

---

# Biochemistry and Medical Treatment of Tobacco Addiction

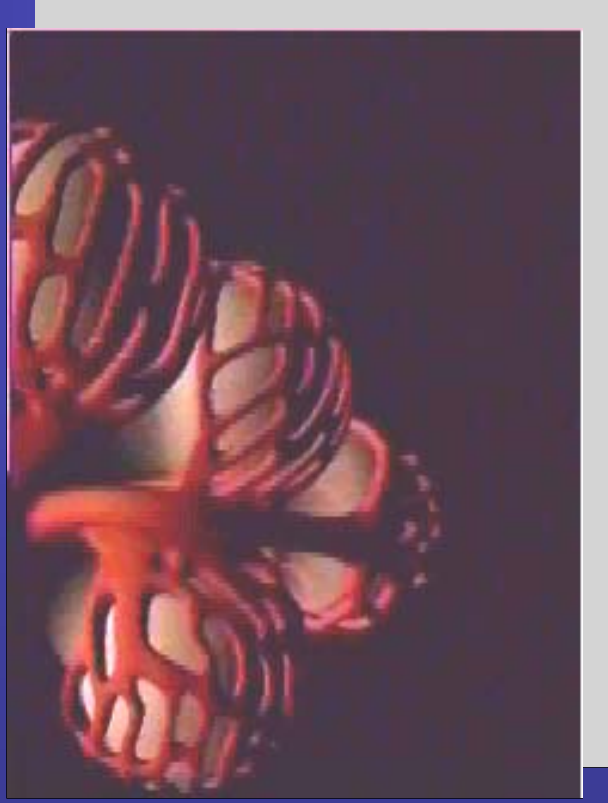
---

# The Biochemistry of Nicotine Addiction



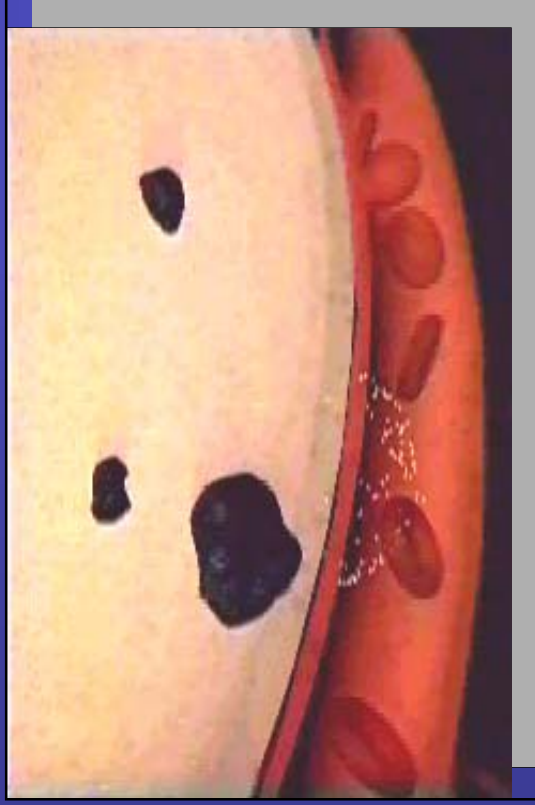
- The most rapid drug delivery is via inhalation such as smoking
- Nicotine reaches the brain within 7 seconds of a puff

# The Biochemistry of Nicotine Addiction



- Here we see, in the lungs, alveolar-pulmonary capillary gas exchange – the most effective method of drug delivery

# The Biochemistry of Nicotine Addiction



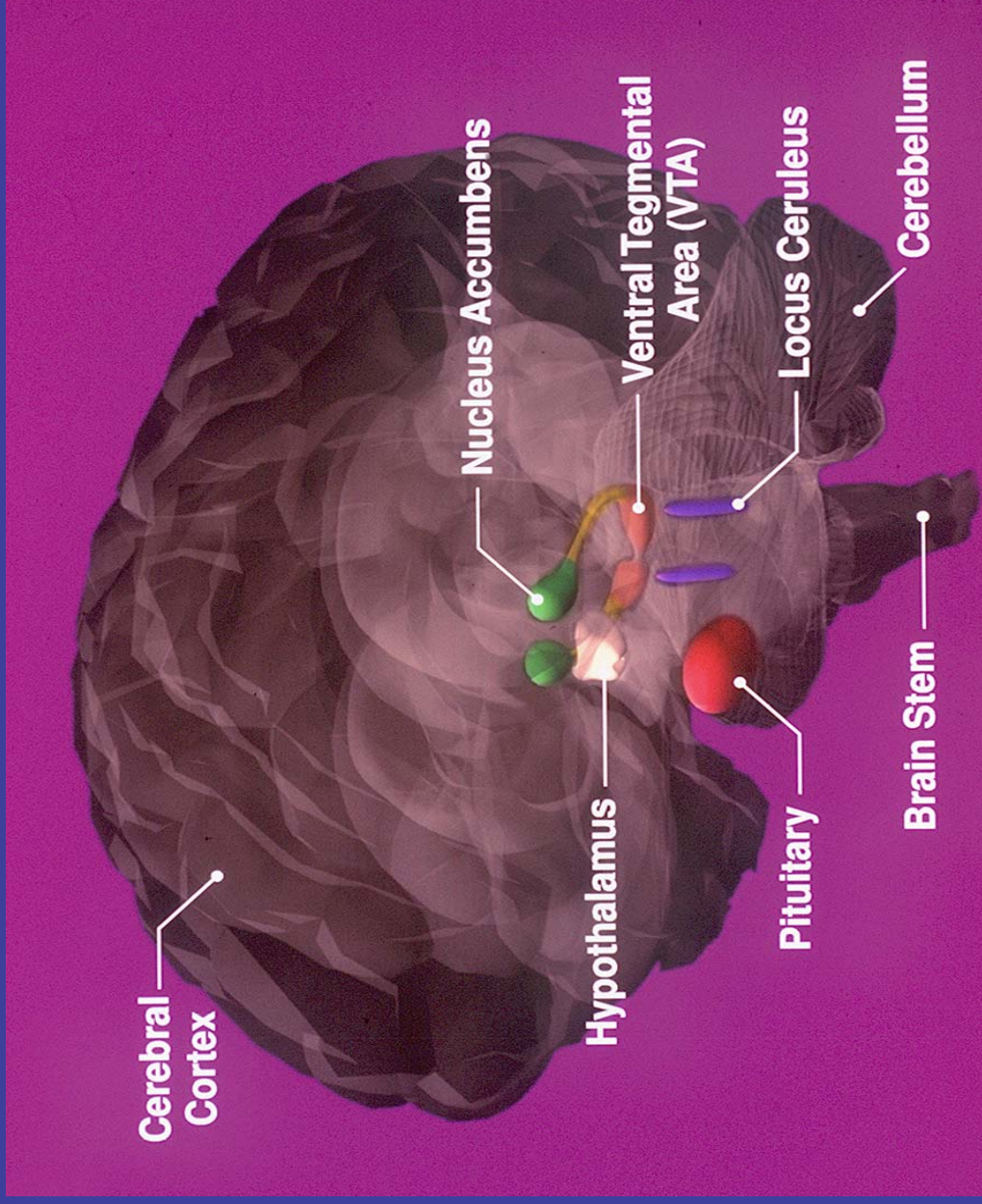
- Nicotine, carried on “tar” particles and in gaseous phase, enters the pulmonary circulation

# The Biochemistry of Nicotine Addiction



- In a heart beat, nicotine floods the smoker's brain changing the brain's chemistry, effecting behavior and emotions

# Biology of Addiction



# Neurochemical Effects of Nicotine

---



Benowitz NL. Nicotine Addiction. *Primary Care* 26: 611-631, 1999

# Nicotine Addiction Cycle

---

Nicotine use for pleasure,  
enhanced performance,  
mood regulation

Tolerance and physical  
dependence

Nicotine use to self-  
medicate withdrawal  
symptoms

Nicotine abstinence produces  
withdrawal symptoms



---

Benowitz NL. *Med Clin North Am.* 1992; 76: 415-437.

Henningfield JE and Kennan RM. *J Consult Clin Psychol.* 1993; 61: 743-750.

# Pharmacotherapies for Smoking Cessation

---

<u>Product</u>	<u>Rx</u>	<u>OTC</u>
Gum	1984	1996
Patch	1991	1996*
Nasal Spray	1996	--
Inhaler	1997	--
Bupropion SR	1997	--
Lozenge	--	2002

---

\* Nicotrol® and Nicoderm® CQ® switched from Rx to OTC in 1996.

# Smoking Cessation Therapies: Increasing the Odds of Success

Therapy	Estimated Odds Ratio (Compared to Placebo)	95% C.I.
Gum	1.6	1.5 to 1.8
Patch	1.9	1.7 to 2.2
Nasal Spray	2.7	1.8 to 4.1
Inhaler	2.5	1.7 to 3.6
Bupropion SR	2.1	1.5 to 3.0
Lozenge	2.1 to 2.7	1.6 to 4.3

Fiore MC, Bailey WC, Cohen SJ, et al. *Treating Tobacco Use and Dependence. Clinical Practice Guideline.* Rockville, MD: U.S. Department of Health and Human Services. Public Health Service. June 2000.

Lancaster T et al. *BMJ.* 2000; 321:355-358

Shiffman S et al. *Arch Intern Med.* 2002; 162:1267-1276

# Nicotine Replacement Therapy (NRT)

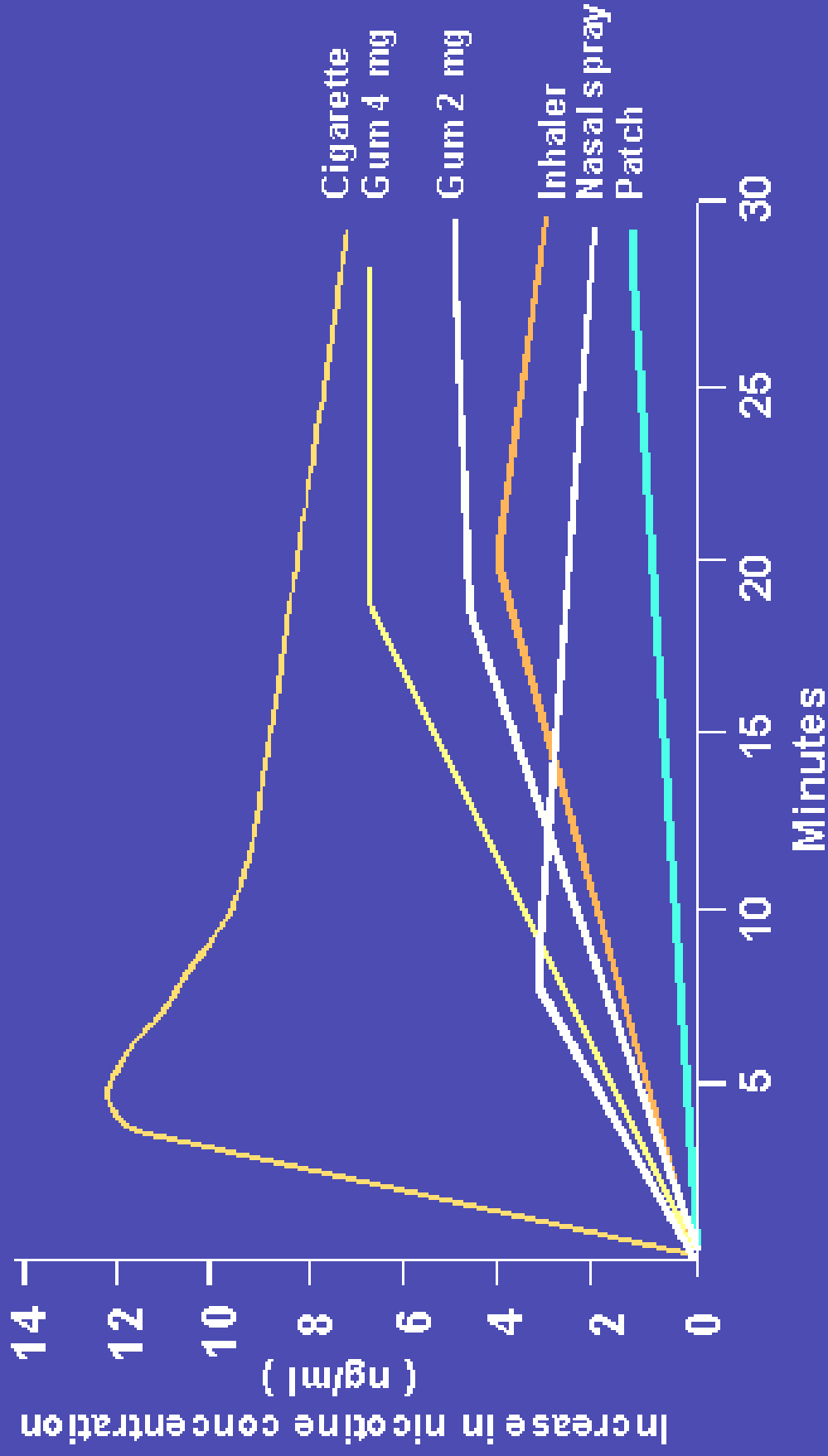
---

- Helps relieve withdrawal symptoms
- Provides lower nicotine levels than smoking; several studies suggest higher levels are better
- Doubles chance of success versus placebo
- Safe, effective

---

Fiore MC, Bailey WC, Cohen SJ, et al. *Treating Tobacco Use and Dependence*. Clinical Practice Guideline. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service. June 2000.

# Plasma nicotine concentrations for smoking and NRT



Source: Balfour DJ & Fagerström KO. *Pharmacol Ther* 1996 72:51-81.

# Plasma Nicotine Concentrations

## Cigarettes versus NRT

---

### *Cigarettes*

- 1 cigarette produces rapid surge of plasma nicotine
- ↑ by about 25 ng/ml in minutes; declines rapidly

### *NRT*

- No form achieves plasma nicotine concentrations as high as those from smoking 20 cigarettes/day
  - Does not reproduce immediate effect of smoking (I.e: no “smoker’s high”)
-

# Nicotine Gum

---

## *Features*

- Nicotine absorbed via buccal mucosa
- Available in 2 mg and 4 mg strengths
  - 4 mg strength more effective for “highly addicted” (>25 cigarettes per day) smokers
- Self-titration (i.e. ad lib)

# Nicotine Gum

---

## *Dosing*

- Chew at least 9 pieces/day during first 6 weeks
  - Chewing technique critical to correct use (chew, park, chew)
- Use for 12 weeks
- Avoid alcohol and caffeinated beverages; they reduce nicotine absorption

## *Side effects*

- Local: irritation of tongue, mouth and throat, ulceration of oral mucosa, jaw-muscle ache
- Systemic: indigestion, nausea, dizziness

# Nicotine Patch

---

## *Features*

- Transdermal delivery system provides regulated, constant level of nicotine
  - Higher dose, 16-hour nicotine patch (25 mg) associated with an increase in long-term success
  - Weaning not proven to provide an advantage (but may be helpful to some smokers)
- 

Tønnesen P et al. *European Respiratory Journal* 1999; 13: 238-246.

# Nicotine Patch

---

## *Dosing*

- At least 1 patch/day worn for 16 or 24 hours
- Available doses range from 5 - 22 mg/patch

## *Side effects*

- Local: skin irritation, rash
  - More predominant for 24-hour patch
- Systemic: insomnia, sleep disturbances, dyspepsia
  - To limit sleep disturbances, e.g., vivid dreams, remove 24-hour patch before bedtime or use 16-hour patch

---

Fiore MC, Bailey WC, Cohen SJ, et al. *Treating Tobacco Use and Dependence*. Clinical Practice Guideline. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service. June 2000.

Nicotrol<sup>®</sup>, ProStep<sup>®</sup>, Nicoderm CQ<sup>®</sup>, Habitrol<sup>®</sup> labeling information, 2001

Krogstad AL et al. *Skin Research and Technology* 1996; 2: 158-163. © 2003 Smoking Consultation Service

# Nicotine Nasal Spray

---

## Features

- Intranasal delivery with fast, effective relief of withdrawal symptoms
- Designed for ad libitum use with dose flexibility
- Significant difference in abstinence rates (active vs. placebo) even after one day
  - Maintained at follow-up visits up to six months after quit date
- Particularly beneficial for highly dependent smokers or individuals not responding to other treatments

---

Blondal T et al. *Euro Resp J* 1997; 10: 1585-90.

Schneider NG et al. *Addiction* 1995; 90: 1671-82.

# Nicotine Nasal Spray

---

## *Dosing*

- 1 spray each nostril (equals 1 dose = 1 mg nicotine) as needed (at least 8 times/day = 1 dose every 1 – 2 hours)
- Do not exceed 5 doses/hr or 40 doses/day

## *Side effects*

- Nasal irritation, runny nose, throat irritation, watering eyes, sneezing and coughing
- Tolerability occurs after a couple days

# Nicotine Nasal Spray: Efficacy in Three Studies

Study	12-week efficacy rate (%)	24-week efficacy rate (%)
Sutherland G et al. <i>Lancet.</i> 1992;340:324	41% active 17% placebo	31% active 12% placebo
Hjalmarson A et al. <i>Arch Intern Med.</i> 1994;154:2567	41% active 20% placebo	34% active 14% placebo
Schneider NG et al. <i>Addiction.</i> 1995;90:1671	34% active 13% placebo	25% active 10% placebo

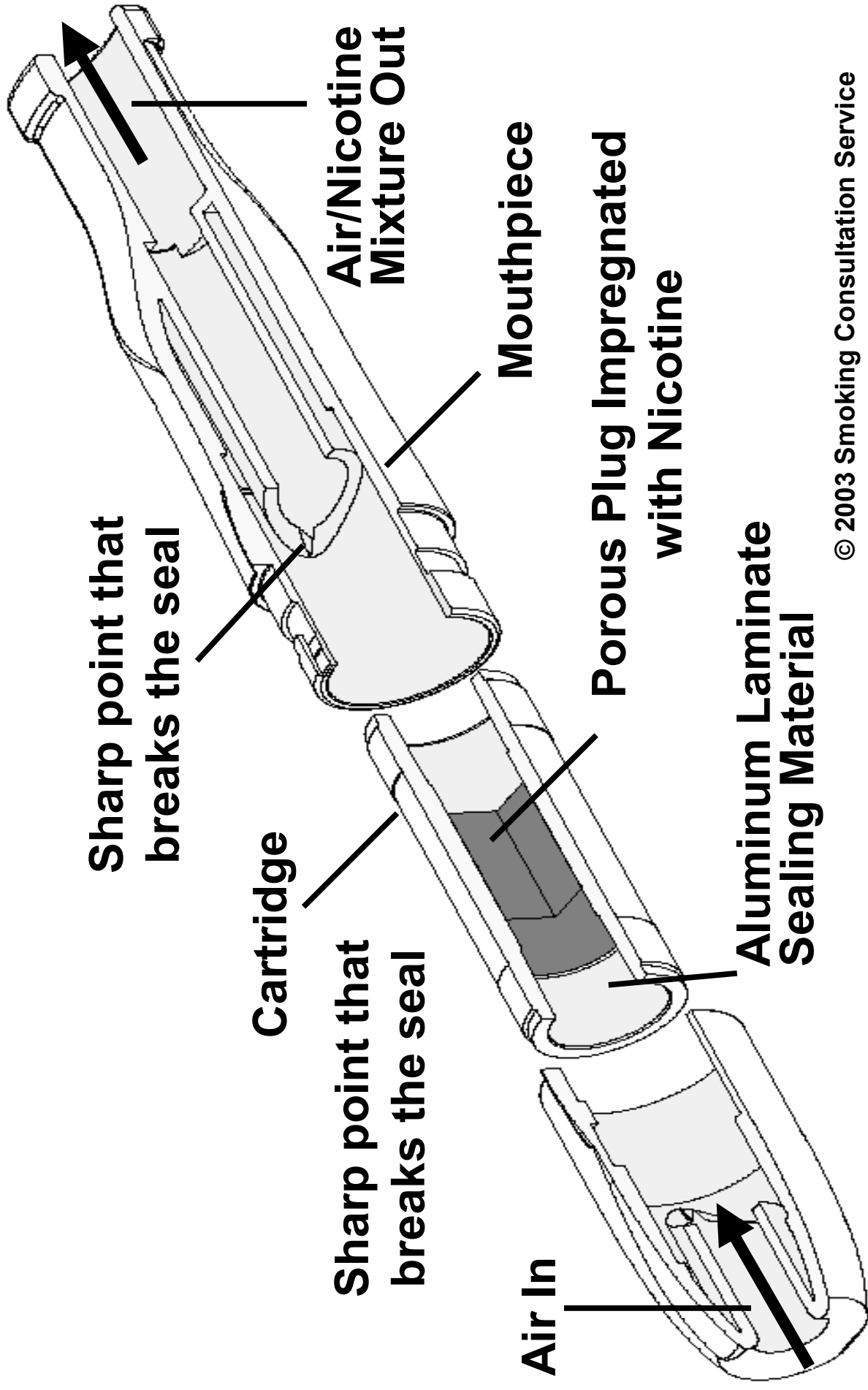
# Nicotine Inhaler

---

## Features

- Unique inhalation system offers pharmacological, behavioral and sensory treatment
- Nicotine is absorbed from upper airways, not lungs
  - Main fraction of dose delivered to and absorbed in mouth
- Rise in blood nicotine is relatively slow
  - Ad-lib use produces nicotine levels about 1/3 of those achieved with cigarette smoking
- As with gum, avoid alcohol and caffeinated beverages

# Schematic of the Nicotine Inhaler



# Nicotine Inhaler

---

## *Dosing*

- May be individualized
- Initial treatment can range from 3-12 weeks
- For best results, use at least 6 cartridges/day for first 3 to 6 weeks
- If needed, gradual reduction can begin after initial treatment period
- Total treatment not to exceed 6 months

---

Nicotrol® Inhaler prescribing information, 2001.

# Nicotine Inhaler

---

## *Side effects*

- Local side effects are cough and irritation in throat and mouth
- Most common nicotine-related side effect is dyspepsia
- Mild and transient and decrease over time

---

Nicotrol® Inhaler prescribing information, 2001.

# Nicotine Lozenge

---

## Features

- Nicotine absorbed via buccal mucosa
- Available in 2 mg and 4 mg strengths
  - 4 mg strength more effective for “highly addicted” (TTFC\* < 30 minutes) smokers
- Self-titration (i.e. ad lib)
- Each lozenge delivers 25% more nicotine than similarly dosed nicotine gum
- Hiccups, heartburn, nausea most common side effects

\*Time to first cigarette

---

Arch Intern Med. 2002; 162:1267-1276

# Bupropion for Smoking Cessation

---

## *Features*

- Atypical antidepressive substance (amfebutamone)
- Exact mechanism of action unknown: dopaminergic/noradrenergic/other
- Active ingredient in Wellbutrin®

## *Dosing*

- 300 mg (150 mg qam x 3 days then BID separated by 8 hours); dosage can be less and titrated more gradually.
- **Begin therapy while still smoking**

# Bupropion for Smoking Cessation

---

## *Side effects*

- Dry mouth, insomnia, headache & dizziness
- Risk of seizure: approximately 1 in 1,000
- Contraindicated for patients with seizure disorder, anorexia nervosa or bulimia and for those taking Wellbutrin® or Wellbutrin SR®

---

Zyban™ prescribing information, 2001.

# Effectiveness of Bupropion for Smoking Cessation

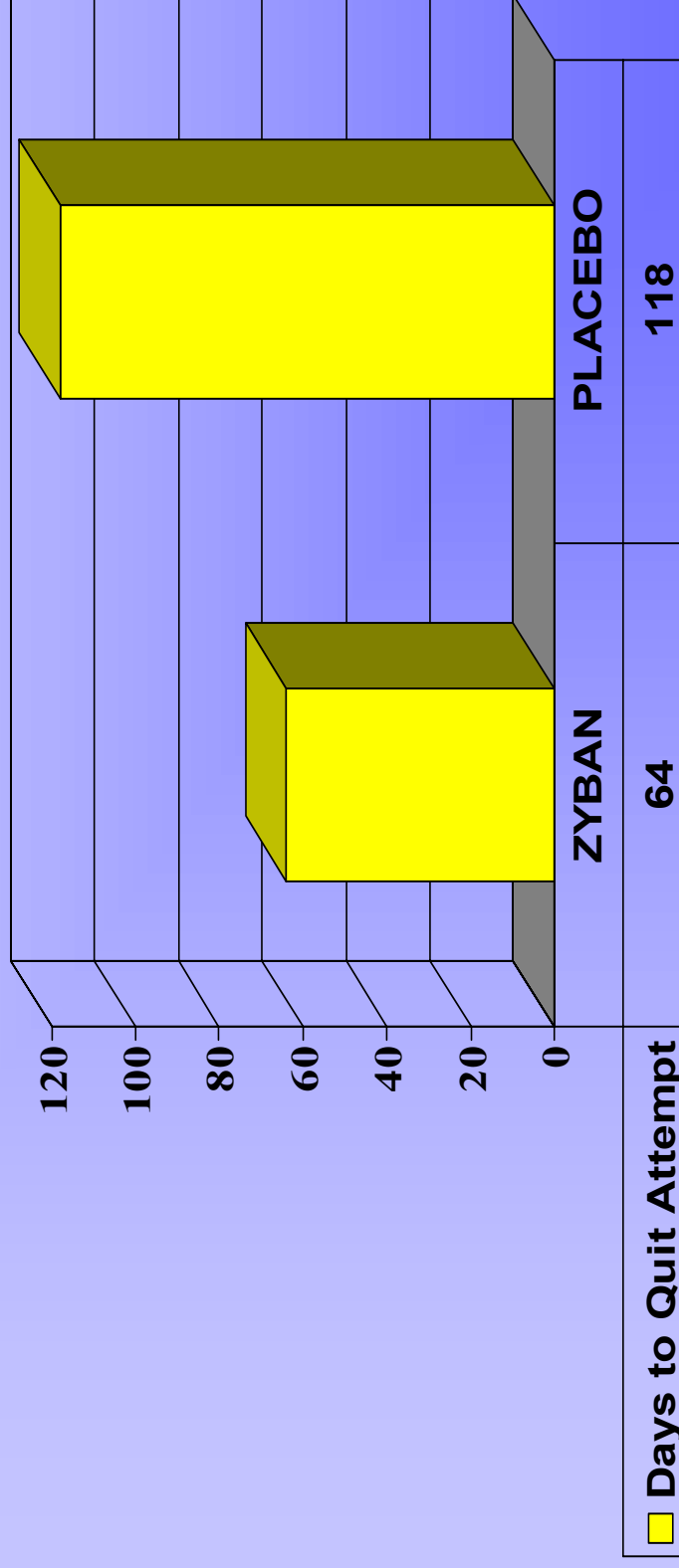
---

- Significantly higher abstinence rates than placebo during treatment and at 6 & 12 month follow up
- Combination therapy (with the nicotine patch)
  - Approved indication
  - Provided higher abstinence rates than bupropion alone

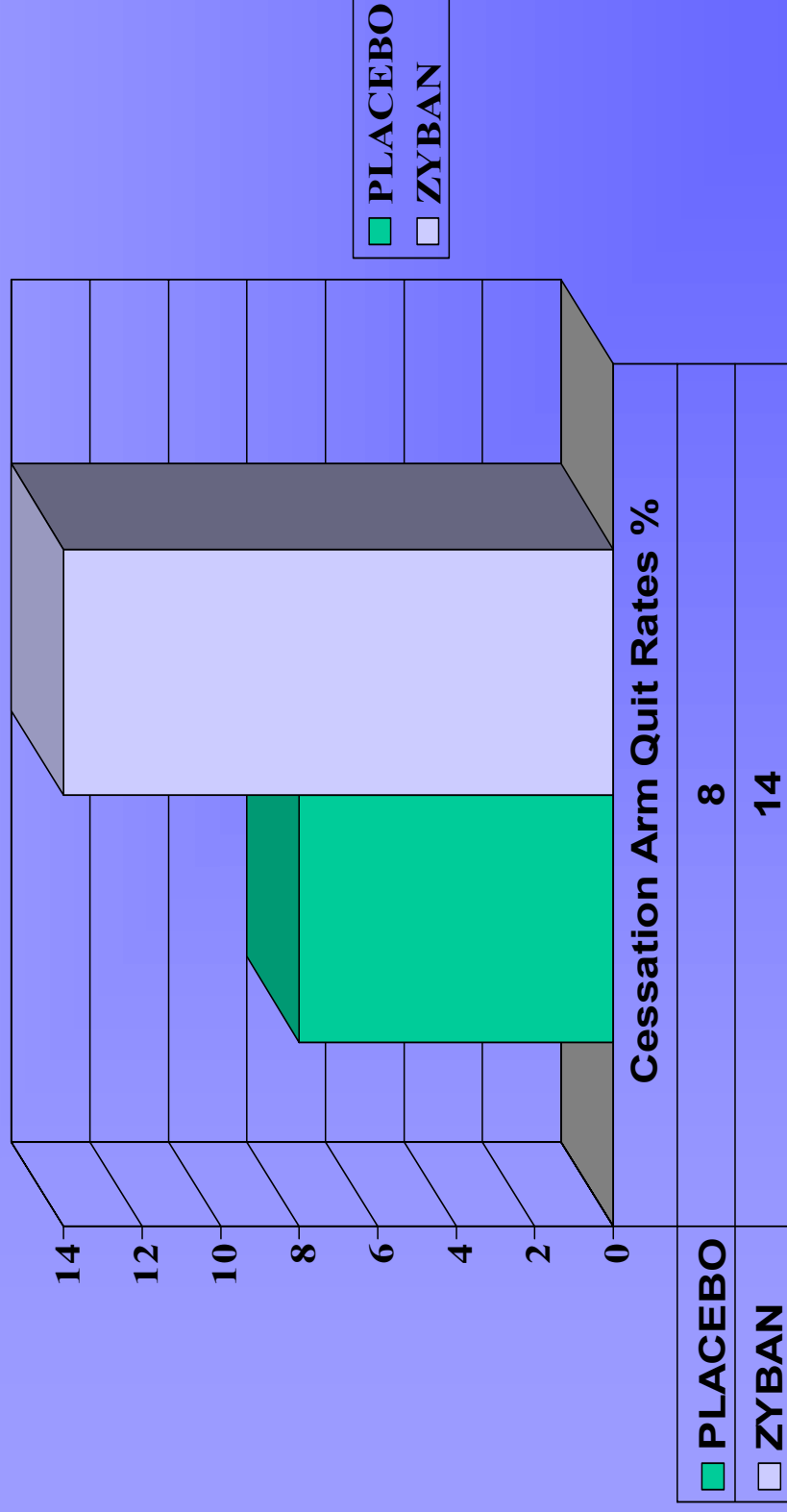
---

Holm, KJ, Spencer, CM. *Drugs* 2000 Apr; 59(4): 1007-24.

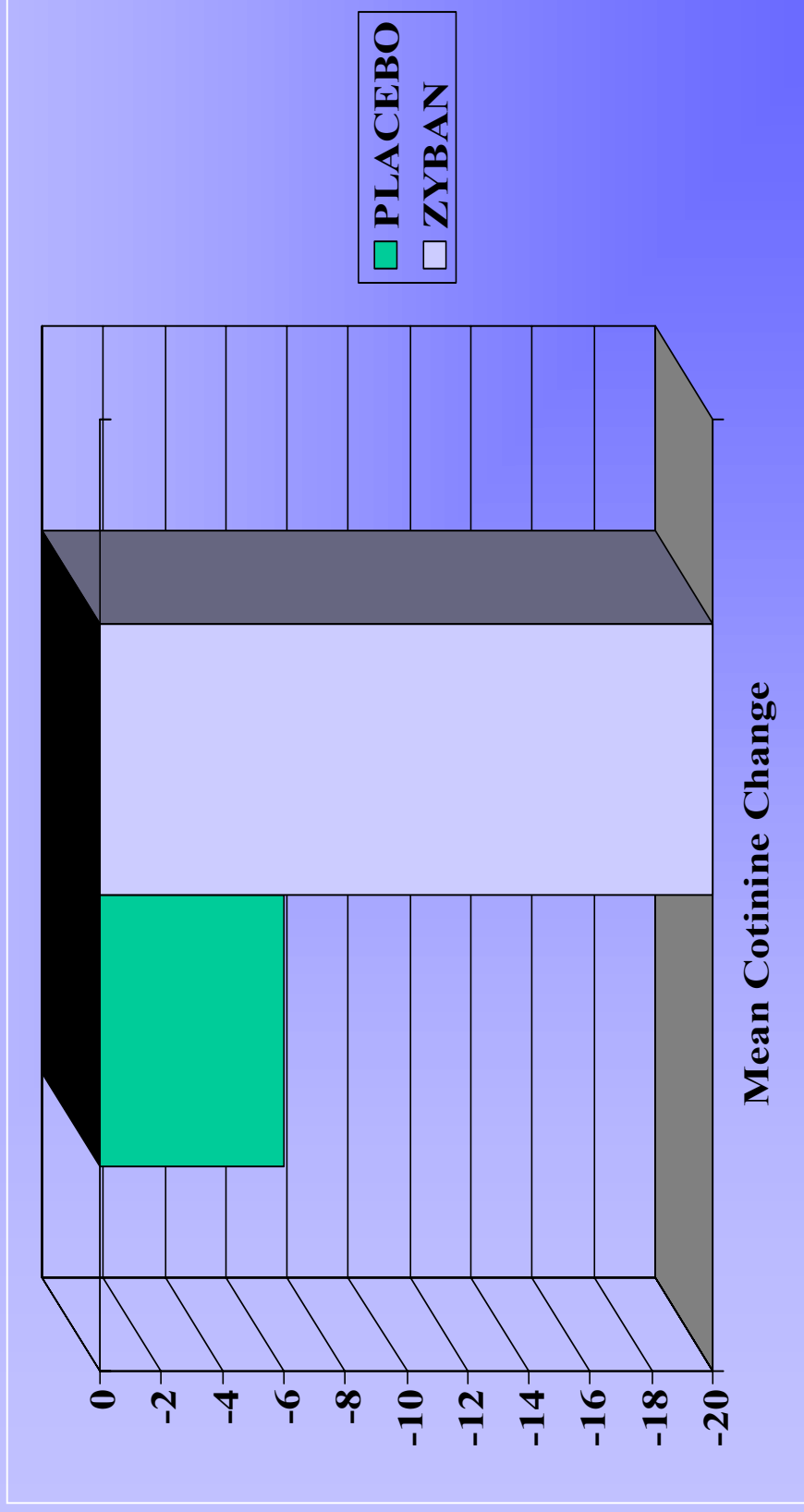
# Reduction to Cessation Study: Bupropion Increases Motivation to Quit



# Bupropion Helps Unmotivated Smokers Quit



# Bupropion Helps Smokers Cut Down Before Quitting



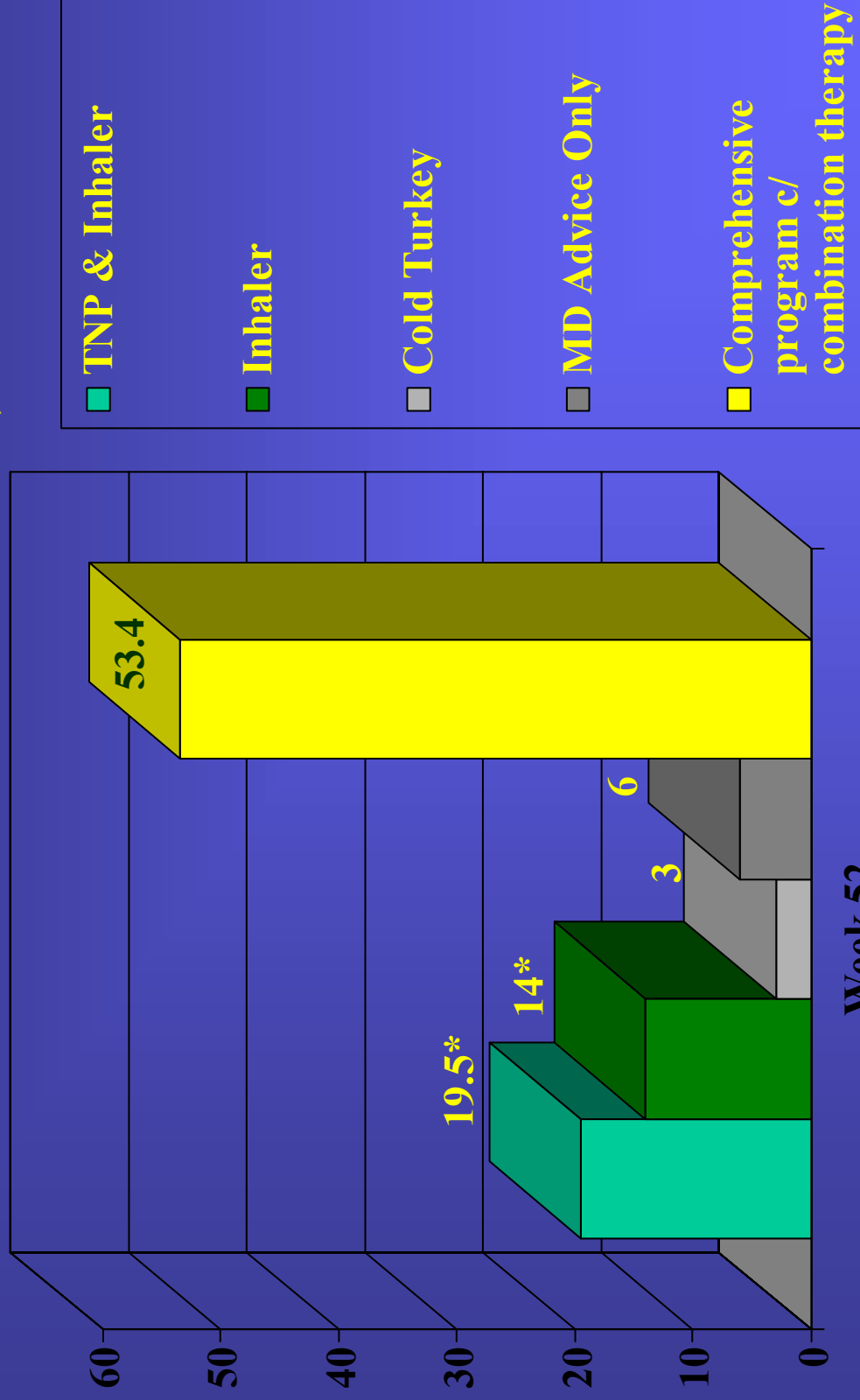
# Bupropion HCL

- First non-nicotine tablet for tobacco dependence
- Active ingredient in Zyban and Wellbutrin
- Can be used while the patient is still smoking
- Mechanism of action: the biochemistry of addiction
- Appears to “increase willpower and motivation” to quit

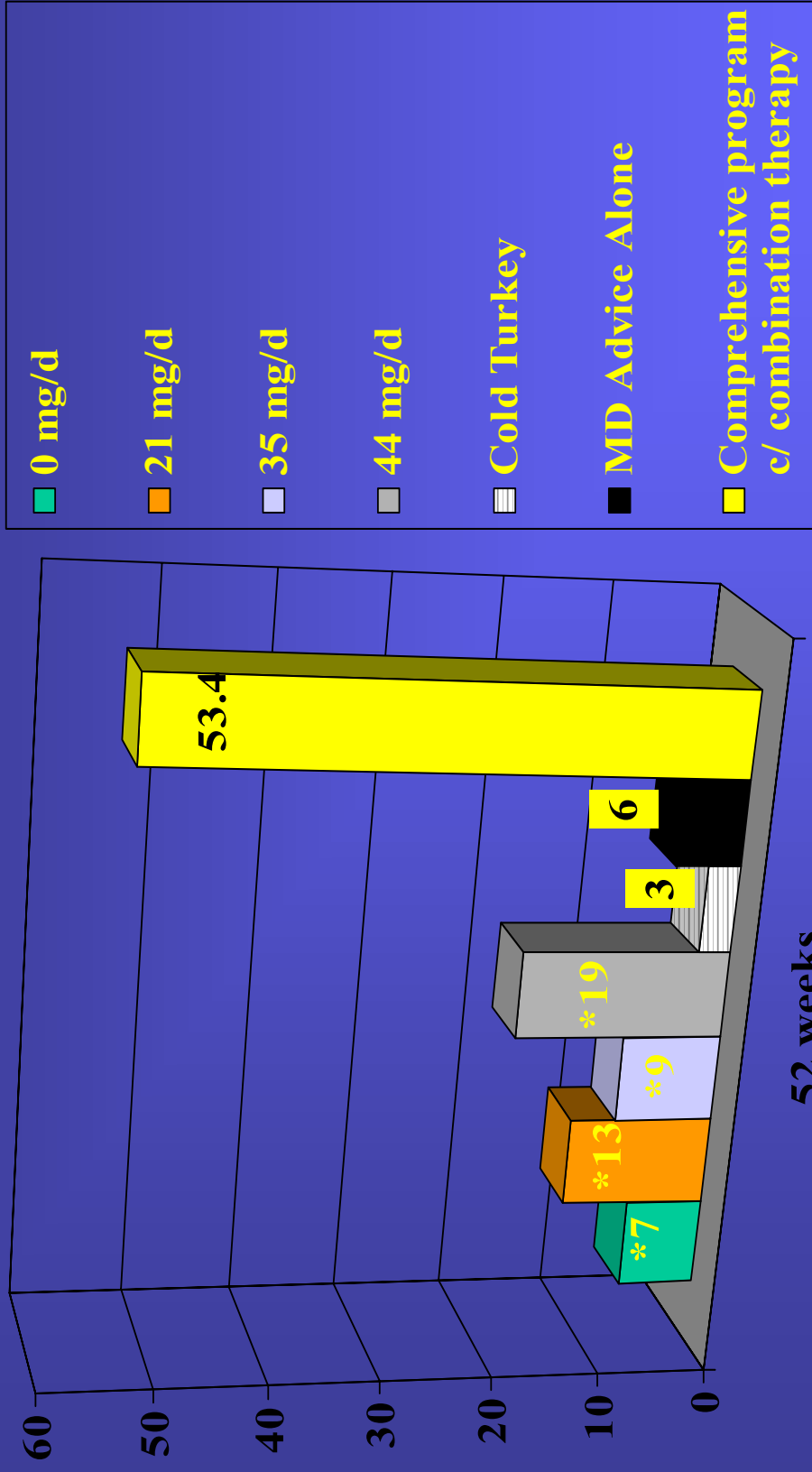


# Combination Treatment: Nicotrol Inhaler and Nicotine Patch

\*Bohadana et al Arch Intern Med Vol 160, 2000



# Effectiveness of higher dose nicotine patches



\*Hughes et al; SRNT 1999

# Combination Therapy

---

- More than one NRT (i.e: Nicotine patch with one or more self-administered form of NRT or more than one self-administered NRT (gum, nasal spray, inhaler, lozenge) or Bupropion with one or more NRTs
- More efficacious than a single form of nicotine replacement
- Patients should use combined treatments if they are unable to quit using a single type of first-line pharmacotherapy
- Recommended by federal treatment guidelines
- **StopSmokingDoctors.com professionals have extensive experience in tailoring combination therapies to individual smokers, especially highly addicted smokers and smokers who have been unsuccessful in the past**