Pharmacologic Therapy for Tobacco Use & Dependence

Nicotine Replacement Therapy (NRT) and Bupropion

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Learning Objectives

- Understand the evidence for expanded NRT dose ranges and combinations
- Develop detailed understanding of the side effects and important interactions of the NRT and bupropion
- Understand the most effective use of NRT and bupropion, and considerations in selected special populations
- Apply knowledge to patient cases

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Pharmacologic Therapy for Tobacco Dependence

- Background
- Review specific medications
  - NRT (patch and combinations)
  - Bupropion SR
- Treatment of special populations

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Trends in smoking prevalence

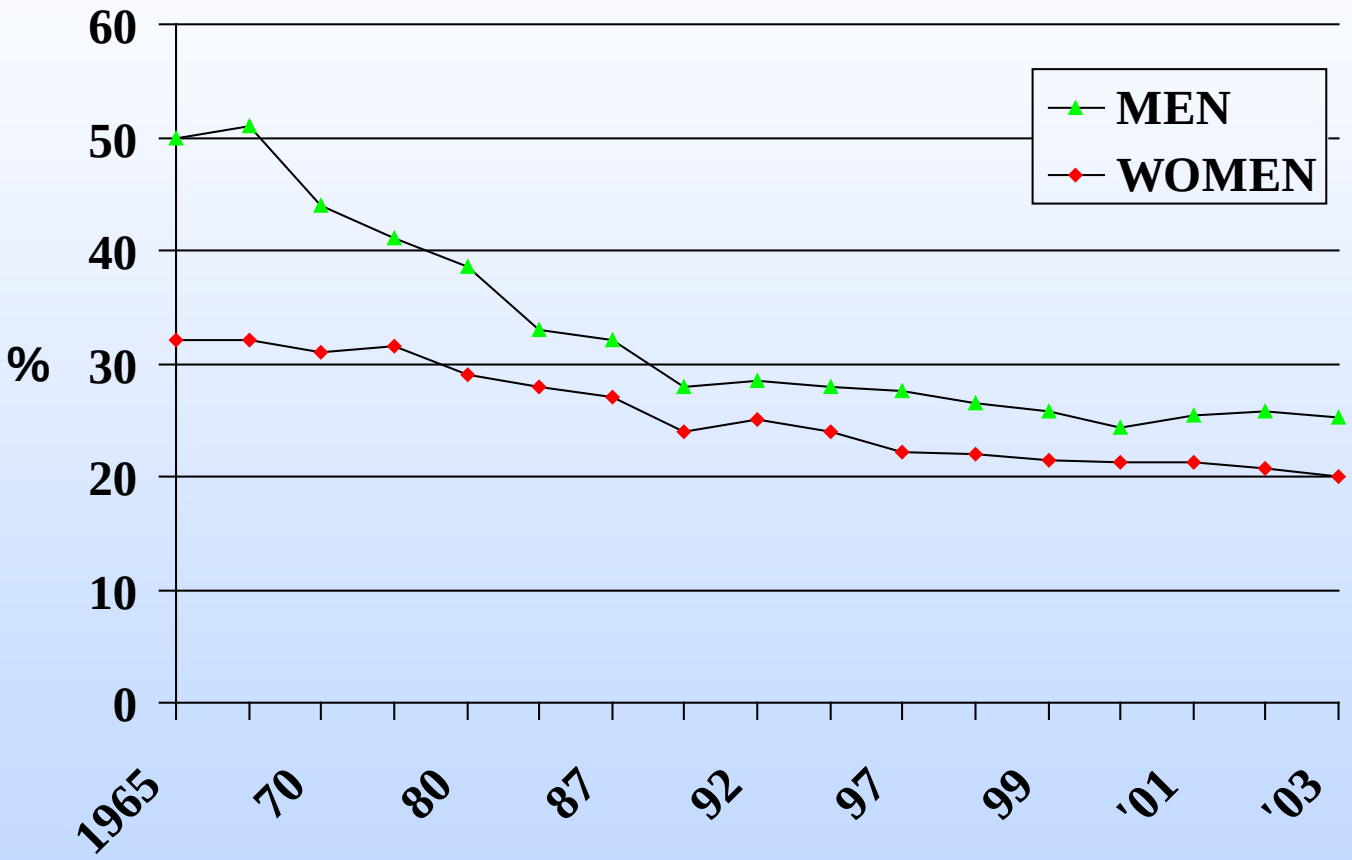
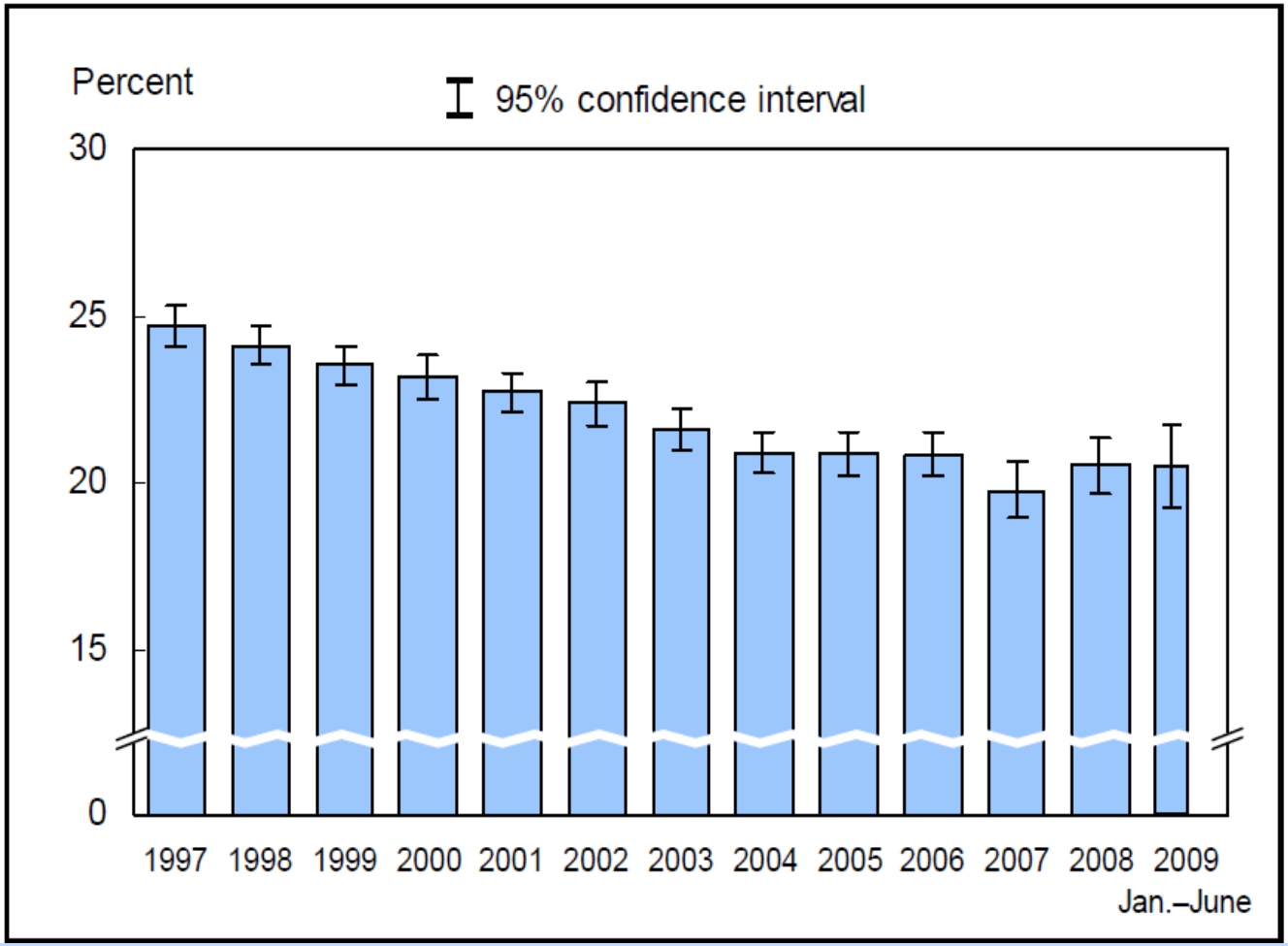


Figure 8.1. Prevalence of current smoking among adults aged 18 and over: United States, 1997-June 2009



http://www.cdc.gov/nchs/data/nhis/earlyrelease/200912_08.pdf

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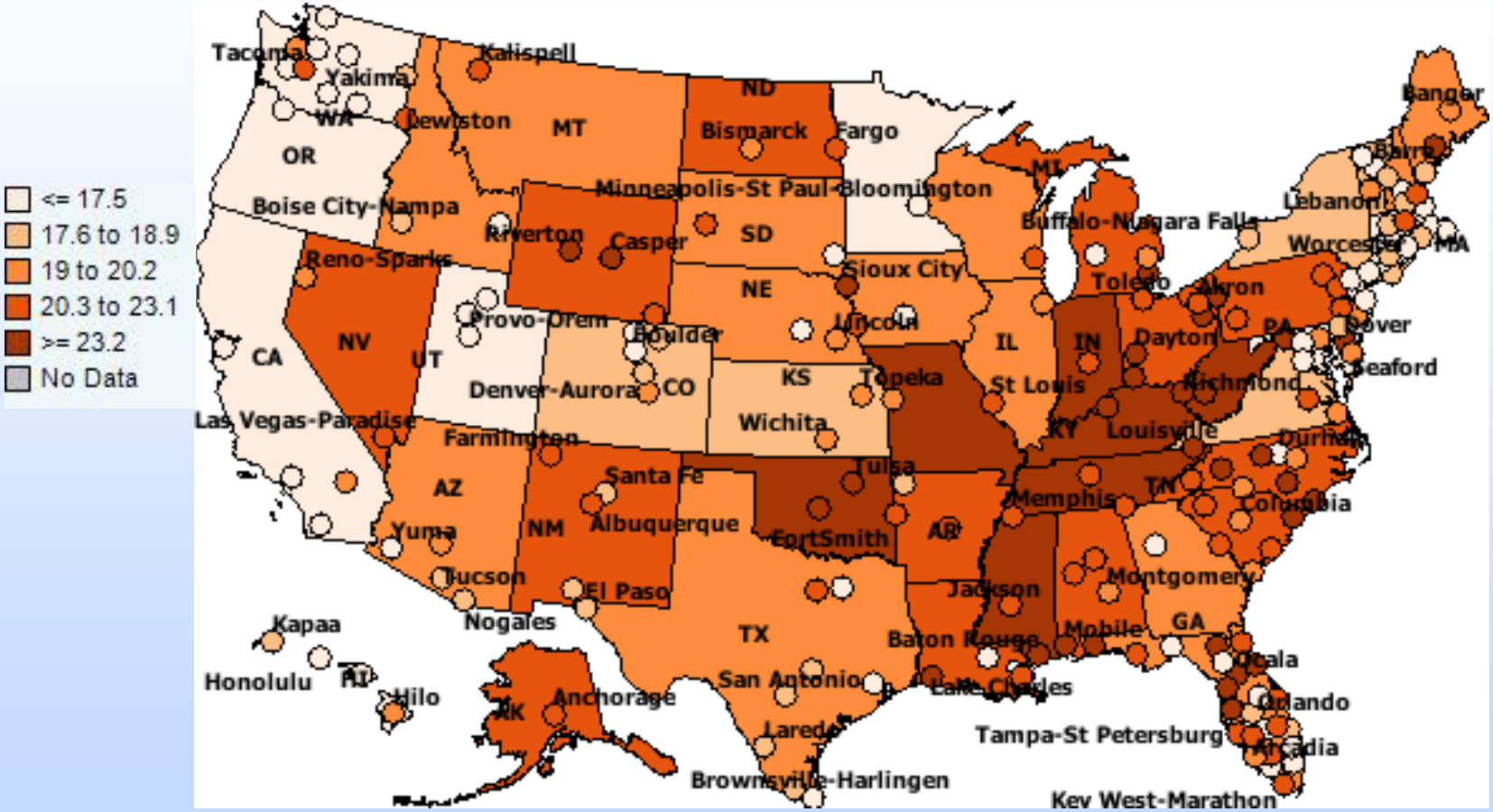
US smoking prevalence 2007



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)
Monotherapies				
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)**

* Quit rates can double with medications

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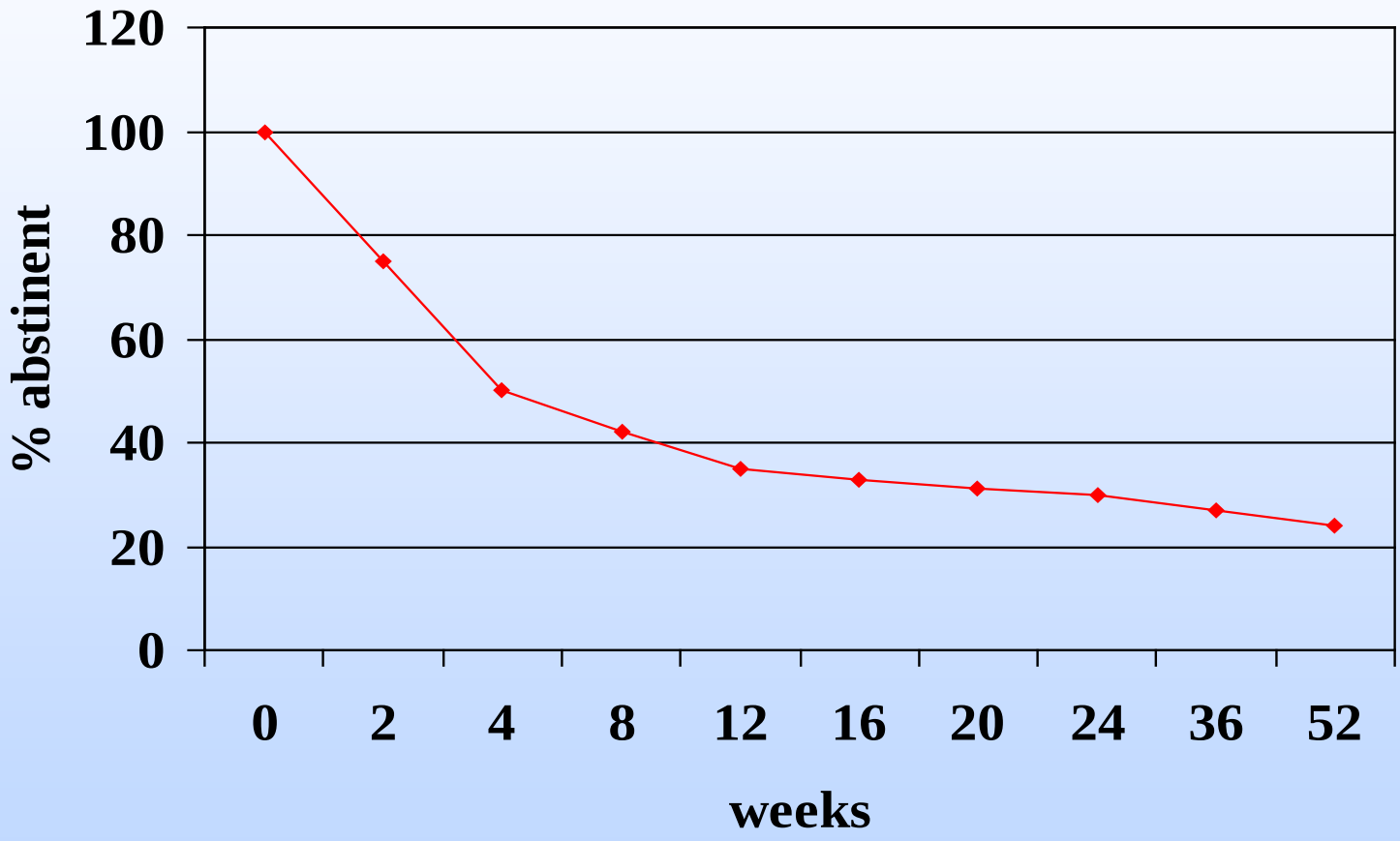
Relapse after cessation



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Hardening through comorbidity

- As smoking prevalence falls the percent of smokers with…
  - Serious psychiatric disease
  - Alcohol abuse
  - Other drug abuse
- … steadily rises

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What new drug treatment approaches to try?

- Alternative dosing strategies
- Combination treatment using first-line medications
- Novel therapies

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When used properly, the nicotine patch is 100% effective.
©1992 Modern Times Syndicate

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

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Withdrawal Symptoms

- Depressed mood
- Insomnia
- Irritability, frustration or anger
- Anxiety
- Difficulty concentrating
- Restlessness
- Shakiness
- Increased appetite or weight gain

American Psychiatric Association. (1994). Diagnostic and Statistical Manual of Mental Disorders (4th ed.)

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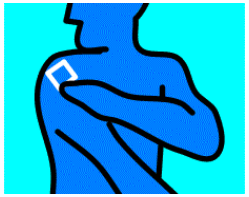
Nicotine Replacement

Expanded treatment options

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

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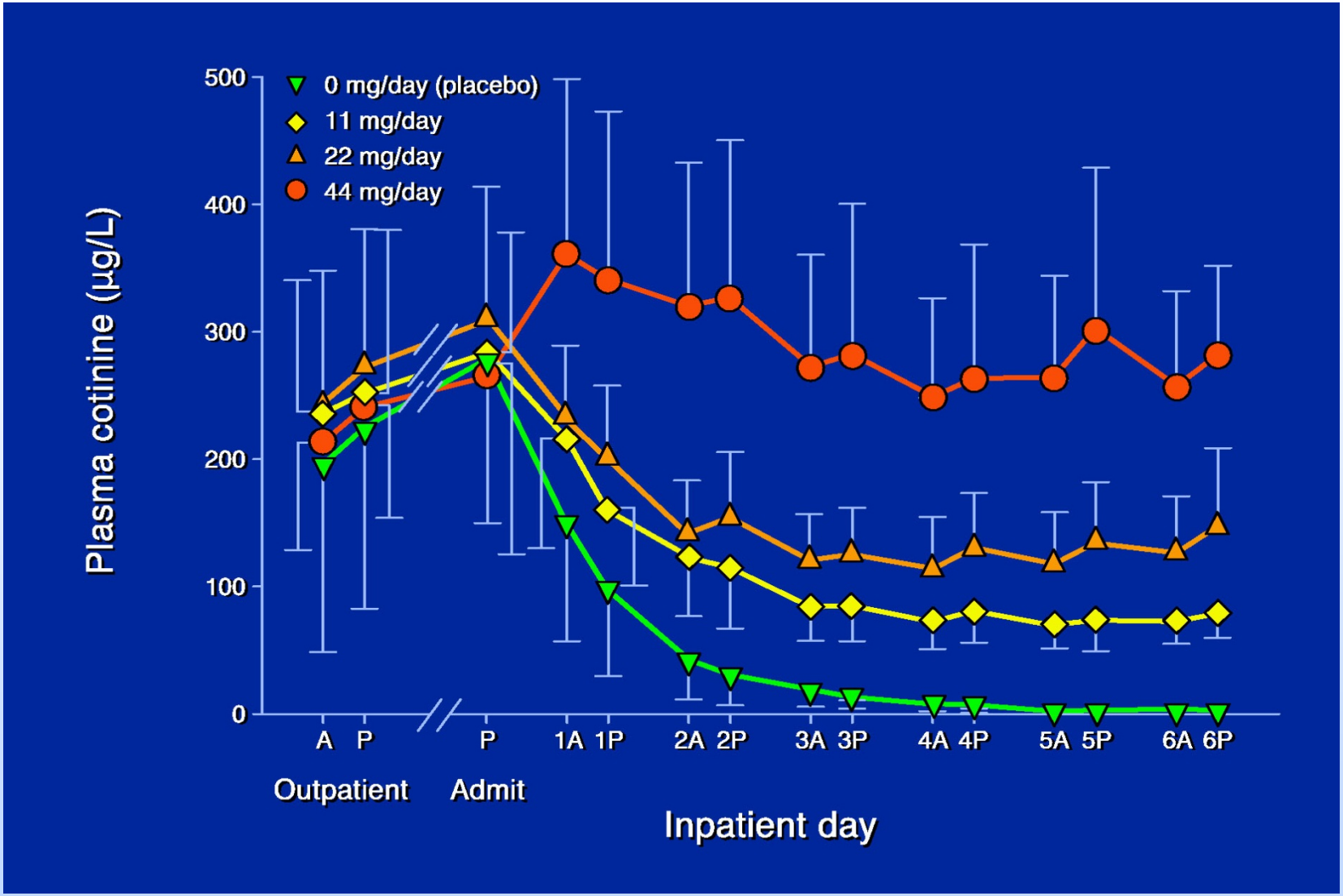

Dale, et al. *JAMA*, 1995.

Findings from Dose Ranging Study:

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

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

Dale, et al. *JAMA*, 1995.

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Nicotine Patch Dose
Based on Cotinine and CPD

Cotinine	Cigs per day	Patch dose
<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

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Patch Dosing

- 40 cpd or greater = 42 mg/day
- 21-39 cpd = 28-35 mg/day
- 10-20 cpd = 14-21 mg/day
- 10 cpd or less = 14 mg/day

* If a dose >42 mg/day may be indicated, contact the patient's prescriber

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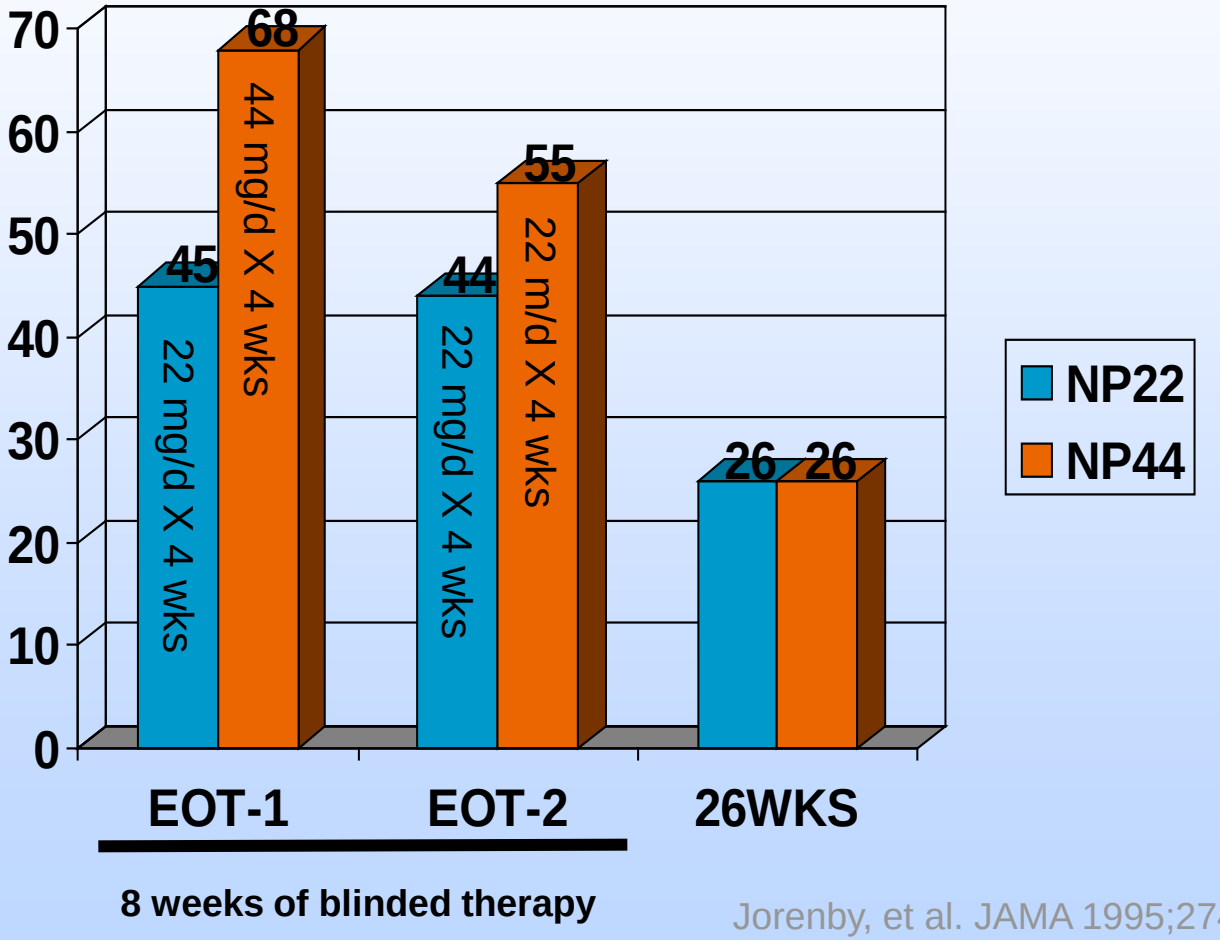
Dose-effect of hi-dose NP

Percent point-prevalence abstinent



Jorenby, et al. JAMA 1995;274:1347-52.

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Higher Dose Nicotine Patch

- There is a dose-response effect
- Long-term abstinence improved; RR of 1.15 (95% CI: 1.01 to 1.30)*
- Treatment-related AE's are uncommon
- Withdrawal symptoms less with higher dose NRT

*Cochrane Database of Systematic Reviews 2008

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Percentage Replacement Case

- Case example
  - 52 yo accountant who smokes 35-40 CPD
  - Baseline cotinine = 293 ng/ml
  - What nicotine patch dose would you advise?

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Percentage Replacement Case

- Received NP 42mg/day
- Steady state cotinine= 292 ng/ml
- Percent replacement= 100%

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Patch Dosing Schedule

- Use initial dose for 4-6 weeks
- After 4-6 weeks of smoking abstinence, taper 7-14mg steps every 2-4 wks
- Length of therapy varies based on patient response
- Withdrawal symptoms while tapering are mild to nonexistent
- Advise using overnight

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Length of Therapy

- Optimal length of treatment not established for most NRT
  - Patients and providers under-treat
  - Minimum 8 weeks
  - Evidence supports 6 months or more
- Rationale: reduce relapse, harm reduction
- Risk: dependence, long-term side effects

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Adherence to NRT Treatment

Balmford J, et al. Nicotine & Tobacco Research 2011;13:94-102

Table 2. Duration of Medication Use by Type (NRT or prescription only) and Source of NRT (OTC or prescription)

Duration of use	NRT (overall, $n = 905$), %	OTC NRT ($n = 621$), %	Prescription NRT ($n = 284$), %	Prescription only ($n = 213$), %
<1 week	20.0	23.0	13.4	2.3
1–2 weeks	12.5	13.5	10.2	7.0
2–4 weeks	22.9	26.4	15.1	23.9
4–8 weeks	16.0	13.4	21.8	26.3
≥8 weeks	28.6	23.7	39.4	40.4

- **Only 28.6% of NRT users completed the recommended 8 weeks of treatment**
- **Most quit prematurely because they believed the medication was not working, had unwanted side effects or believed that they no longer needed treatment.**

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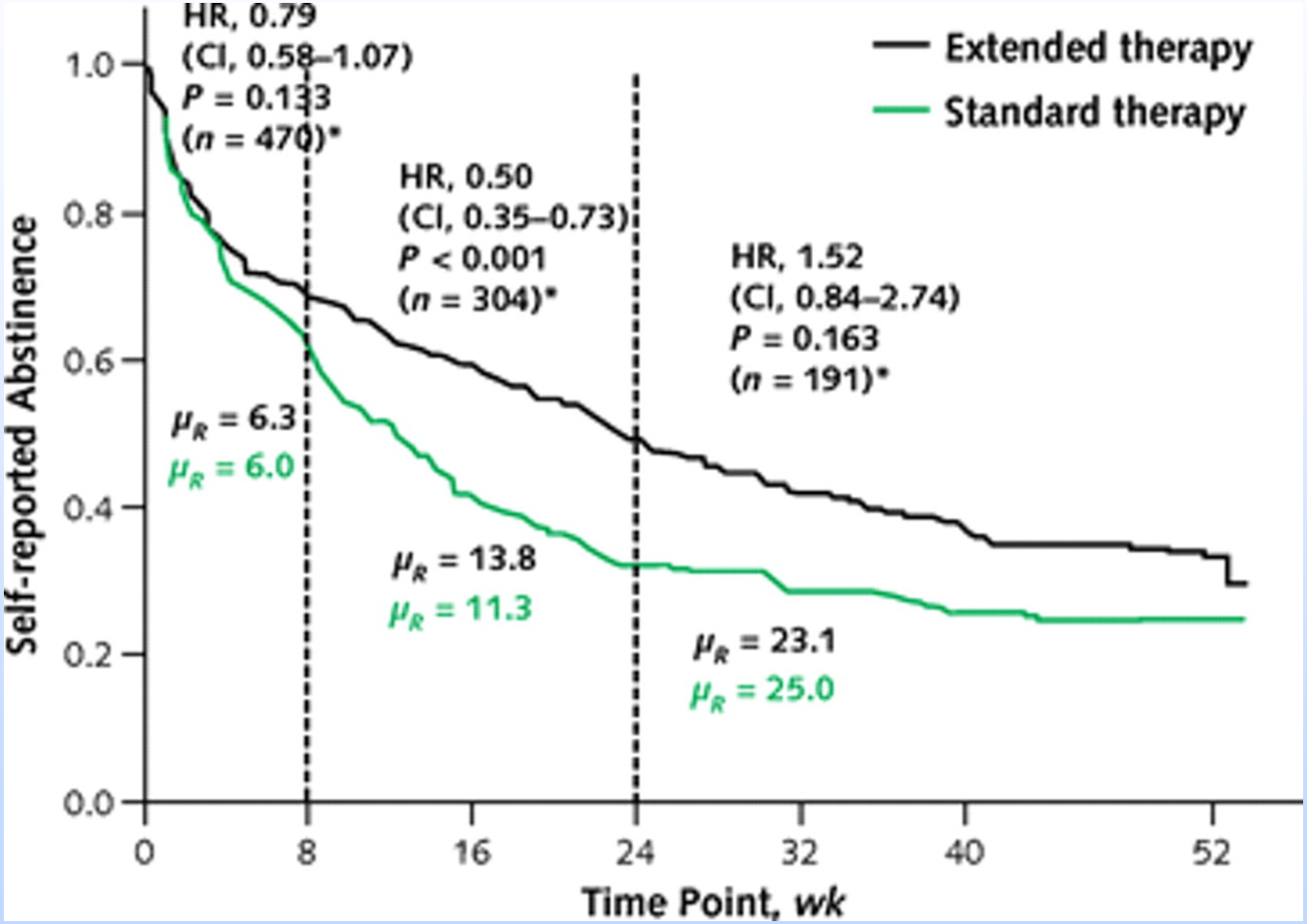
Nicotine Patch 8 wk vs. 24 wk Treatment



Schnoll R A et al. Ann Intern Med 2010;152:144-151

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Combination NRT

Nicotine patch plus immediate release NRT

Combination NRT rationale

Combine long-acting patch with *ad libitum* short-acting medication (gum, lozenge, inhaler, nasal spray)

- Encourages patient to be in control of cravings and withdrawal symptoms, while keeping a consistent baseline
- Improves compliance with treatment plan
- Achieves higher drug concentrations
- Allows further dose adjustments
- Replace tactile stimulus by mimicking smoking

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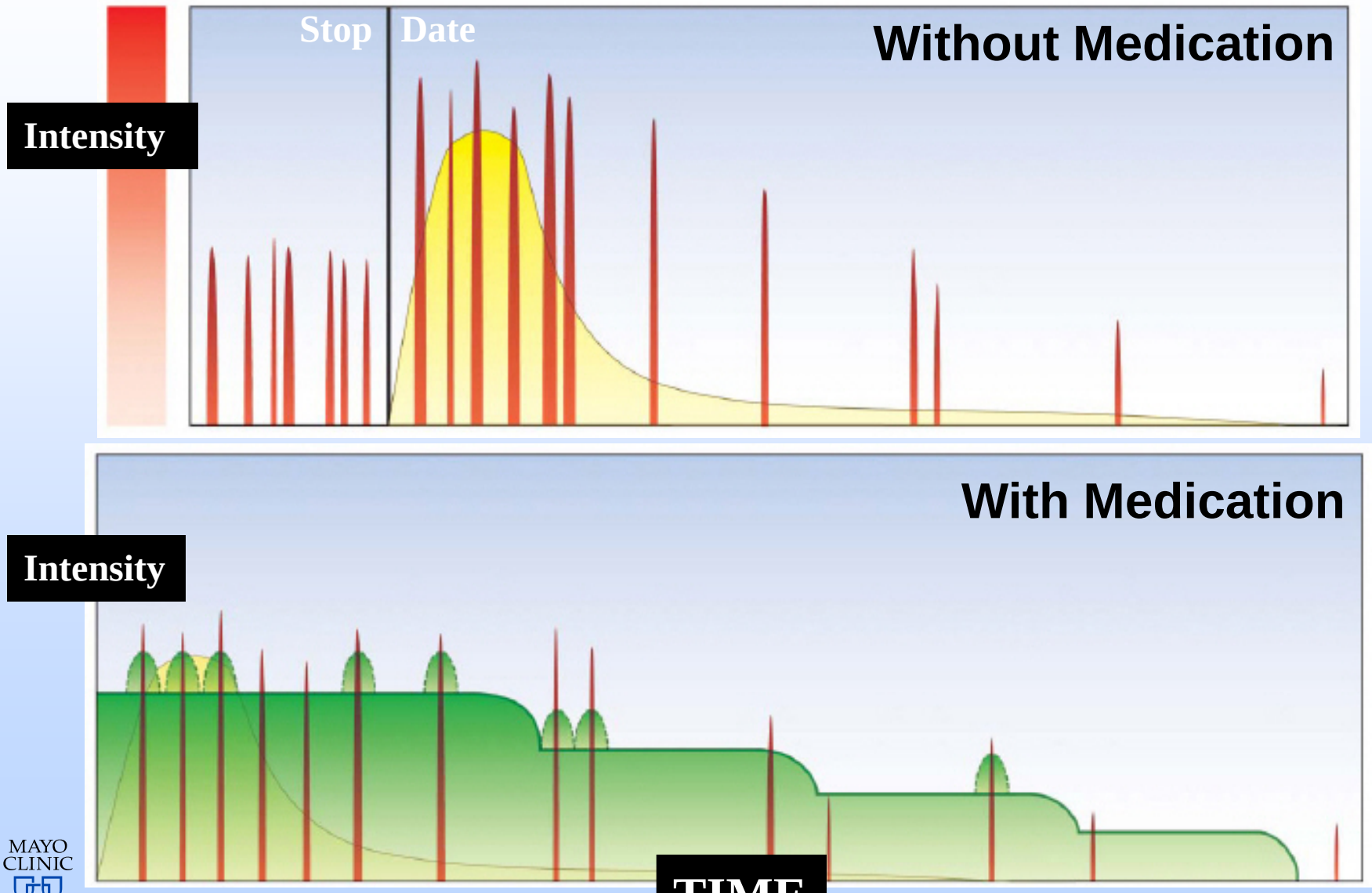
Medication:



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Immediate-release NRTs

- Nicotine gum, lozenge and inhaler
  - Buccal mucosal absorption
  - Affected by pH
  - Technique important with NG, NL
  - Peak absorption in 15-20 min.
- Nicotine nasal spray peak absorption in 5-10 min.

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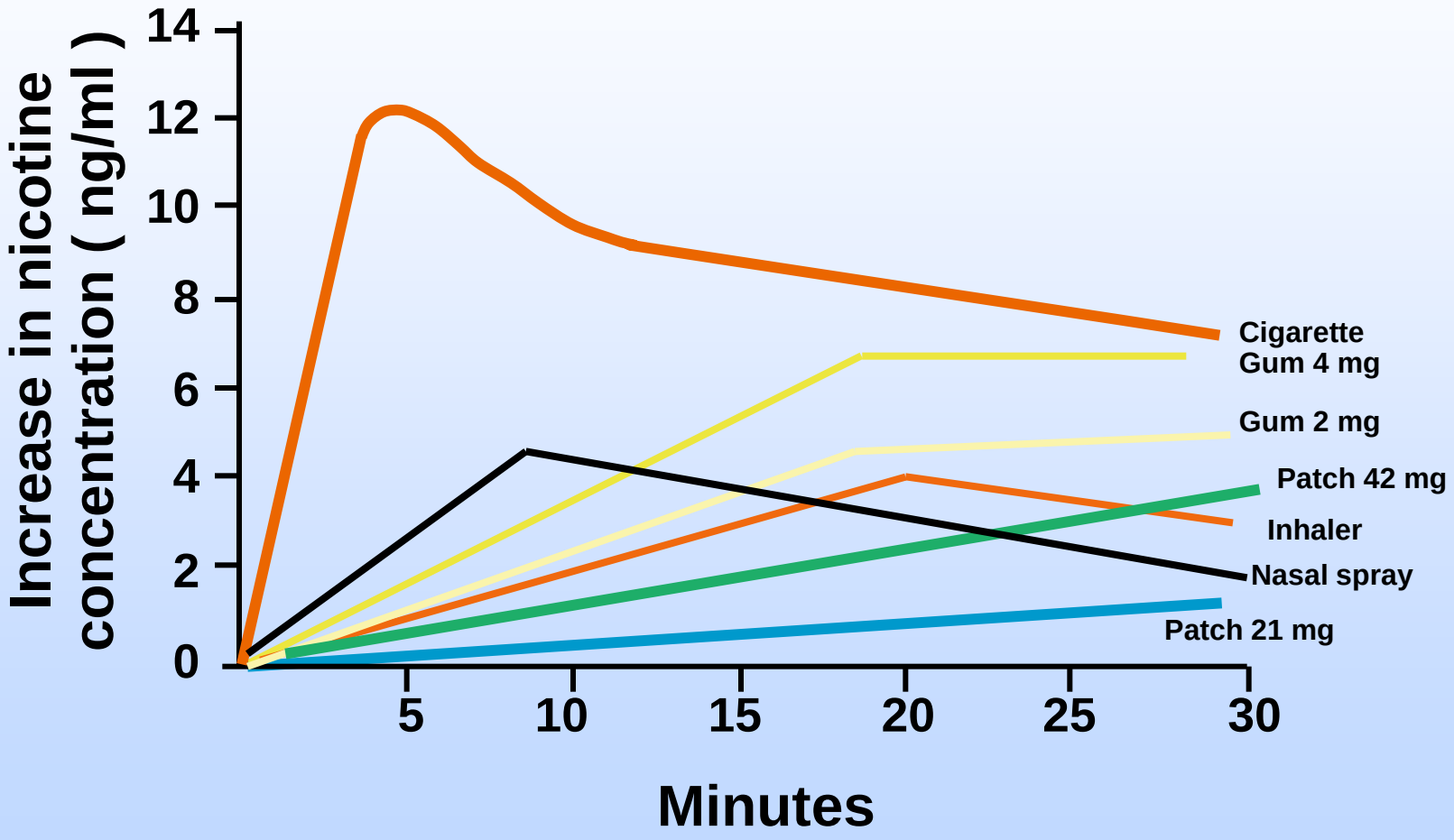
Smoking produces much higher nicotine levels and much more rapidly than NRT



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

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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

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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

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Nicotine Lozenge and Gum Dosing

- Based on time to first cigarette

  < 30 minutes = 4 mg

  > 30 minutes = 2 mg

Based on cpd

  >20 cpd = 4 mg

  ≤20 cpd = 2 mg

- Monotherapy:
  - 1-2 pieces every 1-2 hours
  - Minimum of 9 lozenge/day or 10-12 gum/day
  - Taper over 12 weeks (or as tolerated)
- Consider in Combination with other NRT
  (Use 2 mg lozenge or gum)

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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

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Nicotine Nasal Spray

- Side Effects -
  - moderate to severe nasal irritation (81-94%)
  - nasal congestion
  - transient change in sense of smell/taste
- Dependency profile between other NRT and cigarettes
- Contraindication - severe reactive airway disease

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Nicotine “Inhaler”

- Porous plug saturated with nicotine
- Delivers vaporized nicotine to oral cavity--not the lungs
- Average nicotine level = 6.3 ng/ml (29% replacement)
- Provides withdrawal symptom relief

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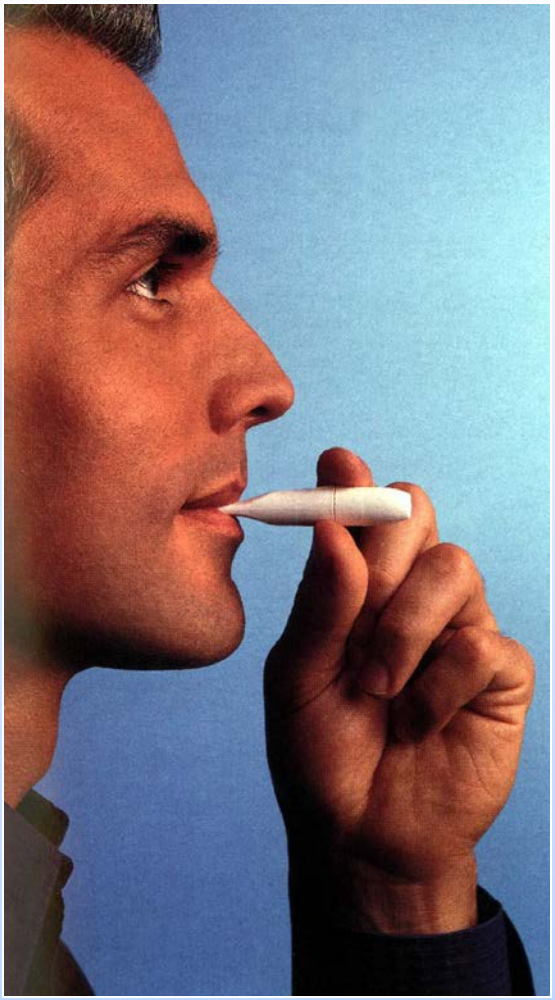
Nicotine "Inhaler"

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



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Nicotine Inhaler: Side Effects

- local irritation throat/mouth (40%)
- coughing (32%)
- rhinitis (23%)
- “puff” not “inhale”

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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

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COMBINATION THERAPY

- RCT of 1504 smokers in a research clinic
- Received 1 of 6 treatments for 8 weeks
- 6 brief counseling sessions
- 7-day point prevalence abstinence at 8 wks and 6 months

Piper M, et al. Arch Gen Psychiat 2009;66:1253-62.

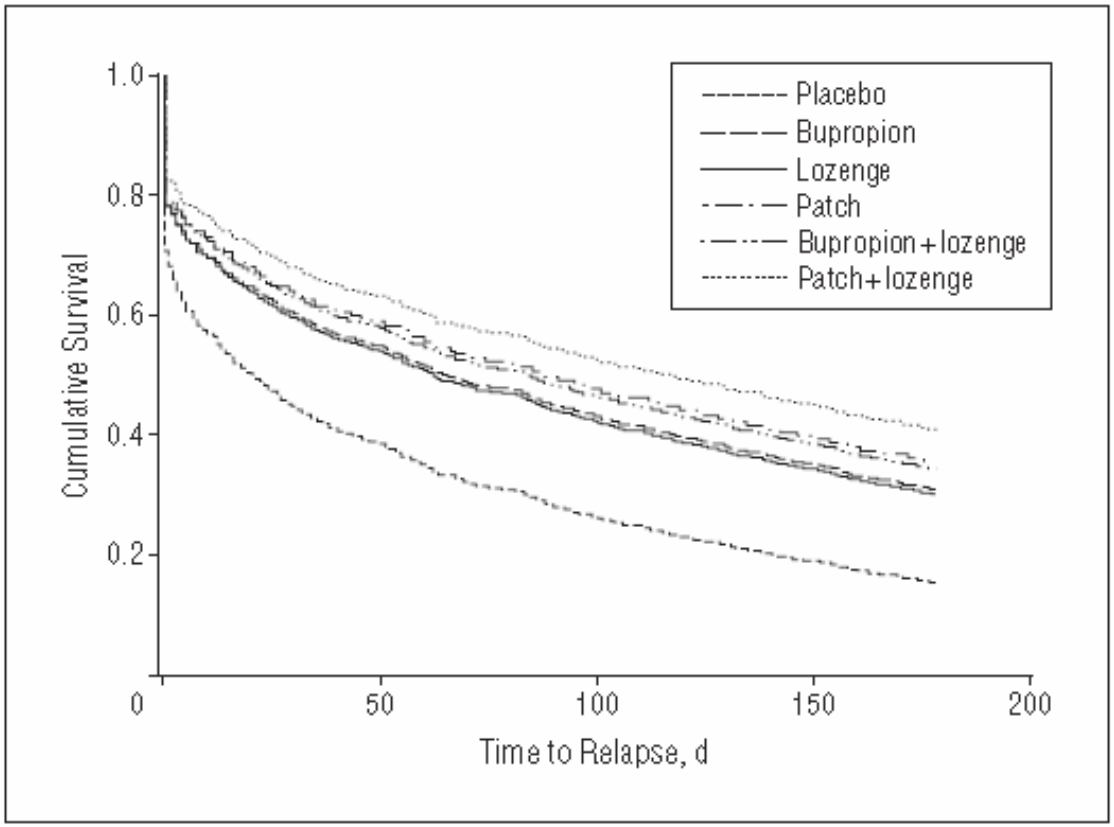

Figure 3. Survival curves for latency to relapse, or the number of days until the participants smoked on 7 consecutive days following the target quit day for the 6 treatment conditions.

Table 2. Carbon Dioxide–Confirmed Point-Prevalent Abstinence and Initial Cessation Rates[a]

	Rate, %					
Smoking Cessation/Abstinence	Placebo	Bupropion	Lozenge	Patch	Bupropion + Lozenge	Patch + Lozenge
Initial cessation[b]	69.4	82.2	81.3	87.7	84.5	91.5
Abstinence						
1 wk	23.3	34.5	29.2	40.5	37.4	43.4
8 wk, end of treatment	30.2	40.2	40.4	44.7	50.4	53.6
6 mo	22.2	31.8	33.5	34.4	33.2	40.1

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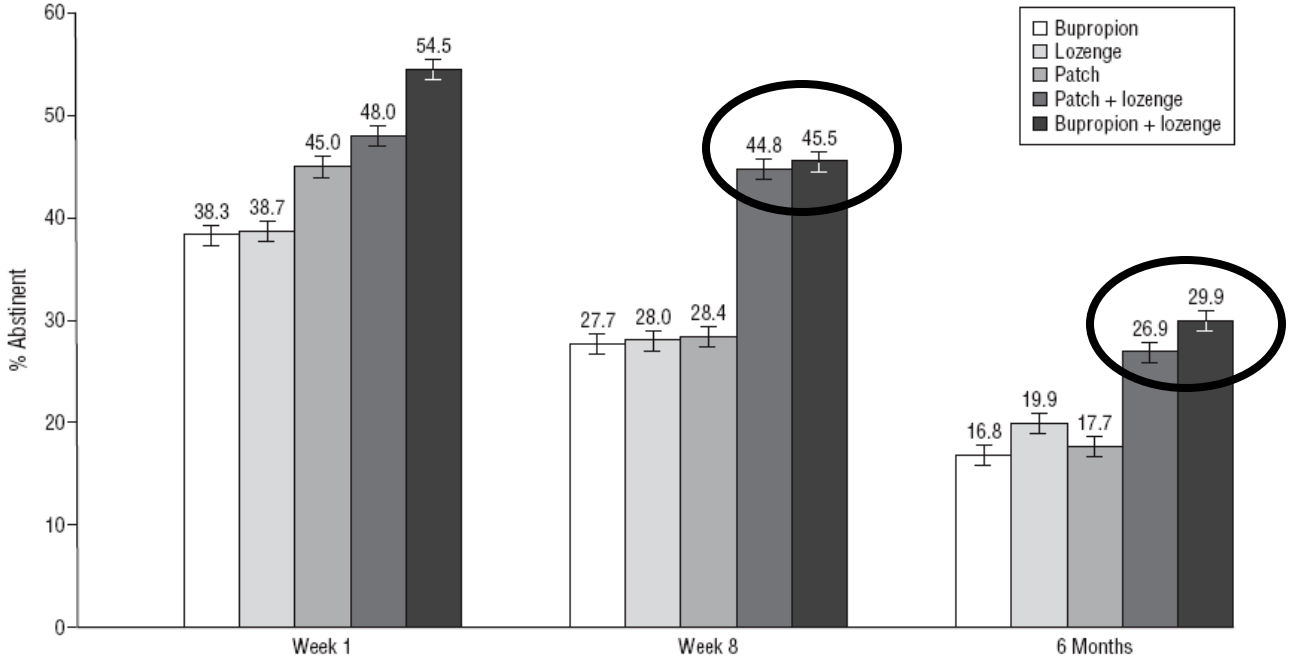
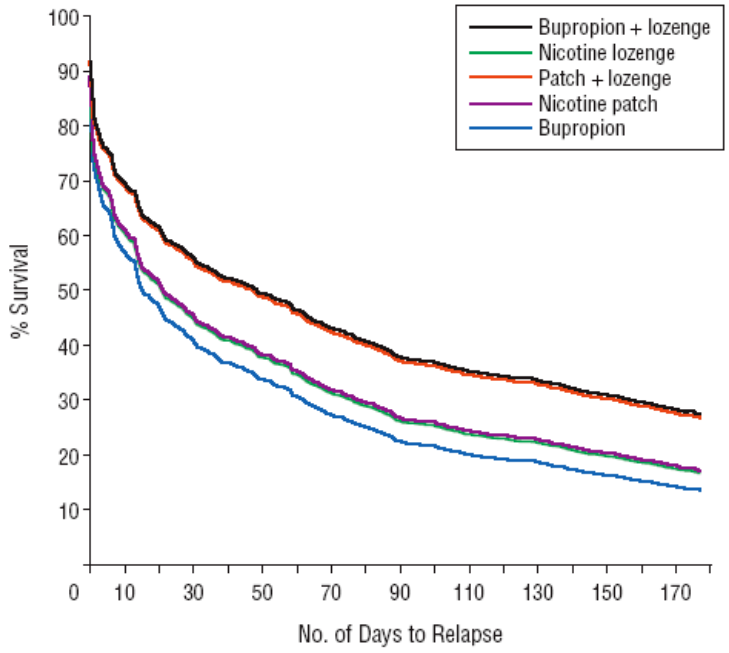


COMBINATION THERAPY

- 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



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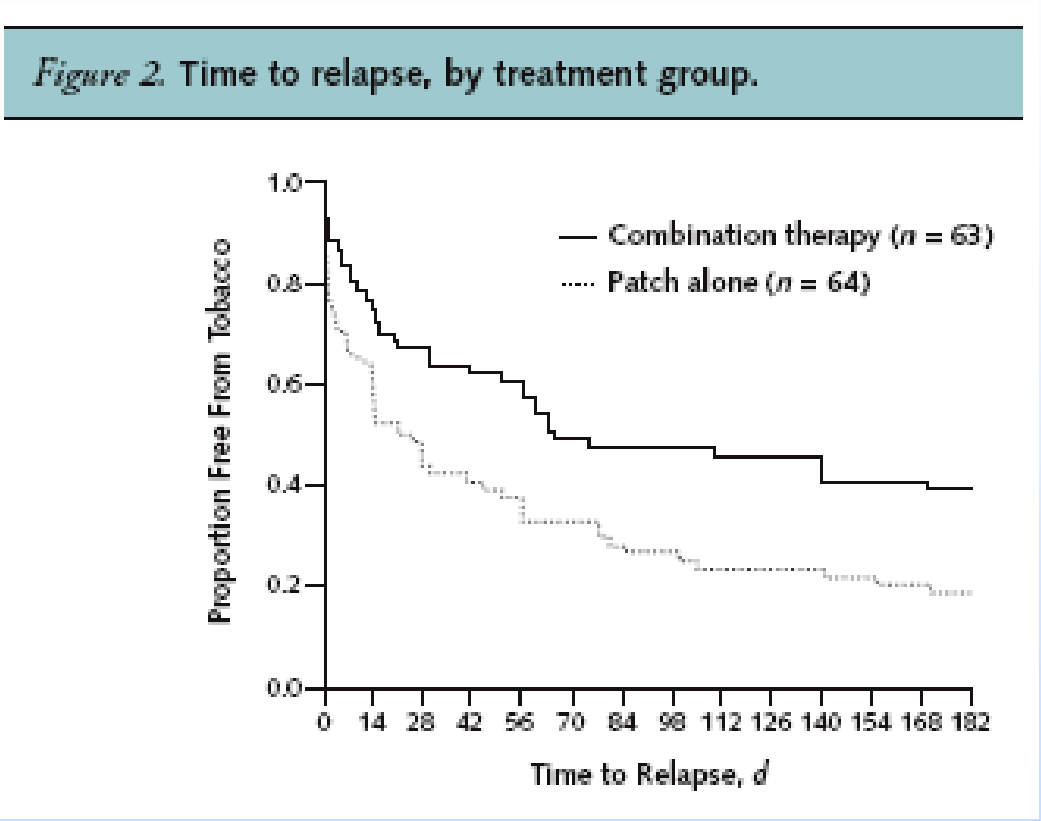
TRIPLE COMBINATION THERAPY

Steinberg MB, et al. Annals Intern Med 2009; 150:447-454.



- RCT of 127 smokers with known CVD, COPD, cancer, diabetes
- Compared triple combination (patch + bupropion + nicotine inhaler) to patch alone; no placebo treatment
- Triple therapy stopped based on symptoms (mean treatment duration 89 days); patch alone to taper and stop after 10 weeks (mean treatment duration 35 days)
- At 6 months 7 day point prevalence abstinence:
  - Triple Rx 35%
  - Patch 19%
  - (OR 2.57, 95% CI 1.05 to 6.32, p-value 0.04)

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How to use Combination Rx

- Use NP at dose adjusted for CPD
- Assess patient preference for immediate-release NRT
- Use IR NRT scheduled or ad lib
  - Every 1-2 hours while awake
  - In response to urges to smoke
- Taper NP as usual
- Taper IR NRT after 12 weeks

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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

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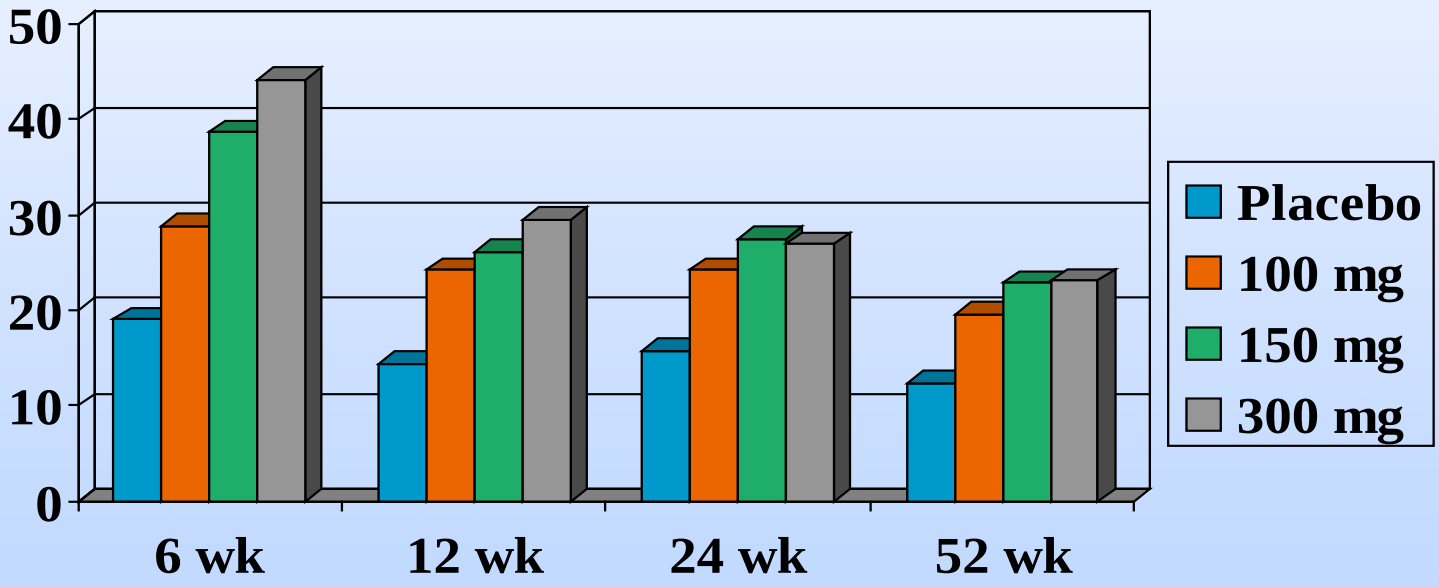
Bupropion SR (Zyban)

- Point-prevalence smoking cessation (%)

(Placebo vs 150 mg and 300 mg $p \leq 0.02$ at all points)



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Bupropion: Relapse prevention

- Point-prevalence abstinence (%)

Time(wk)	12*	24*	52*	104
Placebo	69	54	42	40
300mg	82	68	55	42

*p<0.05 for placebo vs active

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Weight Gain in Abstainers

Time (wk)	7	52	104
bupropion	4.1	4.7	6.9
control	5.4	7.9	8.6

$p<0.05$ at all times

(weight in kg)

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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

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Bupropion SR prescribing

- Set target quit date 1 week from start of medication
- Begin with 150 mg daily for 3 days
- Increase to 150 mg twice daily at least 8 hrs apart
- Evening dose before 6PM
- Treat for 8-52 weeks

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

AE	Mean %	Range	Studies
Insomnia	32.3	(10 to 53)	25
Dry mouth	23.9	(6 to62)	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

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Serious adverse effects with bupropion SR

- Seizure rate about 1/1000 treated
  - 7/6409 subjects on active therapy in RCT's
  - Post marketing studies show seizures in people with known predisposition
  - Contraindications: known seizure (ever); structural brain abnormality; serious closed head injury
- Hypersensitivity (about 1%)
  - Hives, urticaria, angioedema
- Neuropsychiatric symptoms

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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, theophyline, ethanol
- Anorexia/Bulimia
- Significant head trauma: prolonged LOC, skull fracture, intracranial bleeding

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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."

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Bupropion/Patch Combination

Abstinence at 12 mos…

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

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Bupropion SR plus Patch

- Begin NP on quit date
- Match NP dose to CPD or cotinine
- Begin bupropion 1 week prior to quit date
- Ramp up bupropion from 150mg to 300mg per day after 3 days
- Treatment duration based on patient response
  - Often 15-52 weeks
- ± Combination with NRT

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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

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Nicotine replacement and CVD

Joseph, et al study results...

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

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Smoking and Pregnancy

- Counsel regarding risks to self and developing fetus
- Pharmacologic treatment if needed
- NRT pregnancy category “D”
- Bupropion SR is category “C”
- Postpartum relapse common
  - Stress continuing benefits to infant and mother

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Drug Risks in Pregnancy

- “C”:Animal studies have shown significant adverse fetal effects, but no controlled studies are available in women
- “D”:Positive evidence of human fetal risk exists, but benefits in certain situations may make use acceptable despite risks

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Tobacco dependence treatment in pregnancy

- Recommendation: Because of the serious risks of smoking to the pregnant smoker and the fetus, whenever possible pregnant smokers should be offered person-to-person psychosocial interventions that exceed minimal advice to quit. (Strength of Evidence = A)
- Recommendation: Although abstinence early in pregnancy will produce the greatest benefits to the fetus and expectant mother, quitting at any point in pregnancy can yield benefits. Therefore, clinicians should offer effective tobacco dependence interventions to pregnant smokers at the first prenatal visit as well as throughout the course of pregnancy. (Strength of Evidence = B)

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Tobacco dependence treatment in pregnancy

- For women who are not able to quit successfully with behavioral treatment alone…
  - Short acting oral NRT ad lib
  - Nicotine patch in lowest effective dose if oral NRT is ineffective
  - Combination NRT if needed
  - Bupropion alone or added to NRT if needed
- No data on varenicline safety

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Summary and Conclusions

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

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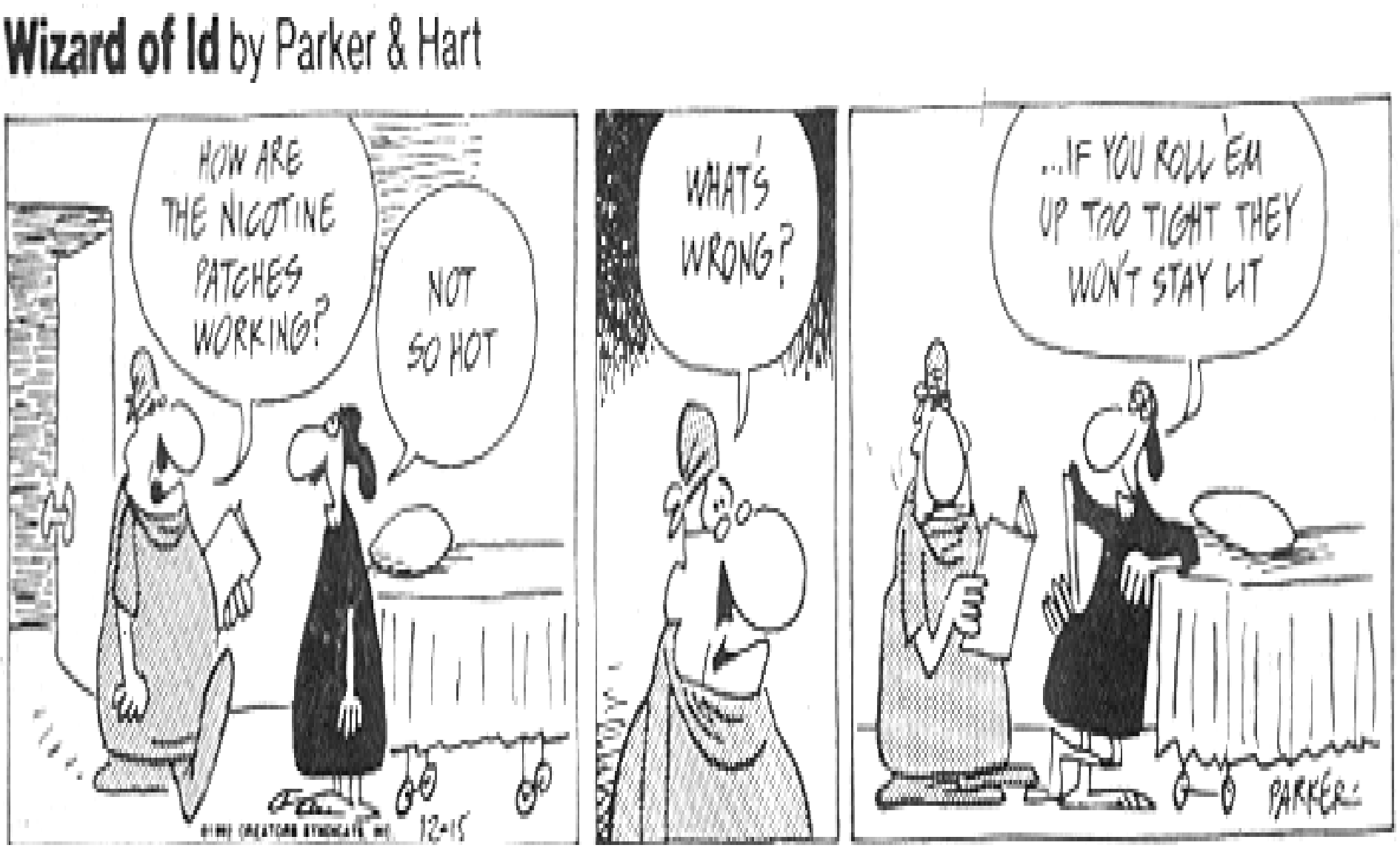
Conclusions

- 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

MAYO CLINIC

Optimizing Pharmacotherapy…



MAYO CLINIC

DISCUSSION