Tobacco Dependence
A Grand Rounds Presentation

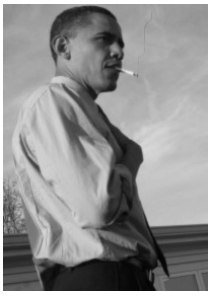
Steven A. Schroeder, MD

March 3, 2010

Courtesy of
The Smoking Cessation Leadership Center
and Rx for Change

Disclosure

I have no real or perceived vested interests that relate to this presentation nor do I have any relationships with pharmaceutical companies, biomedical device manufacturers, and/or other corporations whose products or services are related to pertinent therapeutic areas.



Composite Case History

52 year old man has smoked 1 ppd for 34 years. He has tried to quit several times, both cold turkey and with nicotine gum, but relapsed after 2 days to 1 week. His wife is a former smoker and would like him to quit. His first cigarette is soon after awakening, and triggers include coffee, alcohol, and stress. He has a history of depression, but is currently stable and not on meds. Other medical problems are obesity, with a BMI of 30, type 2 diabetes mellitus, mild COPD, elevated lipids, and hypertension (130/90 on double therapy) with mild renal and retinal complications.

Case History (2)

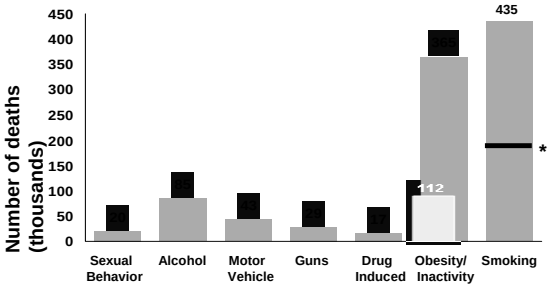
The patient is ambivalent about quitting. His questions include:

1. Why should I quit when I enjoy smoking so much?
2. Will I gain weight?
3. Should I use smoking cessation medications?
4. What if I can't stop?

Tobacco's Deadly Toll

- 453,000 deaths in the U.S. each year
- 4.8 million deaths world wide each year
- 10 million deaths estimated by year 2030
- 50,000 deaths in the U.S. due to second-hand smoke exposure
- 8.6 million disabled from tobacco in the U.S. alone

Behavioral Causes of Annual Deaths in the United States, 2000



Source: Mokdad et al, JAMA 2004; 291:1238-1245
Mokdad et al; JAMA. 2005; 293:293

* Also suffer from mental illness and/or substance abuse

Annual U.S. Deaths Attributable to Smoking, 2000–2004

		Percent of all smoking-attributable deaths
Cardiovascular diseases	128,497	**29%**
Lung cancer	125,522	**28%**
Respiratory diseases	103,338	**23%**
Second-hand smoke	49,400	**11%**
Cancers other than lung	35,326	**8%**
Other	1,512	**<1%**

TOTAL: 443,595 deaths annually

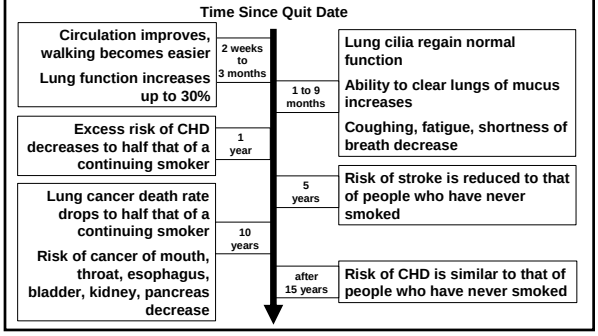
Centers for Disease Control and Prevention. *MMWR* 2008;571226–1228.

Health Consequences of Smoking

- Cancers
  - Acute myeloid leukemia
  - Bladder and kidney
  - Cervical
  - Esophageal
  - Gastric
  - Laryngeal
  - Lung
  - Oral cavity and pharyngeal
  - Pancreatic
- Pulmonary diseases
  - Acute (e.g., pneumonia)
  - Chronic (e.g., COPD)
- Cardiovascular diseases
  - Abdominal aortic aneurysm
  - Coronary heart disease
  - Cerebrovascular disease
  - Peripheral arterial disease
  - Type 2 diabetes mellitus
- Reproductive effects
  - Reduced fertility in women
  - Poor pregnancy outcomes (e.g., low birth weight, preterm delivery)
  - Infant mortality
- Other effects: cataract, osteoporosis, periodontitis, poor surgical outcomes, cognitive decline

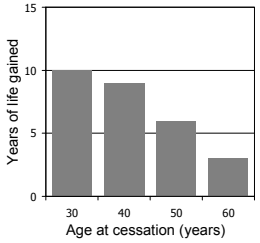
U.S. Department of Health and Human Services. *The Health Consequences of Smoking: A Report of the Surgeon General,* 2004.

QUITTING: HEALTH BENEFITS



Smoking Cessation: Reduced Risk of Death

- Prospective study of 34,439 male British doctors
- Mortality was monitored for 50 years (1951–2001)

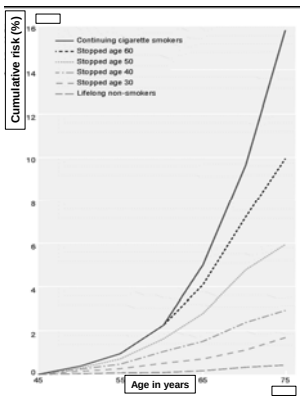


On average, cigarette smokers die approximately 10 years younger than do nonsmokers.

Among those who continue smoking, at least half will die due to a tobacco-related disease.

Doll et al. (2004). *BMJ* 328(7455):1519–1527.

Reduction in cumulative risk of death from lung cancer in men



Reprinted with permission. Peto et al. (2000). *BMJ* 321(7257):323–329.

Smoking and Mental Illness: The Heavy Burden

- 200,000 of the 435,000 annual deaths from smoking occur among patients with CMI and/or substance abuse
- This population consumes 44% of all cigarettes sold in the United States
  - -- higher prevalence
  - -- smoke more
  - -- more likely to smoke down to the butt
- People with CMI die on average 25 years earlier than others, and smoking is a large contributor to that early mortality

Causal Associations with Second-hand Smoke

There is no safe level of second-hand smoke.

- Developmental
  - Low birthweight
  - Sudden infant death syndrome (SIDS)
  - Pre-term delivery
- Carcinogenic
  - Lung cancer
  - Nasal sinus cancer
  - Breast cancer (younger, premenopausal women)
- Respiratory
  - Asthma induction and exacerbation
  - Eye and nasal irritation
  - Bronchitis, pneumonia, otitis media in children
- Cardiovascular
  - Heart disease mortality
  - Acute and chronic coronary heart disease morbidity
  - Altered vascular properties

USDHHS. (2006). *The Health Consequences of Involuntary Exposure to Tobacco Smoke: Report of the Surgeon General.*

Compounds in Tobacco Smoke

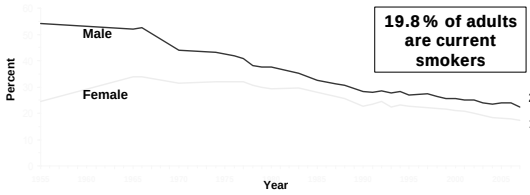
An estimated 4,800 compounds in tobacco smoke, including 11 proven human carcinogens

Gases	Particles
– Carbon monoxide	– Nicotine
– Hydrogen cyanide	– Nitrosamines
– Ammonia	– Lead
– Benzene	– Cadmium
– Formaldehyde	– Polonium-210

Nicotine does NOT cause the ill health effects of tobacco use.

TRENDS in ADULT SMOKING, by SEX—U.S., 1955–2007

Trends in cigarette current smoking among persons aged 18 or older



19.8% of adults are current smokers

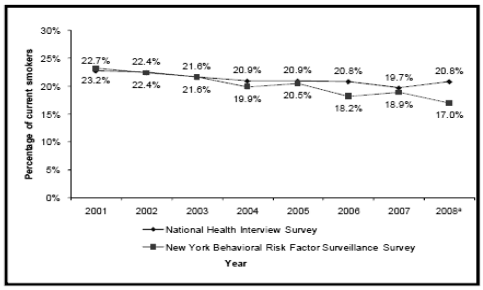
22.3%

17.4%

70% want to quit

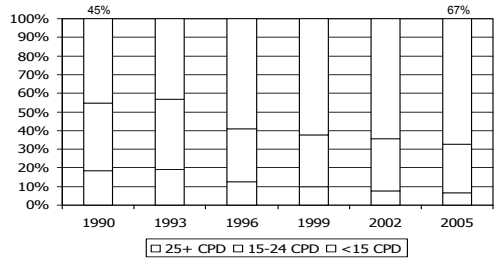
Graph provided by the Centers for Disease Control and Prevention. 1955 Current Population Survey; 1965–2005 NHIS. Estimates since 1992 include some-day smoking.

Percentage of Adults Who Currently Smoke in NY (BRFSS) and Nationally (NHIS) 2001-2008



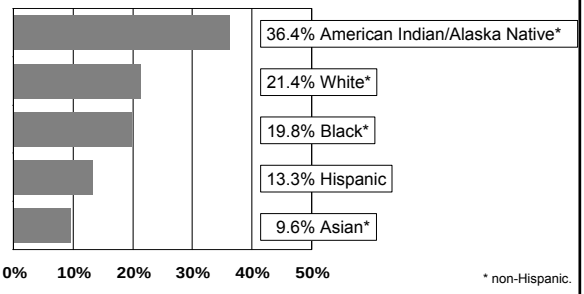
[a]NHIS data are reported for Q1 2008. BRFSS data are reported for Q1–Q2 2008.

Heavy, Medium and Light/Nondaily Smokers in California 1990-2005



Source: California Tobacco Surveys (CTS) and University of California San Diego

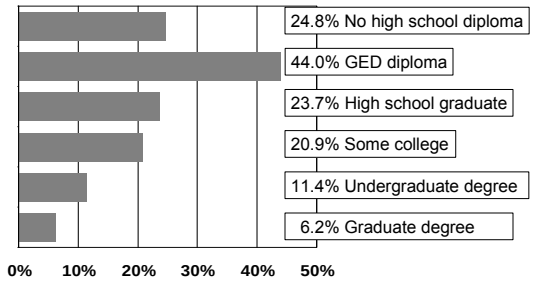
PREVALENCE of ADULT SMOKING, by RACE/ETHNICITY—U.S., 2007



* non-Hispanic.

Centers for Disease Control and Prevention. (2008). *MMWR 57*:1221–1116.

PREVALENCE of ADULT SMOKING, by EDUCATION—U.S., 2007

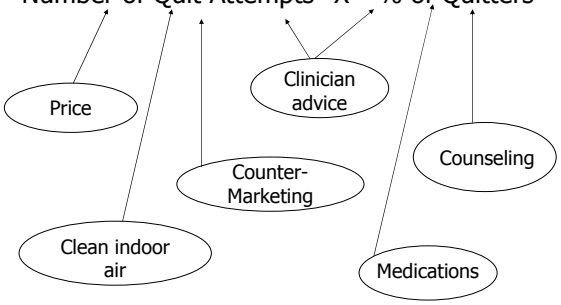


Centers for Disease Control and Prevention. (2008). *MMWR 57*:1221–1116.

Number of Smokers =
New Smokers + Old Smokers - Quitters

Number of Quitters =

Number of Quit Attempts X % of Quitters



Physicians Under-treat Smokers*

- AAMC survey of 3012 physicians representing FM, GIM, Ob-Gyn, Psych
- Only 1% were current smokers
- 84% asked about smoking
- 86% advised to quit
- 31% recommended NRT
- 17% arranged follow-up
- 7% referred to quitlines

*AAMC-Legacy survey: Physician behavior and practice patterns related to smoking cessation, 2007.

Reasons for Not Helping Patients Quit

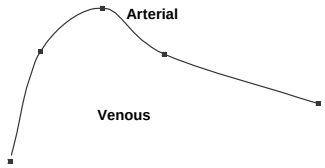
1. Too busy
2. Lack of expertise
3. No financial incentive
4. Lack of available treatments and/or coverage
5. Most smokers can't/won't quit
6. Stigmatizing smokers
7. Respect for privacy
8. Negative message might scare away patients
9. I smoke myself

Responses to Patient Who Smokes

- Unacceptable: "I don't have time."
- Acceptable
  - Refer to a quit line
  - Establish systems in your office and hospital
  - Become a cessation expert

Nicotine Distribution

Nicotine reaches the brain within 11 seconds.



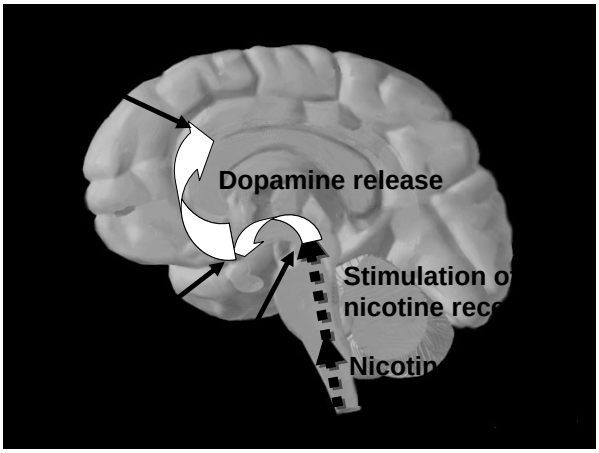
Data from Henningfield et al., *Drug Alcohol Depend* 1993;33:23-29.
Graph reprinted with permission, Rx for Change, The Regents of the University of California.

Nicotine Pharmacodynamics

Central nervous system
- Pleasure
- Arousal, enhanced vigilance
- Improved task performance
- Anxiety relief

Other
- Appetite suppression
- Increased metabolic rate
- Skeletal muscle relaxation

Cardiovascular system
- ↑ Heart rate
- ↑ Cardiac output
- ↑ Blood pressure
- Coronary vasoconstriction
- Cutaneous vasoconstriction



Chronic Administration of Nicotine: Effects on the Brain

Image courtesy of George Washington University / Dr. David C. Perry

Perry et al. (1999). *J Pharmacol Exp Ther* 289:1545–1552.

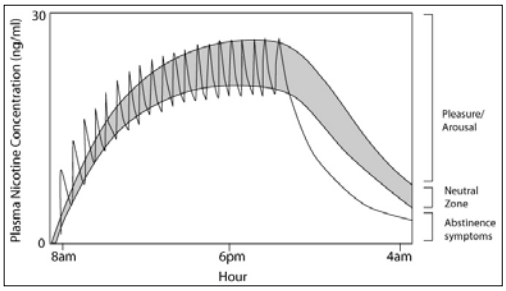
Nicotine Pharmacodynamics: Withdrawal Effects

- Irritability/frustration/anger
- Anxiety
- Difficulty concentrating
- Restlessness/impatience
- Depressed mood/depression
- Insomnia
- Impaired performance
- Increased appetite/weight gain
- Cravings

Most symptoms manifest within the first 1–2 days, peak within the first week, and subside within 2–4 weeks.

Hughes. (2007). *Nicotine Tob Res* 9:315–327.

Nicotine Addiction Cycle



Reprinted from *Med Clin N Am* 76(2), Benowitz NL, Cigarette smoking and nicotine addiction, pp. 415–437, Copyright 1992, with permission from Elsevier.

The 5 A's: Review

ASK	about tobacco USE
ADVISE	tobacco users to QUIT
ASSESS	readiness to make a QUIT attempt
ASSIST	with the QUIT ATTEMPT
ARRANGE	FOLLOW-UP care

Fiore et al. (2008). *Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline.* Rockville, MD: USDHHS, PHS, May 2008.

Cognitive Strategies for Cessation

- Review commitment to quit, focus on downsides of tobacco use
- Reframe the way a patient thinks about smoking
- Distractive thinking
- Positive self-talks, "pep talks"
- Relaxation through imagery
- Mental rehearsal, visualization

Behavioral Strategies for Cessation (Avoiding Stimuli that Trigger Smoking)

- Stress
  - Anticipate future challenges
  - Develop substitutes for tobacco
- Alcohol
  - Limit or abstain during early stages of quitting
- Other tobacco users
  - Stay away
  - Ask for cooperation from family and friends

Behavioral Strategies for Cessation (Part 2)

- Oral gratification needs
  - Use substitutes: water, sugar-free chewing gum or hard candies
- Automatic smoking routines
  - Anticipate routines and develop alternative plans, e.g., with morning coffee
- Weight gain after cessation
  - Anticipate; use gum or bupropion; exercise
- Cravings
  - Distractive thinking; change activities

SOCIAL SUPPORT for QUITTING

- Key ingredients for successful quitting:
  - Social support as part of treatment (intra-treatment)
  - Social support outside of treatment (extra-treatment)

PATIENTS SHOULD BE ADVISED TO:

- Ask family, friends, and coworkers for support – ask them not to smoke around you and not to leave cigarettes out
- Get individual, group, or telephone counseling

Patients who receive social support and encouragement are more successful in quitting

PHARMACOTHERAPY

"Clinicians should encourage all patients attempting to quit to use effective medications for tobacco dependence treatment, except where contraindicated or for specific populations* for which there is insufficient evidence of effectiveness."

** Includes pregnant women, smokeless tobacco users, light smokers, and adolescents.*

Medications significantly improve success rates.

Fiore et al. (2008). *Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline.* Rockville, MD: USDHHS, PHS, May 2008.

Pharmacologic Methods: First-line Therapies*

Three general classes of FDA-approved medications for smoking cessation:

- Nicotine replacement therapy (NRT)
  -- nicotine gum, patch, lozenge, nasal spray, inhaler
- Partial nicotine receptor agonist
  -- varenicline
- Psychotropics
  -- sustained-release bupropion

* Counseling plus meds better than either alone

Currently, no medications have an FDA indication for use in spit tobacco cessation.

Nicotine Gum

Advantages

- Might satisfy oral cravings.
- Might delay weight gain (4-mg strength).
- Patients can titrate therapy to manage withdrawal symptoms.
- A variety of flavors are available.

Disadvantages

- Need for frequent dosing can compromise compliance.
- Might be problematic for patients with significant dental work.
- Patients must use proper chewing technique to minimize adverse effects.
- Gum chewing might not be socially acceptable.

Transdermal Nicotine Patch

Advantages

- The patch provides consistent nicotine levels.
- Two strengths-14, 21 mg
- The patch is easy to use and conceal.
- Fewer compliance issues are associated with the patch.

Disadvantages

- Patients cannot titrate the dose.
- Allergic reactions to adhesive may occur.
- Patients with dermatologic conditions should not use.

Nicotine Lozenge

Advantages

- Might satisfy oral cravings.
- Might delay weight gain (4-mg strength).
- Easy to use and conceal.
- Patients can titrate therapy to manage withdrawal symptoms.
- A variety of flavors are available.

Disadvantages

- Need for frequent dosing can compromise compliance
- Gastrointestinal side effects (nausea, hiccups, and heartburn) may be bothersome.

Nicotine Nasal Spray

Advantages

- Patients can easily titrate therapy to rapidly manage withdrawal symptoms.

Disadvantages

- Need for frequent dosing can compromise compliance.
- Nasal/throat irritation may be bothersome.
- Higher dependence potential.
- Patients with chronic nasal disorders or severe reactive airway disease should not use the spray.

Nicotine Inhaler

Advantages

- Patients can easily titrate therapy to manage withdrawal symptoms.
- The inhaler mimics hand-to-mouth ritual of smoking.

Disadvantages

- Need for frequent dosing can compromise compliance.
- Initial throat or mouth irritation.
- Can't store cartridges in very warm conditions or use in very cold conditions.
- Patients with underlying bronchospastic disease must use with caution.

VARENICLINE

- Chantix, marketed by Pfizer
- Partial nicotinic receptor agonist
  - Approved by the FDA May 2006
  - Much DTC marketing
- Early trials (JAMA) show better results than bupropion
- Lessens withdrawal symptoms and inhibits the "buzz" from a smoke
- Common side effect is nausea

VARENICLINE: Mechanism of Action

- Binds with high affinity and selectivity at $\alpha_4\beta_2$ neuronal nicotinic acetylcholine receptors
  - Stimulates low-level agonist activity
  - Competitively inhibits binding of nicotine
- Clinical effects
  - ↓ symptoms of nicotine withdrawal
  - Blocks dopaminergic stimulation responsible for reinforcement & reward associated with smoking

VARENICLINE: Dosing

Patients should begin therapy 1 week PRIOR to their quit date. The dose is gradually increased to minimize treatment-related nausea and insomnia.

	Treatment Day	Dose
Initial dose titration	Day 1 to day 3	0.5 mg qd
	Day 4 to day 7	0.5 mg bid
	Day 8 to end of treatment*	1 mg bid

* Up to 12 weeks

VARENICLINE: Adverse Effects

Common side effects (≥5% and twice the rate observed in placebo-treated patients) include:

- Nausea
- Sleep disturbances (insomnia, abnormal dreams)
- Constipation
- Flatulence
- Vomiting

VARENICLINE: Advantages and Disadvantages

Advantages

- Varenicline is an oral formulation with twice-a-day dosing
- Varenicline offers a new mechanism of action for persons who previously failed using other medications
- Early industry-sponsored trials suggest this agent is superior to bupropion SR

Disadvantages

- May induce nausea in up to one third of patients
- Avoid in chronic renal failure
- Post-marketing surveillance data just emerging
- New warning about rare but important psychiatric symptoms; hard to distinguish from nicotine withdrawal; 100 reported suicides since 2006

VARENICLINE: Warning

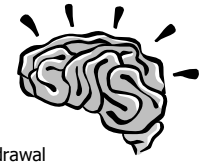
In 2008, Pfizer added a warning label advising patients and caregivers:

> Patients should stop taking varenicline and contact their healthcare provider immediately if agitation, depressed mood, or changes in behavior that are not typical for them are observed, or if the patient develops suicidal ideation or suicidal thoughts.

In July 2009 this was made into a black box warning for both varenicline (Chantix) and bupropion (Zyban)

BUPROPION SR: Mechanism of Action

- Atypical antidepressant thought to affect levels of various brain neurotransmitters
  - Dopamine
  - Norepinephrine
- Clinical effects
  - ↓ craving for cigarettes
  - ↓ symptoms of nicotine withdrawal



BUPROPION SR: DOSING

Patients should begin therapy 1 to 2 weeks PRIOR to their quit date to ensure that therapeutic plasma levels of the drug are achieved.

Initial treatment

- 150 mg po q AM x 3 days

Then…

- 150 mg po bid
- Duration, 7–12 weeks

BUPROPION SR: Advantages and Disadvantages

Advantages

- Easy to use.
- Bupropion SR can be used with NRT.
- Might be beneficial for patients with depression.

Disadvantages

- Seizure risk is increased.
- Bupropion SR should be avoided or used with caution in patients with:
  - History of seizures or cranial trauma
  - Anorexia or bulimia nervosa
  - Medications that lower seizure threshold
  - Severe hepatic cirrhosis
  - Concurrent use of any form of Wellbutrin, or any MAO inhibitor in preceding 14 days
  - Patients undergoing abrupt discontinuation of alcohol or sedatives

Combination Therapy

- Combination NRT
  - Long-acting formulation (patch)
    - Produces relatively constant levels of nicotine

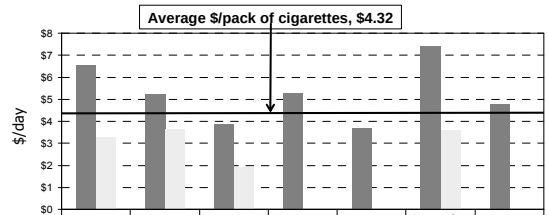
    PLUS
  - Short-acting formulation (gum, lozenge, inhaler, nasal spray)
    - Allows for acute dose titration as needed for withdrawal symptoms
- Bupropion SR + NRT
- The safety and efficacy of combination of varenicline with NRT or bupropion has not been established.

  Use of combination therapies is becoming normalized.

Combination Therapy for the Heavily Addicted Smoker—Mayo Clinic Style

- Nicotine patch
  - Strongest dose, can use more than one
- Shorter acting nicotine replacement
- Bupropion SR

COMPARATIVE DAILY COSTS of PHARMACOTHERAPY



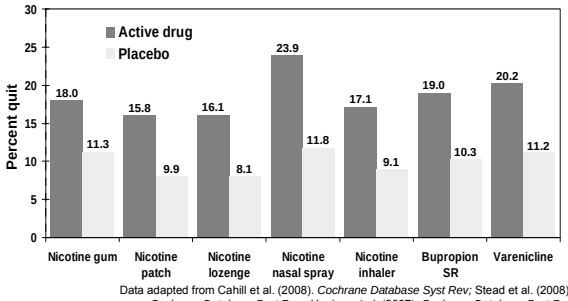
	Gum	Lozenge	Patch	Inhaler	Nasal spray	Bupropion SR	Varenicline
Trade	$6.58	$5.26	$3.89	$5.29	$3.72	$7.40	$4.75
Generic	$3.28	$3.66	$1.90	-	-	$3.62	-

Graph reprinted with permission, Rx for Change, The Regents of the University of California.

Caveats About Cessation Literature

- Smoking should be thought of as a chronic condition, yet drug treatment often short (12 weeks) in contrast to methadone maintenance
- Great spectrum of severity and addiction; treatment should be tailored accordingly
- Volunteers for studies likely to be more motivated to quit
- Placebo and drug groups tend to have more intensive counseling than found in real practice world
- Most drug trials exclude patients with mental illness
  - Sharon Hall (UCSF) studies show 50% 52-wk point-prevalence cessation after long-term drug use plus extended counseling ("cold turkey rates <5%, most drug trials <25%)

LONG-TERM (≥6 month) QUIT RATES for AVAILABLE CESSATION MEDICATIONS



Data adapted from Cahill et al. (2008). *Cochrane Database Syst Rev;* Stead et al. (2008). *Cochrane Database Syst Rev;* Hughes et al. (2007). *Cochrane Database Syst Rev*

What Are "Tobacco Quitlines"?

- Tobacco cessation counseling, provided at no cost via telephone to all Americans
- Staffed by trained specialists
- Up to 4–6 personalized sessions (varies by state)
- Some state quitlines offer nicotine replacement therapy at no cost (or reduced cost)
- Up to 30% success rate for patients who complete sessions

Most health-care providers, and most patients, are not familiar with tobacco quitlines.

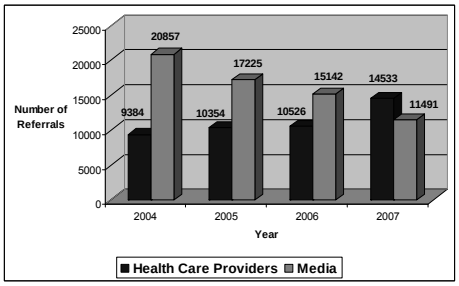
Efficacy and Average Sample Size of Tobacco Cessation Studies Reviewed by the Cochrane Library†

Type of Intervention	Odds Ratio (95% CI*)	Average Sample Size, per trial
Nicotine Replacement Therapy (NRT, n=98*)	1.74 (1.64, 1.86)	385
Telephone Counseling (TC, n=13*)	1.56 (1.38, 1.77)	1,100

*n indicates number of studies; CI. Confidence interval.

†Based on Silagy et al. (2004) and Stead et al. (2004). *The Cochrane Library.*

Referrals by Type to the California Smokers' Helpline, 2004-2007



Tobacco Tipping Point?

- California 13% adult smoking prevalence
- National prevalence in 2007 at modern low—(19.8%), up to 20.6% in 2008, ? lower in 2009
- Smokers smoke fewer cigarettes
- Northern California Kaiser Permanente at 9%
- Physicians around 1%
- Proliferation of smoke-free areas
- April 2009 62 cent/pack federal tax increase
- Increasing stigmatization of smoking

Back to the Patient

The patient is ambivalent about quitting. His questions include:

1. Why should I quit when I enjoy smoking so much? Health reasons (heart, lungs, DM with complications, stroke risk) plus stigma & $. Look for life motivations (weddings, graduations, etc.)
2. Will I gain weight? Probably, but can minimize with exercise.
3. Should I use smoking cessation medications? Medications plus counseling will increase probability of quitting. Would start on triple therapy: patch, gum, plus bupropion. Reserve varenicline for Rx failure. Then must monitor for suicide risk.
4. What if I can't stop? Motivational interviewing. Remind him that it often takes 8-10 attempts before quitting, and that there are now more ex-smokers than current smokers. Don't moralize and don't give up. Accept relapses.

Power of Intervention

- ⅓ to ½ of the 43.4 million smokers will die from the habit. Of the 30.5 million who want to quit, 10 to 15 million will die from smoking.
- Increasing the 3% base line cessation rate to 10% would save 1 million additional lives.
- If cessation rates rose to 15%, 1.5 million additional lives would be saved.
- No other health intervention could make such a difference!

New York State Smokers' Quitline

What is the New York State Smokers' Quitline?

The Quitline is a free and confidential program providing evidence-based cessation services to NYS residents who want to stop using tobacco.

Hours of Operation:

Live Coaching Support:

Monday – Wednesday 9 a.m.-12 a.m.

Thursday – Friday 9 a.m.- 6 p.m.

Saturday – Sunday 9 a.m. - 1 p.m.

Taped Message Library:

24 hours/7days

Tip of the Day:

24 hours/7days

Website access: www.nysmokefree.com

Quitline's Scope of Services

- **Information Clearinghouse**
- **Cessation Coaching**
- **NRT**
  - **Online Fulfillment**
- **Provider Services**
- **Print Materials**
- **Web Site Information**
- **Information Technology**

Health Care Organization and Provider Awareness of Cessation Resources in New York State, HCOPS 2004–2005 and 2007