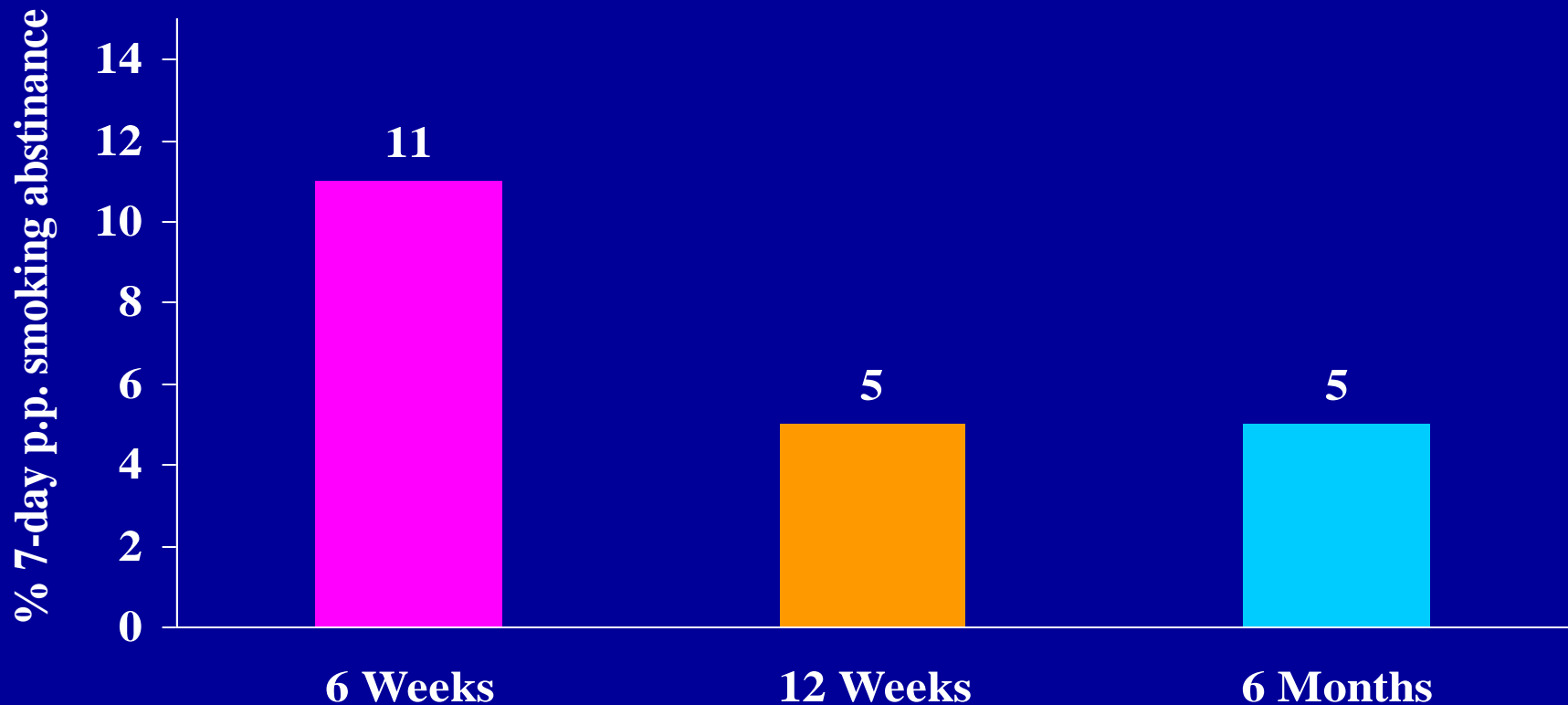
- Bupropion (Zyban): Effective for persons with Schizophrenia (depending on type of anti-psychotic treatment) and major depression
- Fluoxetine (Prozac): Effective for persons with a history of major depression and current depression symptoms
- Naltrexone: Some evidence for efficacy in the general population of smokers; effectiveness in persons with psychiatric illness unknown

# Adolescent Smoking

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- ~ 23% of adolescents smoke
- Adolescent smoking prevention programs have limited success.
- Adolescent smoking cessation program quit rates are poor.
- Pharmacological treatment outcomes for adolescent smoking have limited success.

# Efficacy of Nicotine Patch Therapy in Adolescent Smokers



Source: Hurt et al., Arch Pediatric Adolesc Med, Jan 2000

# RCT of Bupropion Combined With Nicotine Patch in the Treatment of Adolescent Smokers

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Treatment Group	Week 10	Week 26
<b>NP + placebo ( n = 108 )</b>		
% abstinent	28	7 (21)
No. assessed	94	70
<b>NP + bupropion ( n = 103 )</b>		
% abstinent	23	8 (16)
No. assessed	83	64

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# Adolescent Smoking

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- We need more research.
- Understanding the determinants of adolescent smoking is key to informing prevention and cessation efforts.
- ~ 75% of adult smokers tried their 1st cigarette before the age of 18 and half become regular smokers by age 18.
- Nicotine exposure in a developing adolescent body and brain may make an adolescent more susceptible to the effects of nicotine and may alter the system permanently creating the context for a life long habit.

# Summary

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- Smoking is a major health problem.
- Regardless of the patient population, smoking will be a risk factor for morbidity and mortality.
- Impact smoking behavior change as a health care provider.
- Provide brief smoking cessation advice, refer to counselor or clinical trial, and offer/provide pharmacotherapy.

# Question 1

## Answer

The percentage of Americans who smoke is approximately:

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B. 17%

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# Question 2

## Answer

For each pack of cigarettes sold in the US, the cost to the US in medical care and lost productivity is :

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## Answer

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  - B. Health concerns
  - **C. Physician**
  - D. Significant other
  - E. Desired lifestyle change