



Pharmacologic Therapy for Tobacco Use & Dependence

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Learning Objectives

- Understand the 7 ‘first line’ medications approved by the FDA.
- Understand the evidence for expanded NRT dose ranges and combinations
- Understand the most effective use of NRT, Varenicline, and bupropion, and considerations in selected special populations

Pharmacotherapy

Give patient a menu of options

Medication options

Your treatment specialist or other health care provider can help complete this page and discuss recommendations with you.



Nicotine patch

Recommendations:

___ mg, daily for ___ weeks
 ___ mg, daily for ___ weeks
 ___ mg, daily for ___ weeks
 ___ mg, daily for ___ weeks
 ___ mg, daily for ___ weeks
 ___ mg, daily for ___ weeks

The suggested taper schedule above can be adjusted if necessary.

Comments:



Nicotine gum

Recommendations:

2 mg
 4 mg

Comments:



Nicotine lozenge

Recommendations:

2 mg
 4 mg

Comments:



Nicotine inhaler

Recommendations:

Comments:



Nicotine nasal spray

Recommendations:

Comments:



Bupropion

Recommendations:

Comments:

Other medications

Recommendations:

Varenicline

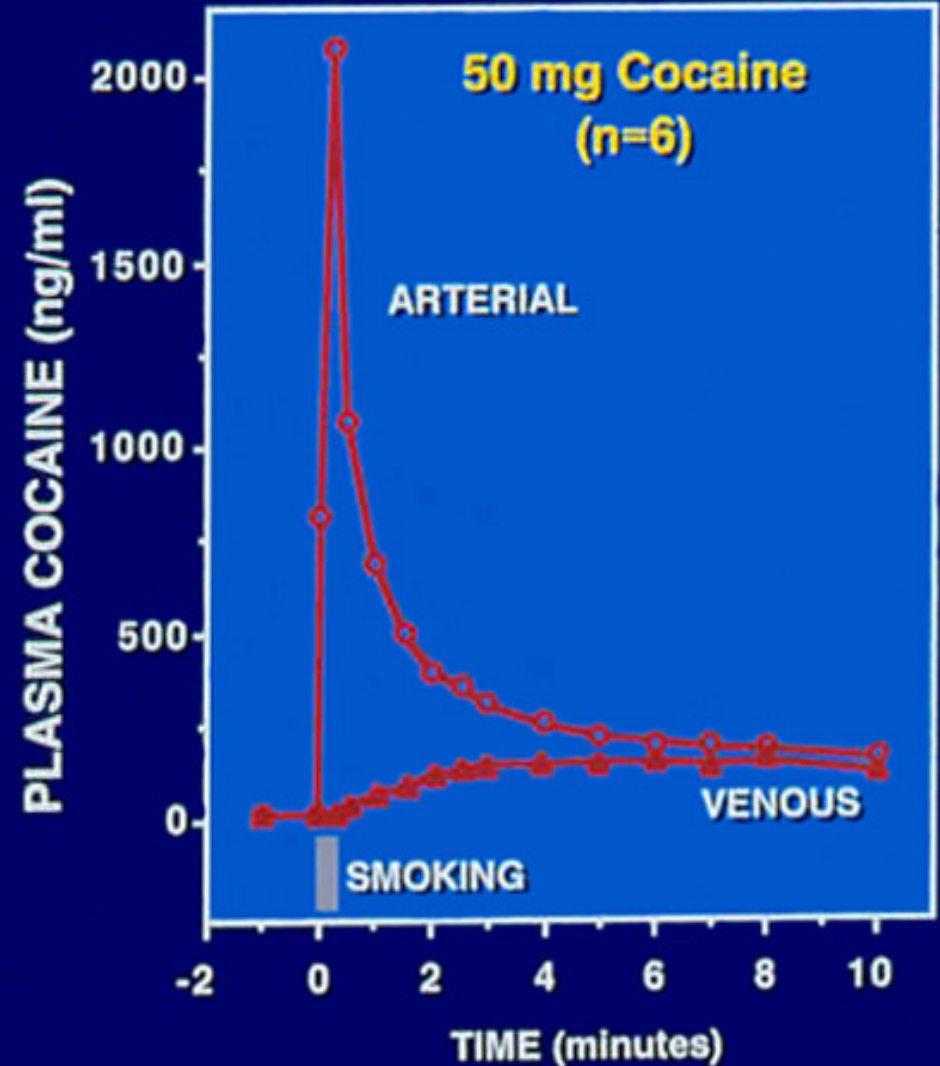
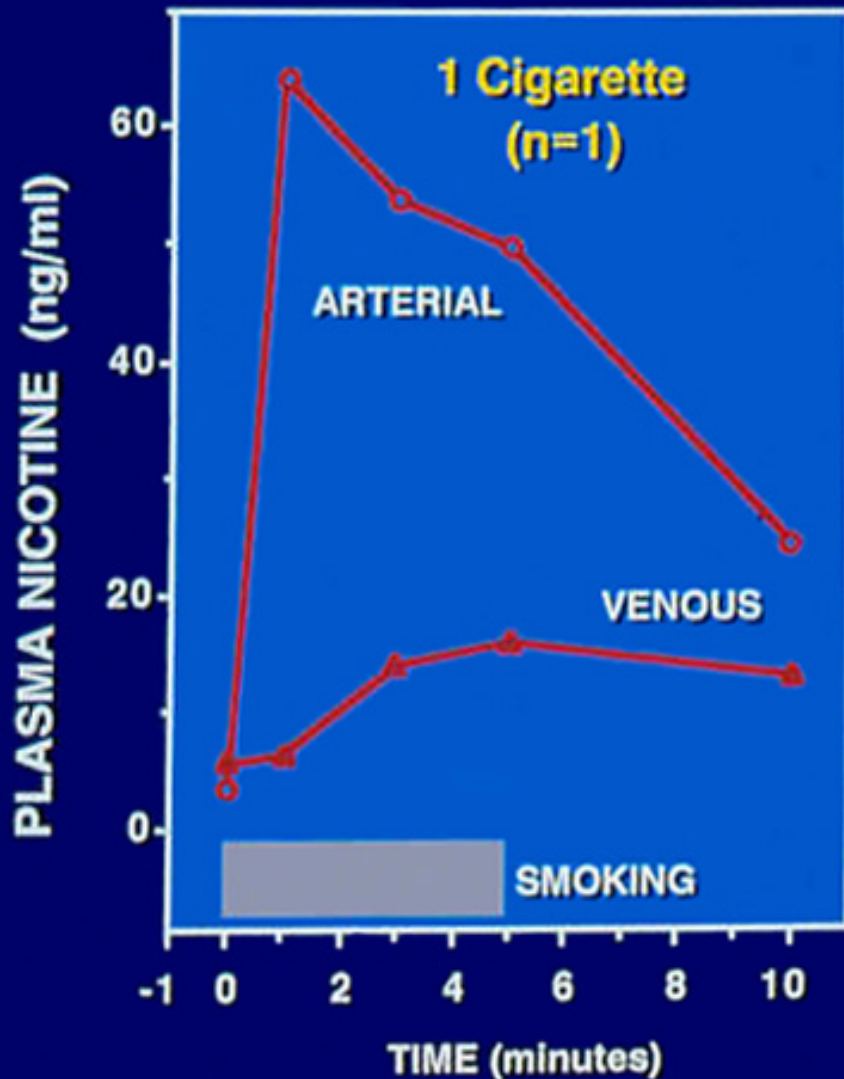
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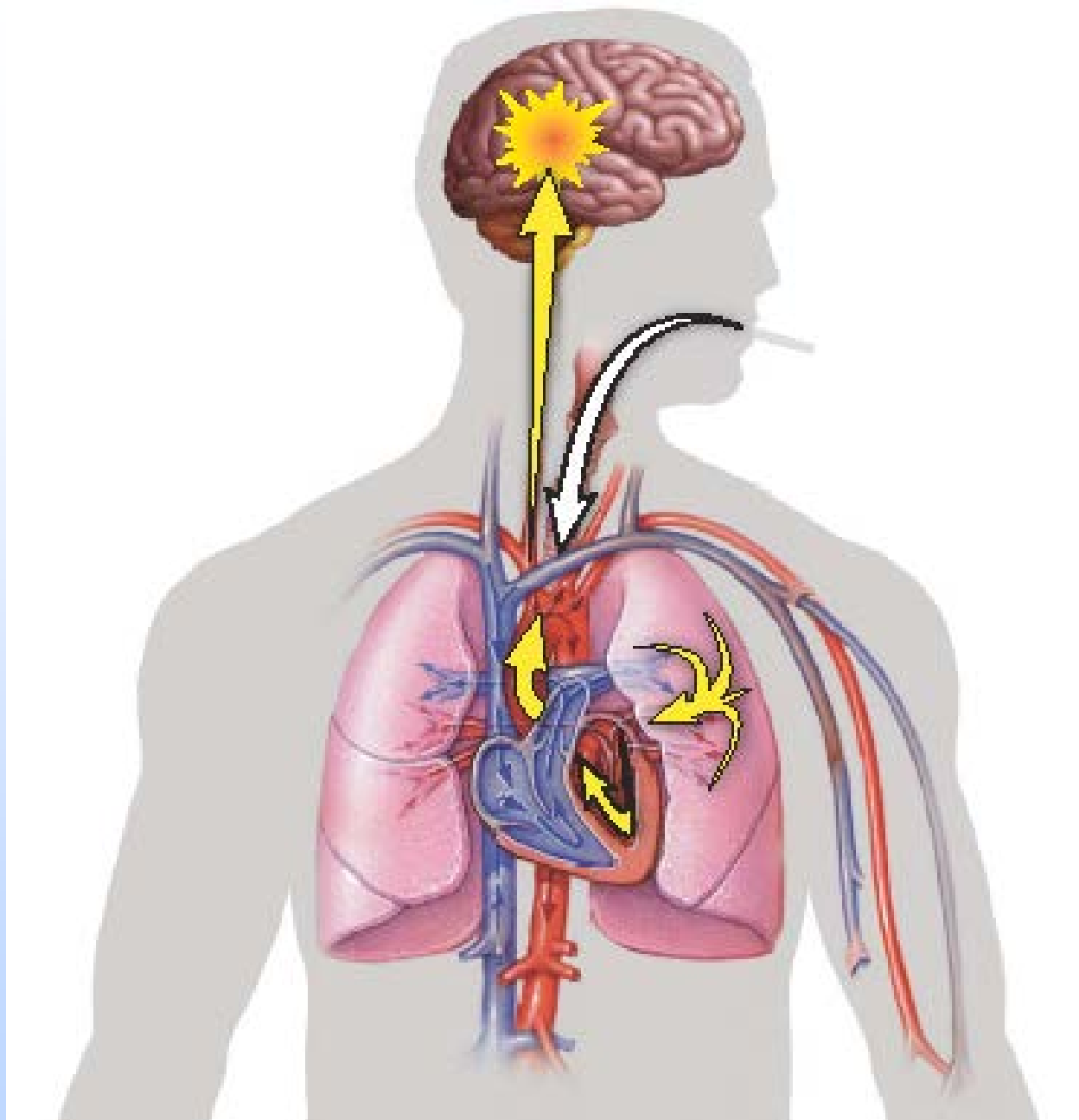


Before using any of these medications, review appropriate use and possible side effects with your health care provider. Ask how and when to use them. If you experience side effects from your medications, check promptly with your health care provider for advice.

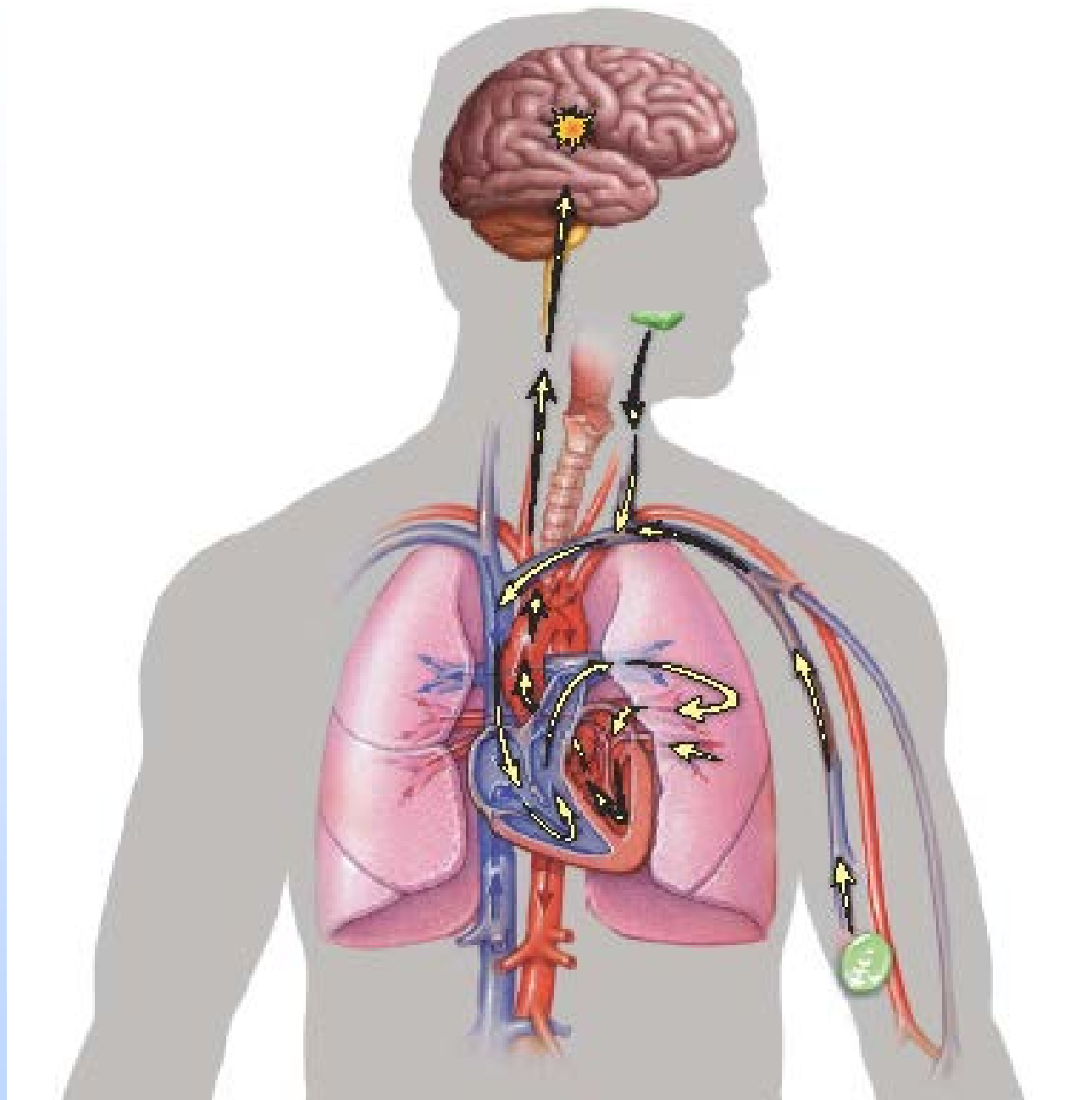
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Plasma Concentration after Smoking

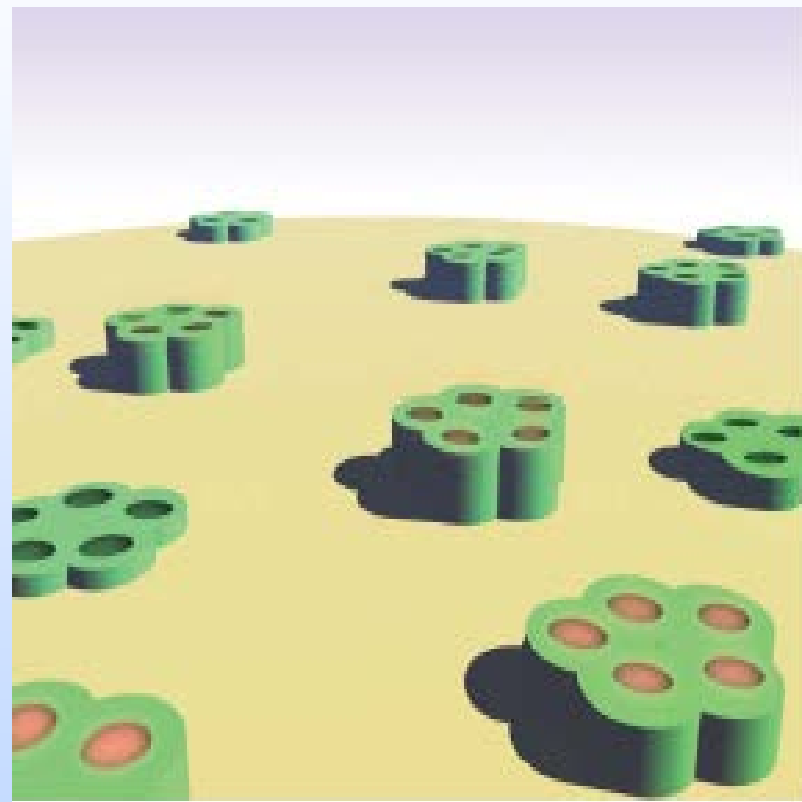
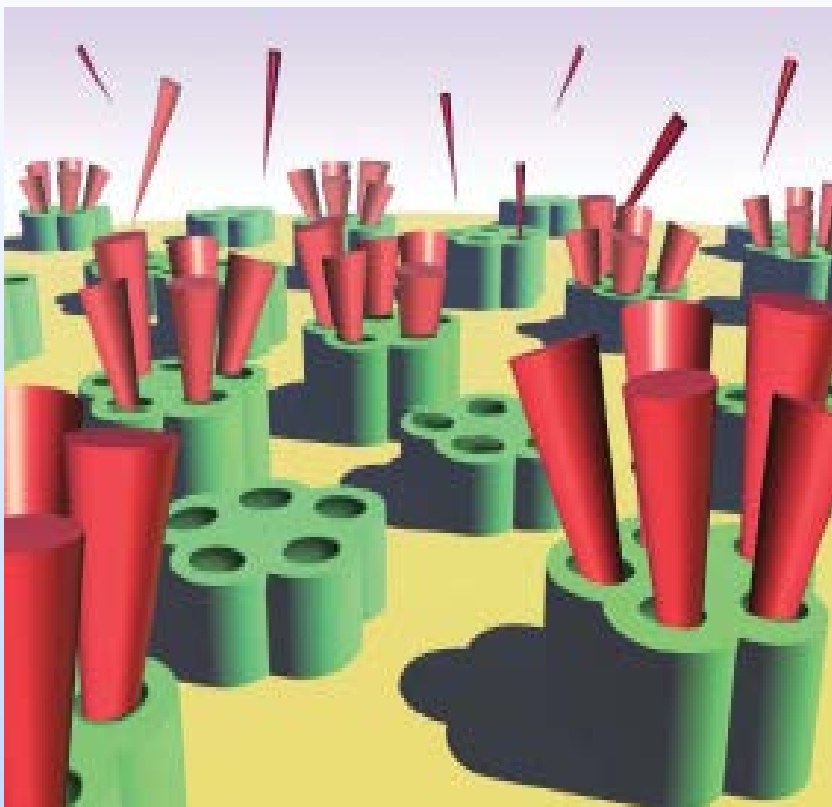




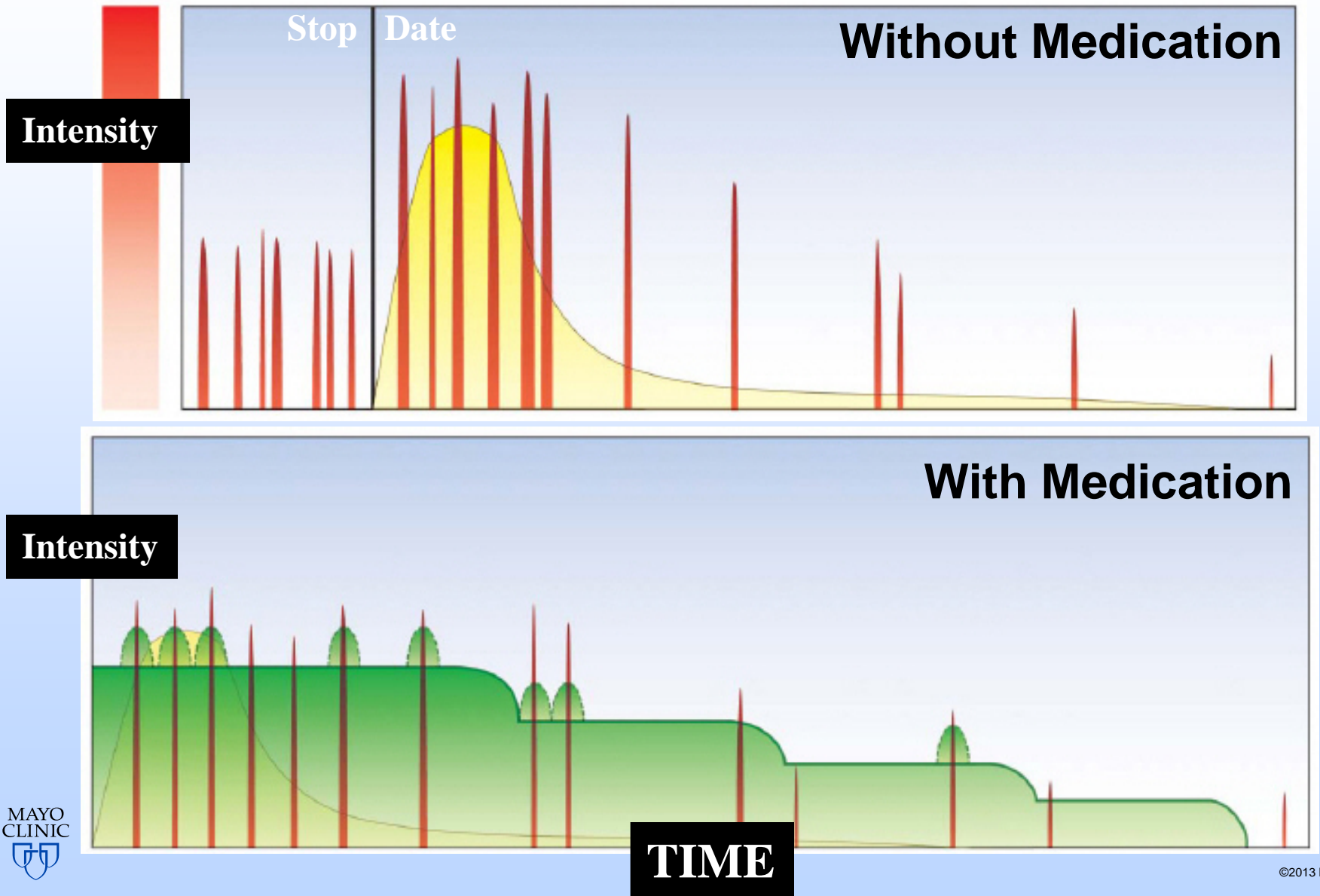
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Medication:



Pharmacotherapy

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Nicotine nasal spray

Recommendations:

Comments:



Bupropion

Recommendations:

Comments:

Other medications

Recommendations:

Varenicline

Comments:



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History of Pharmacotherapy

- Nicotine polacrilex (gum) 1982
- Nicotine patch 1992
- Nicotine patch and gum OTC 1996
- Bupropion SR 1997
- Nicotine lozenge OTC 2002
- Varenicline 2006

Pharmacotherapies for smoking cessation: a meta-analysis of randomized controlled trials

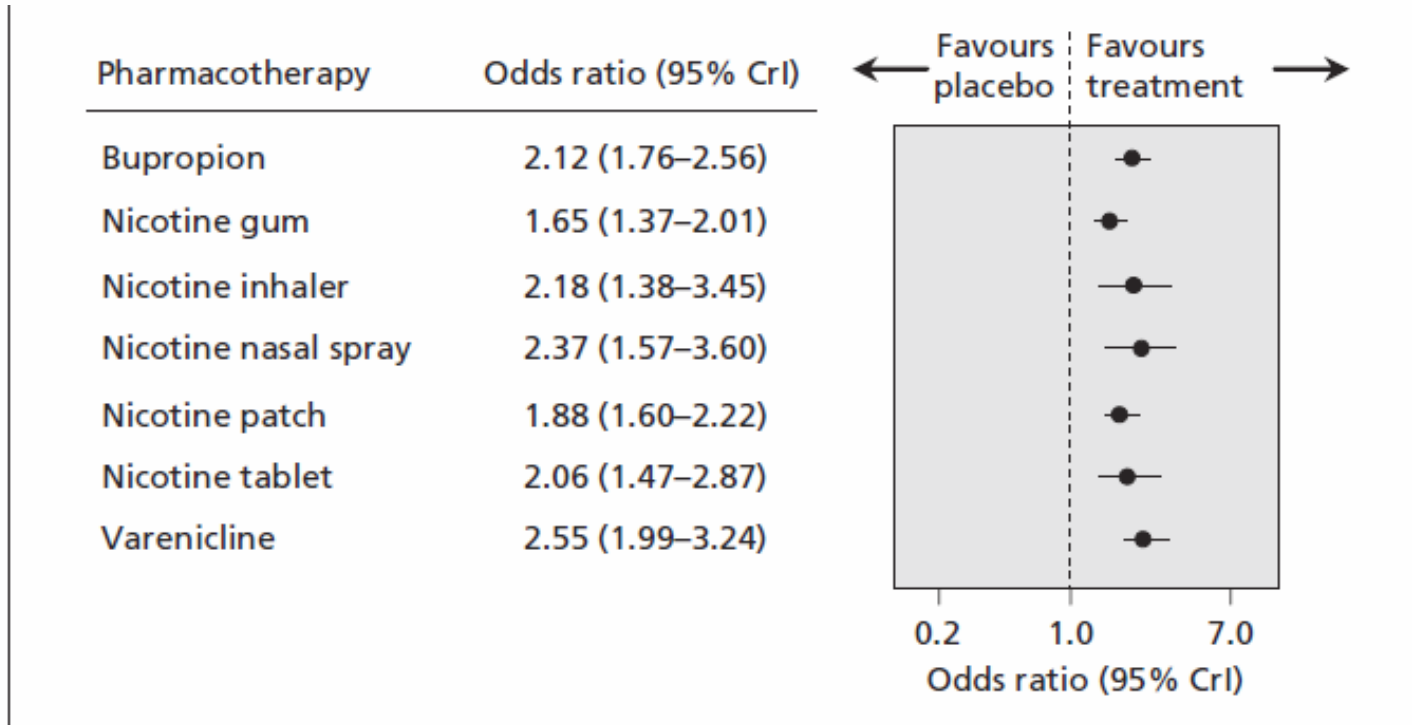


Figure 6: Summary estimates of the effect of pharmacotherapies for smoking cessation on the odds of smoking cessation. Smoking cessation is defined by the most rigorous criterion of abstinence (see Figure 2 caption for definition and ranking). Data have been adjusted for mean age, sex and mean number of cigarettes per day. CrI = credible interval.

Eisenberg MJ, et al. CMAJ 2008; 179:135-144

Populations for Special Consideration

- Individuals with potential contraindications for medication use
- Pregnant women
- Breast feeding women
- Adolescents
- Individuals who smoke less than 10 cpd

U.S. Department of Health and Human Services, June 2000. [Treating Tobacco Use and Dependence](#)

Factors for Consideration

- Contraindications
- Patient preference
- Previous patient experience
- Patient characteristics

Effectiveness and Abstinence Rates Compared With Placebo or Nicotine Patch at 6-Months

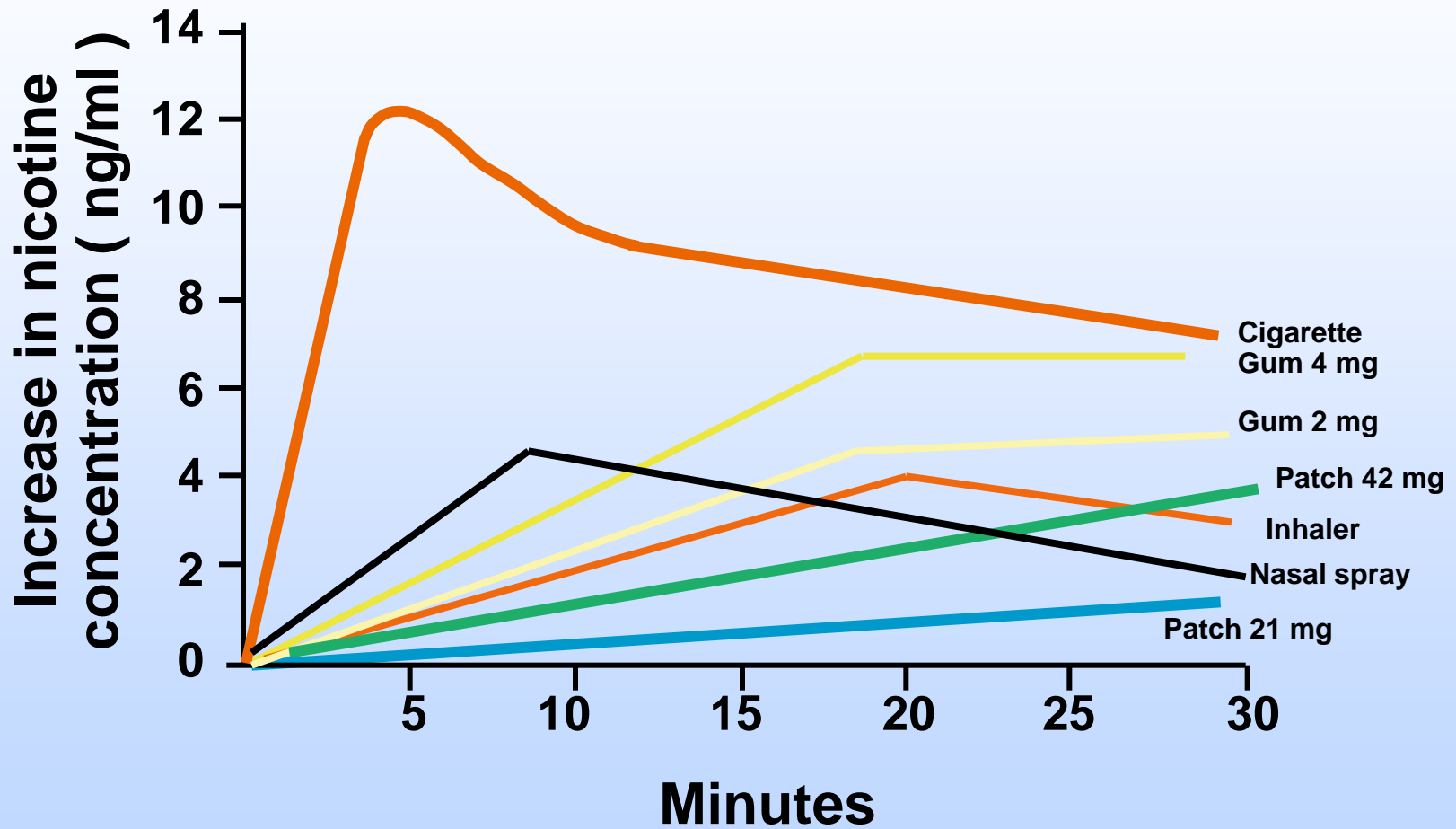
Medication	Arms	Estimated abstinence rate (95% CI)	Estimated OR vs Placebo (95% CI)	Estimated OR vs Nicotine patch* (95% CI)
<i>Monotherapies</i>				
Varenicline (2 mg/d)	5	33.2 (28.9-37.8)	3.1 (2.5-3.8)	1.6 (1.3-2.0)
Nicotine nasal spray	4	26.7 (21.5-32.7)	2.3 (1.7-3.0)	1.2 (0.9-1.6)
High-dose nicotine patch (>25 mg) (includes both standard or long-term duration)	4	26.5 (21.3-32.5)	2.3 (1.7-3.0)	1.2 (0.9-1.6)
Long-term nicotine gum (>14 weeks)	6	26.1 (19.7-33.6)	2.2 (1.5-3.2)	1.2 (0.8-1.7)
Varenicline (1 mg/d)	3	25.4 (19.6-32.2)	2.1 (1.5-3.0)	1.1 (0.8-1.6)
Nicotine inhaler	6	24.8 (19.1-31.6)	2.1 (1.5-2.9)	1.1 (0.8-1.5)
Bupropion SR	26	24.2 (22.2-26.4)	2.0 (1.8-2.2)	1.0 (0.9-1.2)
Nicotine patch (6-14 weeks)	32	23.4 (21.3-25.8)	1.9 (1.7-2.2)	1.0
Long-term nicotine patch (>14 weeks)	10	23.7 (21.0-26.6)	1.9 (1.7-2.3)	1.0 (0.9-1.2)
Nortriptyline	5	22.5 (16.8-29.4)	1.8 (1.3-2.6)	0.9 (0.6-1.4)
Nicotine gum (6-14 weeks)	15	19.0 (16.5-21.9)	1.5 (1.2-1.7)	0.8 (0.6-1.0)



When used properly, the
nicotine patch is 100%
effective.

©1992 Modern Times Syndicate

Smoking produces much higher nicotine levels and much more rapidly than NRT

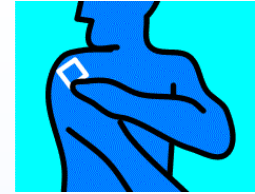


Source: Balfour DJ & Fagerström KO. Pharmacol Ther 1996 72:51-81.

Optimizing Pharmacotherapy

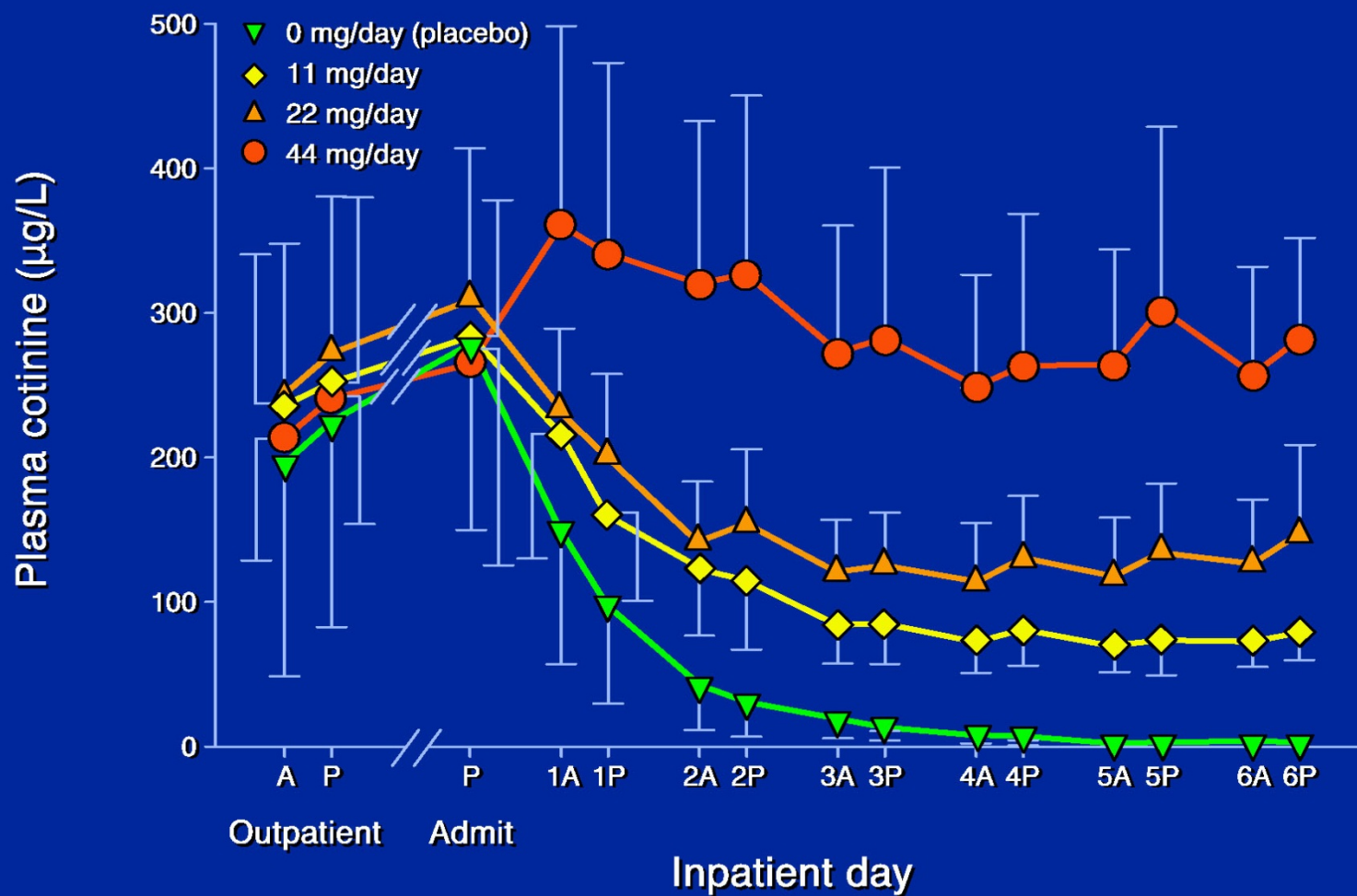
- Goals of treatment
 - Withdrawal symptom relief
 - Control of cravings/urges
 - Abstinence
- Modification of medication doses may be necessary to achieve these targets
 - Higher doses
 - Multi-drug regimens
 - Longer course of treatment

Nicotine Patch



- Standard: 21mg for 6 weeks, 14mg for 4 weeks, 7mg for 2 weeks
- Evidence for tapering or length of therapy is minimal
- Dose ranging studies suggest 50% of smokers are inadequately treated in this fashion





Dale, et al. *JAMA*, 1995.

Findings from Dose Ranging Study:

- Dose associated with cessation @ 8 weeks ($P = .007$; OR 2.5; 95% CI:1.3-4.9)

	<u>8 weeks</u>	<u>6 months</u>	<u>1 year</u>
11 mg	59%	59%	41%
22 mg	62%	54%	35%
44 mg	100%	78%	67%

Dale, et al. *JAMA*, 1995.

Nicotine Patch Dose

Based on Cotinine and CPD

<u>Cotinine</u>	<u>Cigs per day</u>	<u>Patch dose</u>
<200 ng/ml	< 15	14-21 mg/d
200-300 ng/ml	16-40	21-35 mg/d
>300 ng/ml	> 40	35-42+ mg/d

Nicotine replacement and CVD

- Joseph, et al *NEJM* 1996;335:1792
- 584 subjects with CVD (8 women)
- RCT of nicotine patch for 10 wks
- Primary end points (14 wks f/u)
 - Death, MI, arrest
 - Hospitalized for increased CVD
- Secondary end points

Nicotine replacement and CVD

Joseph, et al study results...

<u>End point</u>	<u>NRT</u>	<u>PBO</u>
Primary:	5.4 %	7.9%
Secondary:	11.9%	9.7%
Total :	16.3%	16.2%
Death(no.):	1	6

Nicotine Gum

- OTC: 2 mg and 4 mg
- Regular, Mint, Orange, other flavors
- “Chew and Park”
- Avoid acidic beverages
- Monotherapy: 10-15/day initially; use 4 mg if first cig. in a.m. is within 30 min.
- Most often used in combination with other NRT



Nicotine Lozenge

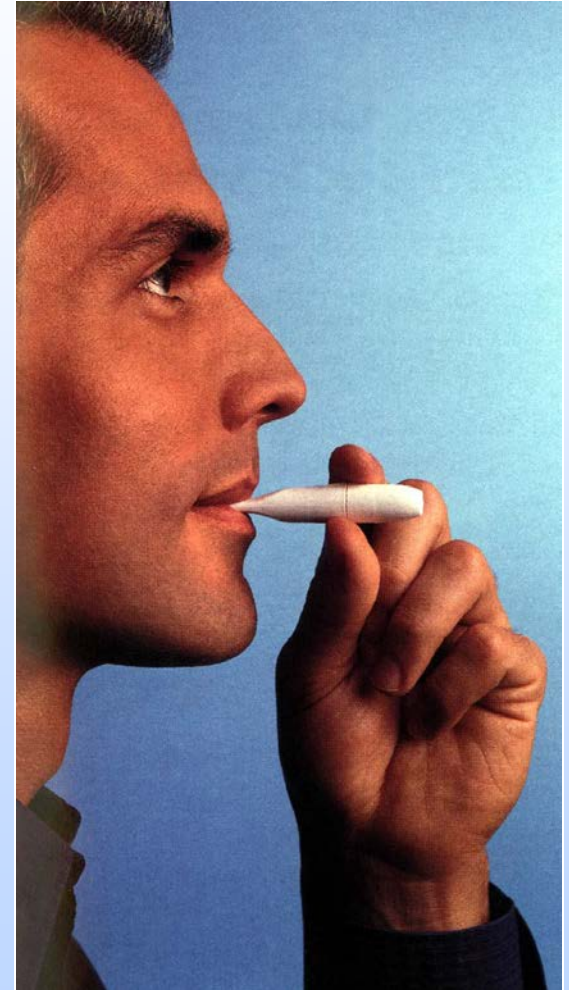
- OTC: 2 mg and 4 mg
- Regular, Mini, Mint, Cherry, other flavors
- Dissolves in mouth over 20-30 minutes
- Avoid acidic beverages
- Not to be chewed or swallowed whole
- Delivers 25% more nicotine than the gum



Nicotine “Inhaler”

Dose Instruction

- Puff on inhaler several times a minute
- Each cartridge will last about 30 minutes of active puffing
- 1 cartridge = as much nicotine as 2-3 cigarettes
- Monotherapy: At least 6 cartridges each day, up to 16/day
- Can be used alone or in combination with other NRT



Nicotine Nasal Spray

- 1 dose = 1 spray in each nostril
- Starting dose: 1 dose 1-2 times/hr, Up to 5 times/hr or 40 times/day
- Most average 14-15 doses/day initially
- Length of Rx: 12 weeks but can be shorter
- Can taper or stop abruptly, as tolerated



Conclusions

- NRT

- Patch dosing matched to CPD is safe and effective
- Combined NRT's are efficacious
- Length of therapy guided by patient response (longer may be better)
- Safe in smokers with CHD
- May be safe in pregnant smokers



Bupropion SR

Wellbutrin
Zyban



Mechanism of Action

- Blocks reuptake of NE and DA
- Increased DA in the mesolimbic “reward center” mimics nicotine
- Uncertain of NE role in smoking cessation
- May act as a nicotinic receptor blocker

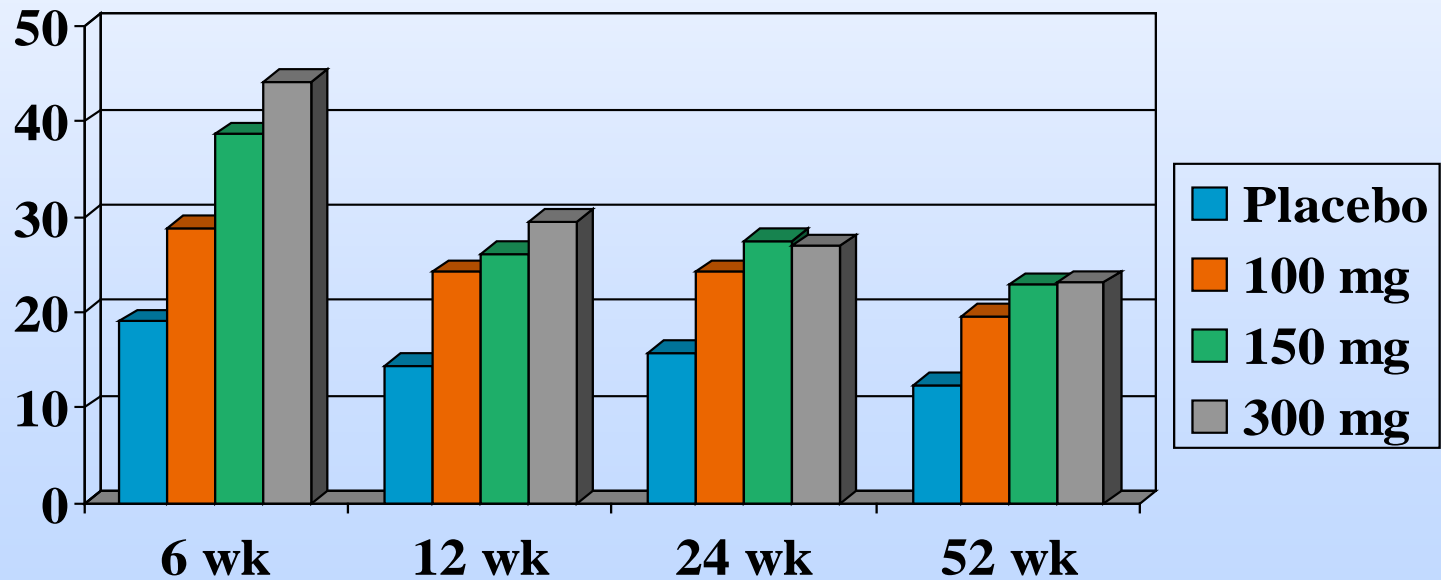
Combination NRT Compared With Single Agent NRT

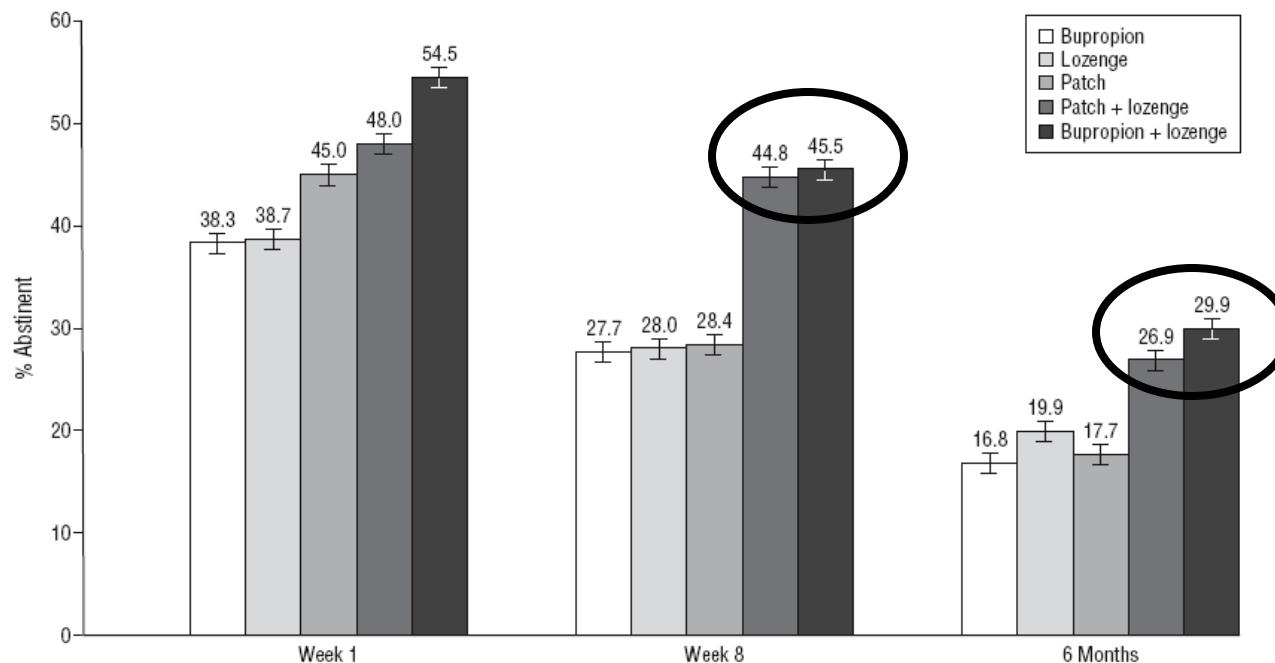
- Nicotine patch + short-acting NRT
 - Patch provides steady baseline
 - NG, NL NNS, NI respond to urges
- Withdrawal may be improved
- Overall abstinence rates at 6 mos. better
 - OR 1.35 (95% CI 1.11-1.63)*

*Cochrane Database of Systematic Reviews 2009

Bupropion SR (Zyban)

- Point-prevalence smoking cessation (%)
(Placebo vs 150 mg and 300 mg $p \leq 0.02$ at all points)

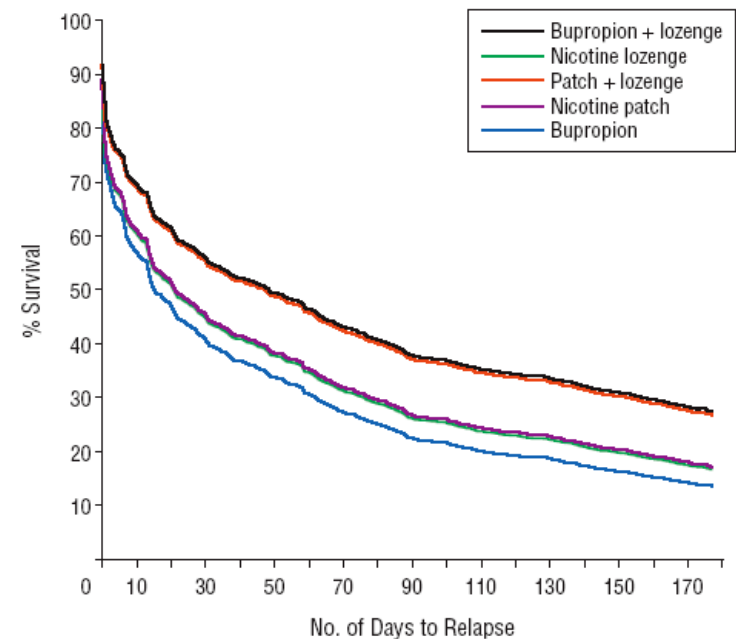




COMBINATION THERAPY

- RCT of 1346 smokers recruited from 12 primary care clinics in Wisconsin
- Received 1 of 5 active treatments for 8 weeks
- Referred for counseling via telephone “quitline”
- 7-day point prevalence at 8 wks and 6 months

Smith SS, et al. Arch Intern Med 2009;169:2148-55



Common adverse events reported in 40 controlled clinical trials of bupropion SR

<u>AE</u>	<u>Mean %</u>	<u>Range</u>	<u>Studies</u>
Insomnia	32.3	(10 to 53)	25
Dry mouth	23.9	(6 to 62)	17
Headache	21.5	(6 to 56)	9
Diarrhea	17.5	(6 to 50)	5
Anxiety	20.3	(10 to 31)	4
Nausea	19.8	(10 to 44)	5

Bupropion Efficacy in Populations

- Psychiatric comorbidity (PTSD, schizophrenia, on SSRI for MDD)
- Medical comorbidity (COPD, CHD)
- Urban African-Americans
- Multiple general populations
- Overall efficacy (36 RCT's and over 11,000 subjects) is OR 1.69 (95% CI 1.53-1.85)-Cochrane Database 2007

Bupropion: Seizure Screen

- Known seizure history: epilepsy, febrile seizure, withdrawal seizure
- Structural brain lesion: tumor, stroke, previous brain surgery
- Drugs that lower seizure threshold: phenothiazines, benzodiazepines, theophylline, ethanol
- Anorexia/Bulimia
- Significant head trauma: prolonged LOC, skull fracture, intracranial bleeding



Bupropion: Boxed Warning (July 2009)

“Serious neuropsychiatric events, including depression, suicidal ideation, suicide attempt, and completed suicide, have been reported in patients with and without pre-existing psychiatric disease who were taking bupropion for smoking cessation; some experienced worsening of their psychiatric illnesses. All patients should be observed for changes in behavior, hostility, agitation, depressed mood, and suicide-related events, including ideation, behavior, and attempted suicide. The patient should stop taking bupropion and contact a healthcare provider immediately if any neuropsychiatric behavior that is not typical for the patient is observed, or if the patient develops suicidal ideation or suicidal behavior. This risk should be weighed against the benefits of its use.”

Bupropion/Patch Combination

Abstinence at 12 mos...

- Placebo 15.6%
- NP alone 16.4%
- Bupropion 30.3%
- Bupropion plus NP 35.5%

Conclusions

- **Bupropion**
- Safe and effective in most populations at 300mg per day
- Increased efficacy combined with NP
- Can be safely combined with SSRI's
- Attenuates post-cessation weight gain
- Safe in smokers with medical comorbidity
- May be safe in pregnancy

Varenicline

- Marketed as Chantix®
- Prescription only
- An agonist—acts like nicotine to reduce withdrawal and cravings—but also an antagonist—blocking the effects of nicotine and reducing its reinforcing (addictive) properties.
- Patients begin use while still smoking
- Dosing

Day 1 to day 3: 0.5 mg tablet, once per day

Day 4 to day 7: 0.5 mg tablet twice per day (a.m. & p.m.)

Day 8 to end of tx: 1 mg tablet twice per day (a.m. & p.m.)

- Duration of use: 6 months

Chantix

- If pt answers “yes” to any of the following, bring to physician’s attention:
 - *Are you pregnant or breastfeeding?*
 - *Do you have any history of kidney disease?*
 - *Have you ever had an adverse reaction (severe rash or swelling of face or tongue) from using varenicline in the past?*
 - *Are you less than 18 years of age?*



Effectiveness and abstinence rates of selected medications and combinations:

Medication	Number of arms	Estimated odds ratio (95% confidence)	Estimated abstinence rate (95% confidence)
Placebo	80	1.0	13.8
Nicotine patch (6-14 weeks)	32	1.9 (1.7-2.2)	23.4 (21.3-25.8)
High dose patch (> 25 mg.)	4	2.3 (1.7-3.0)	26.5 (21.3-32.5)
Patch + ad-lib gum or spray	3	3.6 (2.5-5.2)	36.5 (28.6-45.3)
Varenicline (2 mg/day)	5	3.1 (2.5-3.8)	33.2 (28.9-37.8)

The “off-label” Dilemma: When Guidelines and Labels Collide



PRESCRIBING INFORMATION

ZYBAN[®] **(bupropion hydrochloride)** **Sustained-Release Tablets**

WARNING

Serious neuropsychiatric events, including but not limited to depression, suicidal ideation, suicide attempt, and completed suicide have been reported in patients taking ZYBAN for smoking cessation. Some cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking ZYBAN who continued to smoke.

CHANTIX[®]

(varenicline) Tablets

WARNING:

Serious neuropsychiatric events, including, but not limited to depression, suicidal ideation, suicide attempt and completed suicide have been reported in patients taking CHANTIX. Some reported cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking CHANTIX who continued to smoke.

Labels Lag Behind Evidence

- FDA approved label
 - NRT for 8 weeks
 - Single agents only
 - Patch 21 mg maximum
 - Bupropion alone
 - Never smoke while using NRT
- UPSPHS Guideline-2008
 - NRT for up to 6 months
 - Combined NRT
 - Higher patch dose
 - Bupropion + NRT
- Published research
 - NRT to reduce smoking
 - Varenicline + short acting NRT
 - Varenicline + bupropion

“But can you tell me
are the medications safe?”



- No one asks me:
“Is smoking safe?”

Smoking Kills More Americans Each Year Than Alcohol, Cocaine, Crack, Heroin, Homicide, Suicide, Car Accidents, Fires and AIDS combined.

Approximate Number of Deaths

Smoking	434,000
Alcohol (incl. Drunk driving)	105,000
Car Accidents (incl. Drunk Driving)	49,000
AIDS	31,000
Suicide	31,000
Homicide	22,000
Fires	4,000
Cocaine/Crack	3,300
Heroin/Morphine	2,400



Causes of Death **Smoking vs. Other**

