2015-05-23

니코틴 대체 요법

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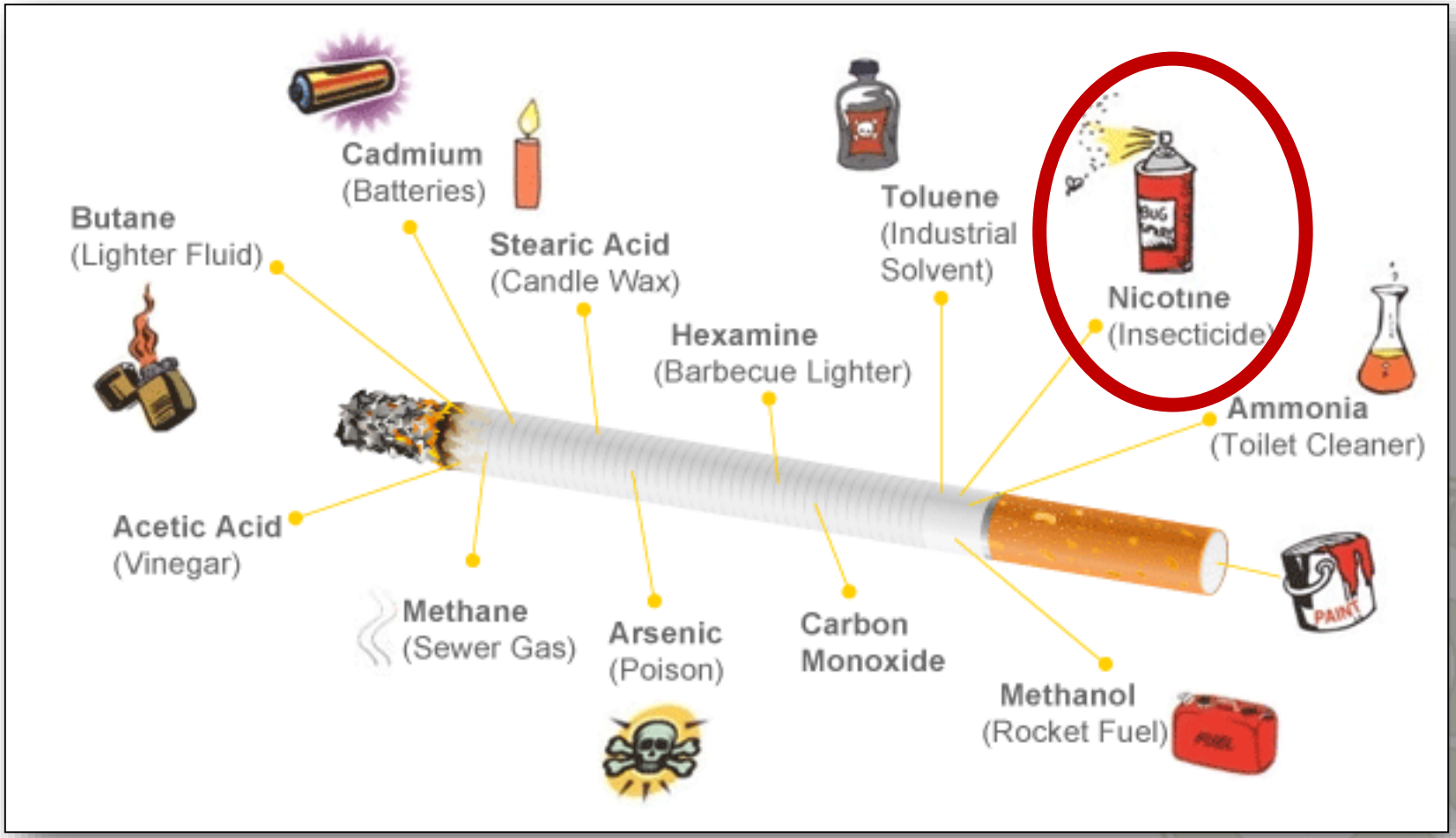
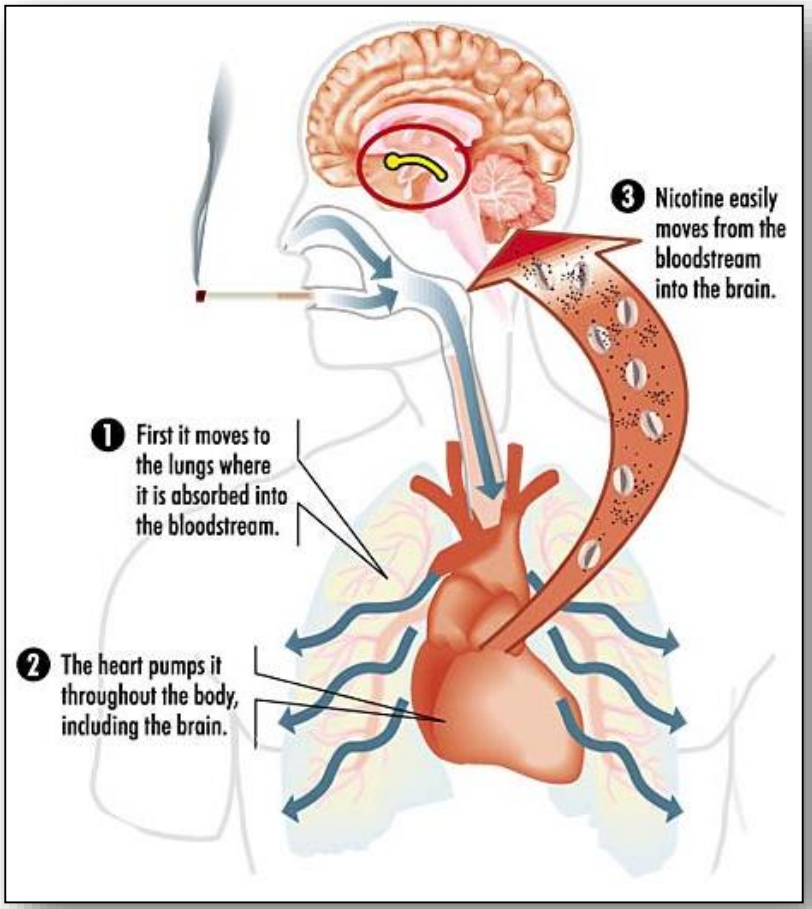
INDEX

Nicotine Withdrawal Symptom

What's in a cigarette?



Nicotine in Smoking



- Nicotine: 0.1-0.2 mg / puff
- 25% of nicotine inhaled reaches blood stream
- Reaches the brain within 15 seconds
- Elimination half life of nicotine is around 2-3 hours

Benowitz et al. Prim Care. 1999

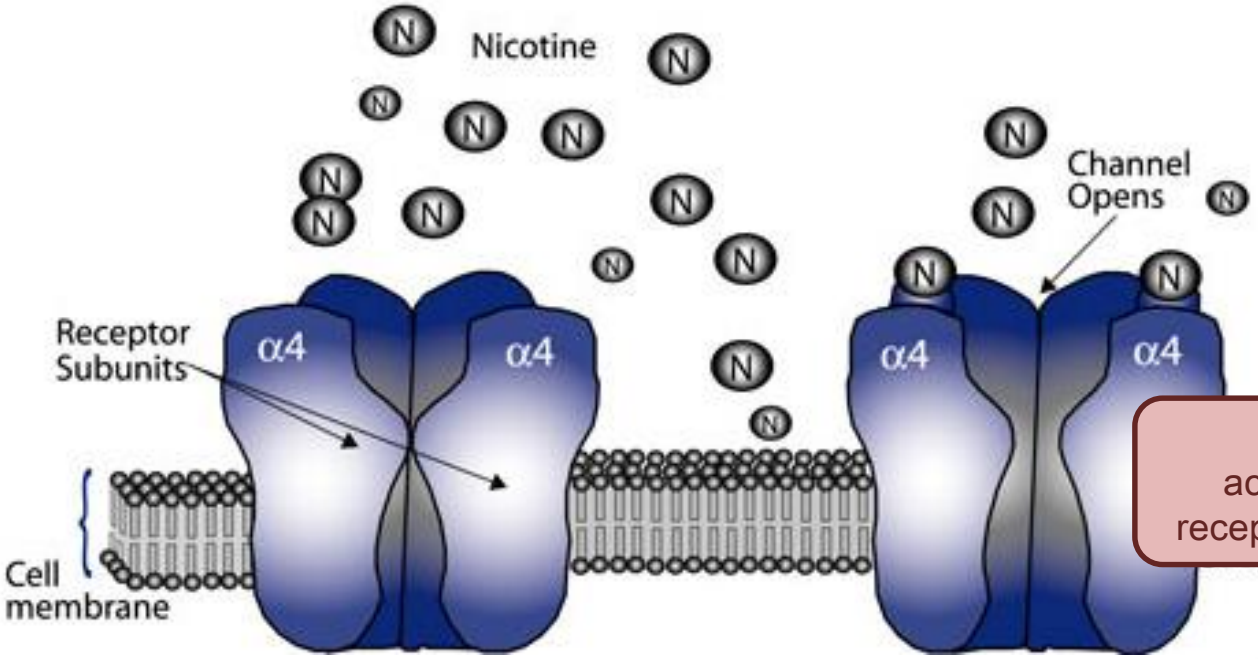
Brain pathway to nicotine addiction

- Maintain plasma nicotine levels that prevent occurrence of withdrawal symptoms: tolerance

- To derive rewarding effects from the conditioned reinforces associated with smoking.

Drug and Therapeutics Bulletin. BMJ 2014

Brain pathway to nicotine addiction



Nicotine acetylcholine receptor (nAChRs)

acetylcholine

dopamine

serototonin

glutamate

norepinephrine

endorphin

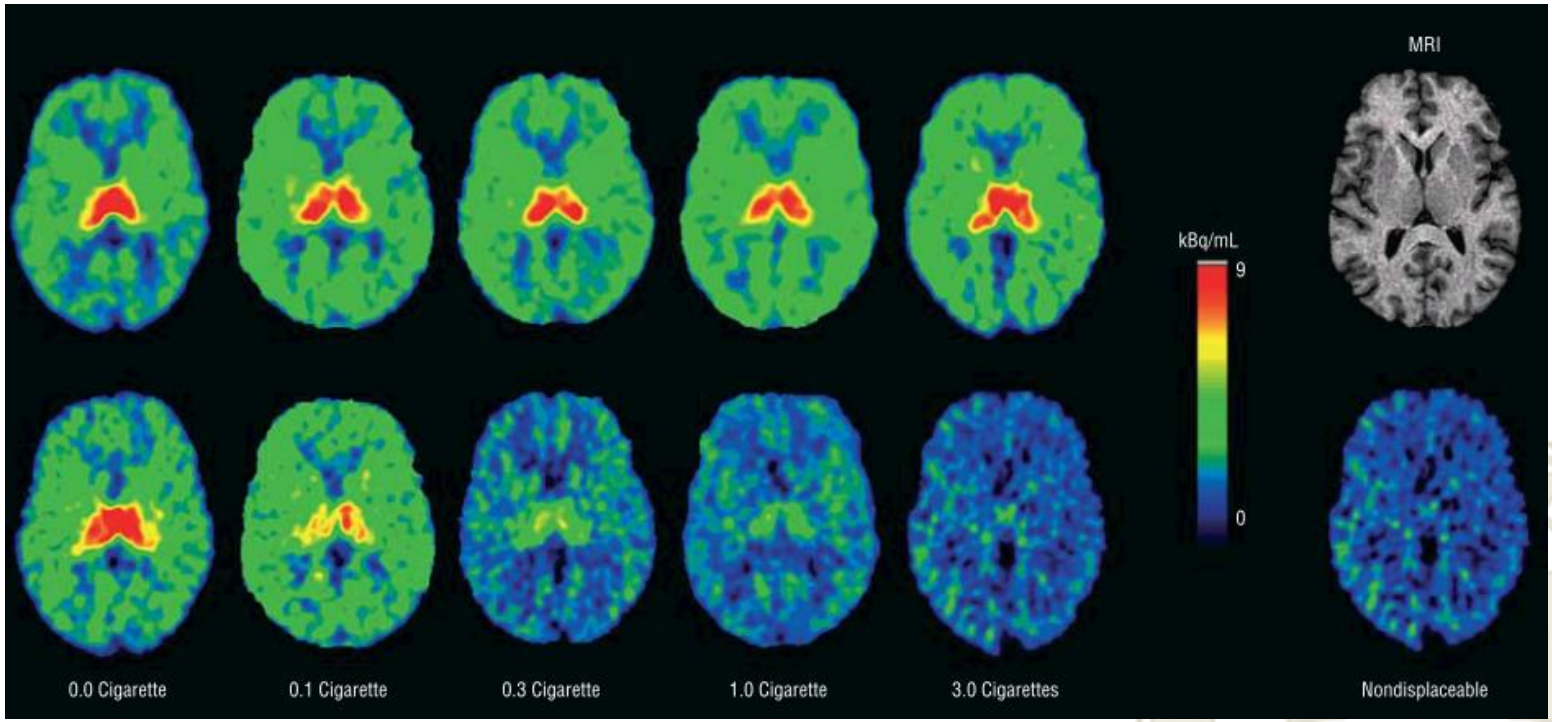
BenowitzNL et al. Annu Rev Pharmacol Toxicol. 2009

Brain pathway to nicotine addiction

Occupancy of nAChR by nicotine after smoking

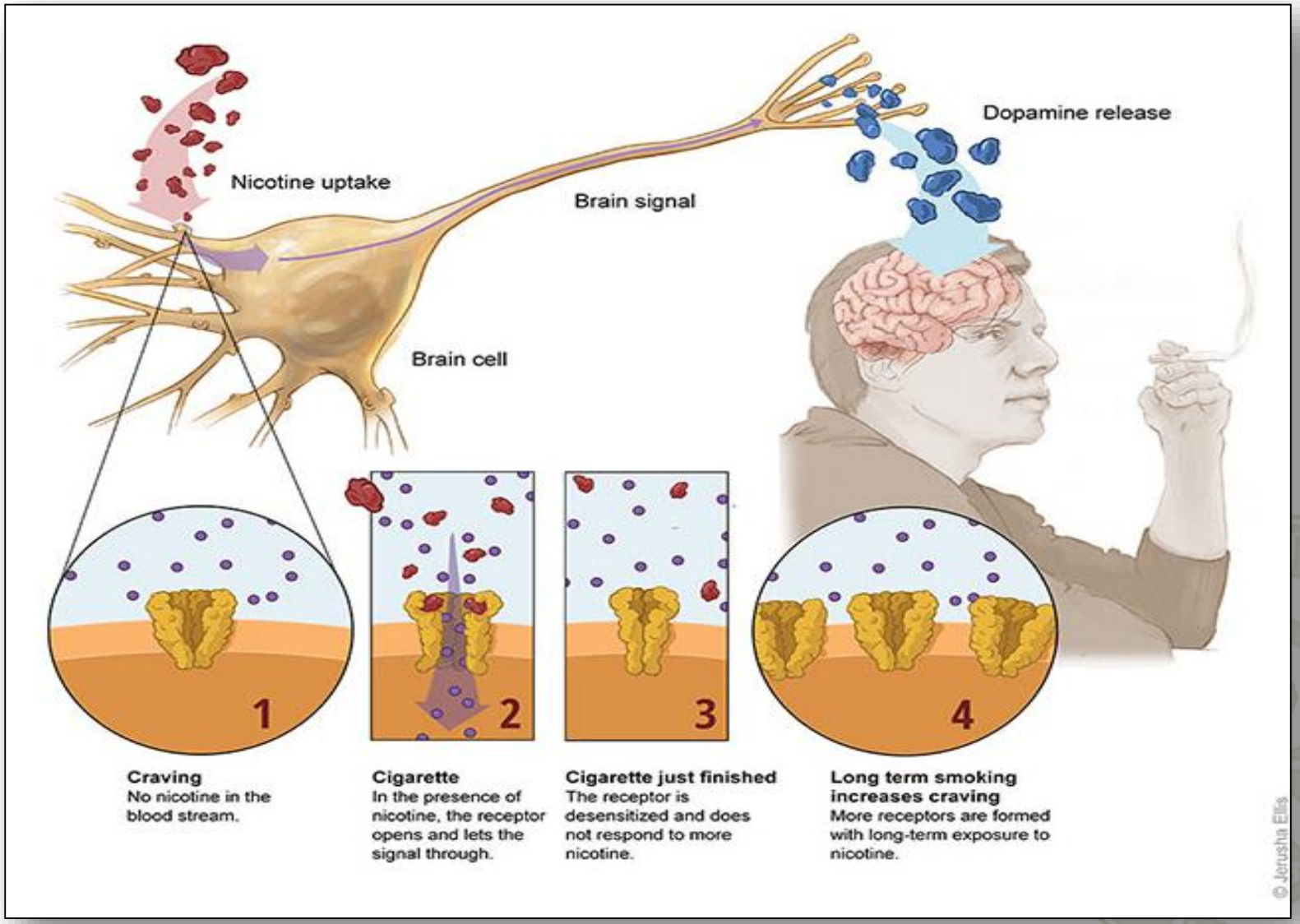
before

3 hours after smoking



Brody et al. Arch Gen Psychiatry. 2006

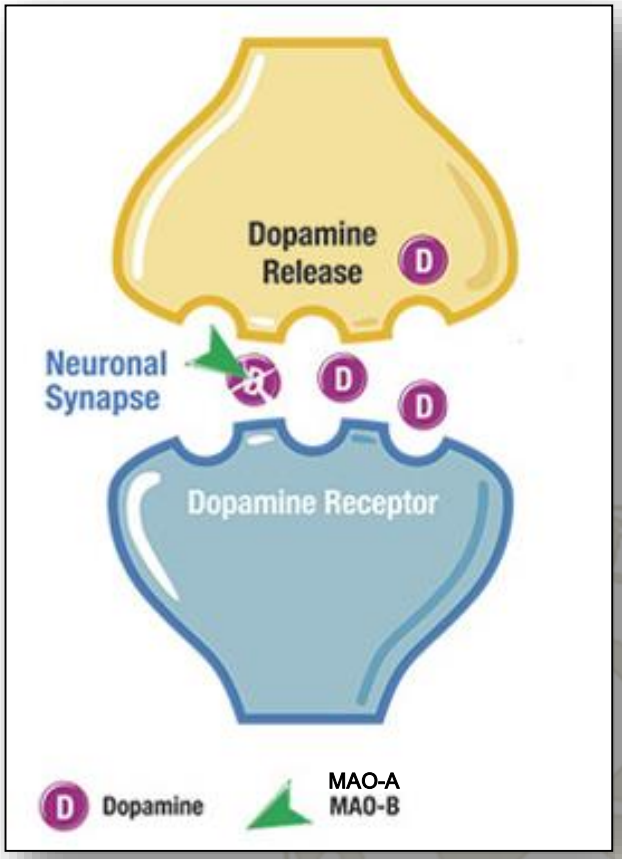
Brain pathway to nicotine addiction



http://jerushaellis.ca/illustrations

Brain pathway to nicotine addiction

- **Continued smoking**
  - Reduce brain monoamine oxidase A and B
  - Increase dopamine and norepinephrine in synapse
  - Augment effects of nicotine



BenowitzNL et al. Annu Rev Pharmacol Toxicol. 2009

Nicotine Replacement Therapy

- **Long acting**
  - Transdermal nicotine patch

- **Short acting**
  - Nicotine gum
  - Nicotine lozenge
  - Nicotine inhaler
  - Nicotine nasal spray
  - Nicotine mouth spray
  - Nicotine sublingual tablets

Transdermal nicotine patch

- Long acting and slow onset

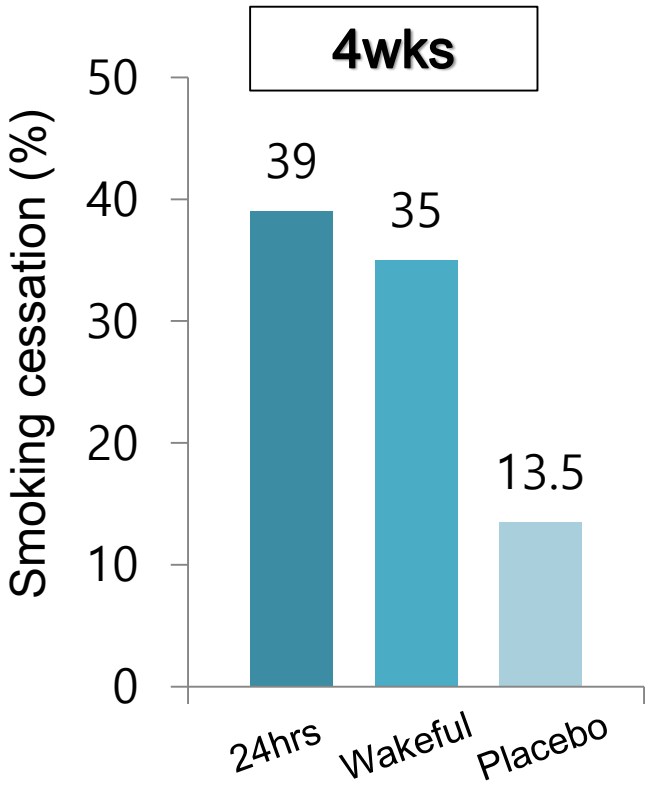
- Dosing
  - 21mg: > 10 cigarettes / day
  - 14mg: ≤ 10 cigarettes / day
  - 7mg used when tapering
  - 6 wks – 2 wks – 2 wks
- Administration
  - Apply 1 new patch daily
  - Rotate application site

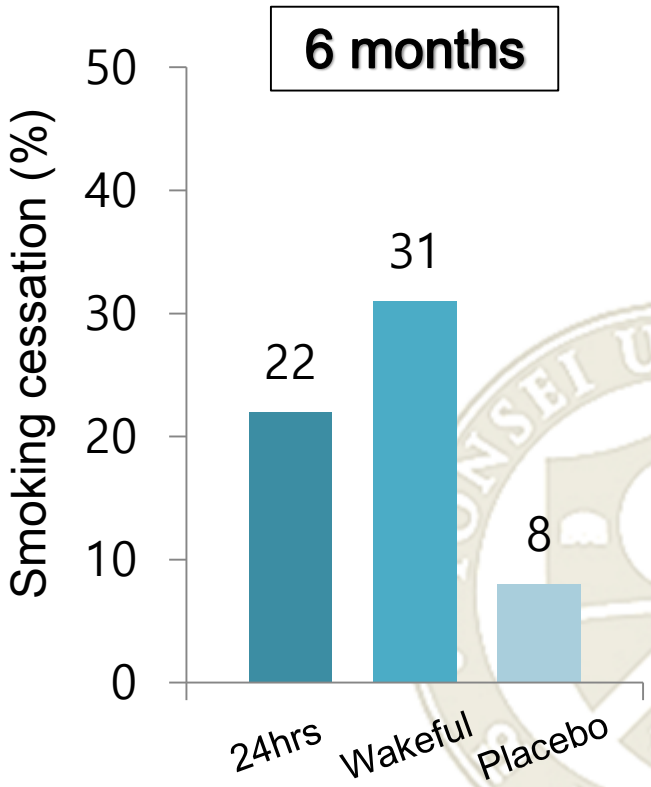
Transdermal nicotine patch

- Advantages
  - steady nicotine level: constant withdrawal relief over 24 hrs
  - Easiest nicotine product to use
- Disadvantages
  - Requiring several hours to reach peak levels
  - User cannot alter nicotine level in case of craving
- Common adverse effects
  - Skin irritation
  - Insomnia
  - Vivid dream

Transdermal nicotine patch

- Insomnia, vivid dreams
  - Removing patch at bedtime, for 4 wks



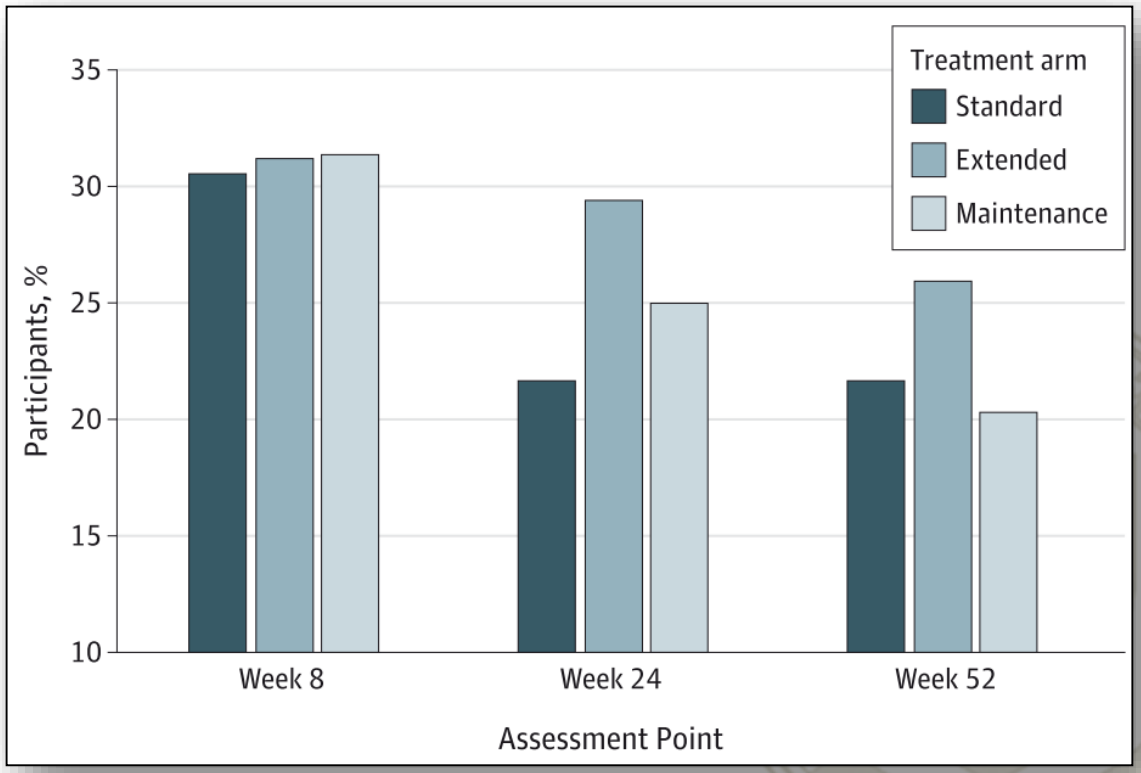


Daughton et al. Arch Intern Med. 1991

Transdermal nicotine patch

Standard	Extended	Maintenance
8 wks (n=180)	24 wks (n=173)	52 wks (n=172)

7-day Point Prevalence of Abstinence Rates



All received 12 smoking cessation behavioral counseling sessions

Schnoll et al. JAMA. 2015

Transdermal nicotine patch

Week 24 abstinence

Covariate	OR (95% CI)	*P* Value
Model 1[a]		
Sex (reference, female)	0.71 (0.44-1.15)	.16
Race (reference, African American)	0.89 (0.53-1.47)	.64
Adherence to patch regimen	1.48 (1.29-1.71)	<.001
Age	1.02 (1.00-1.04)	.07
Educational level (reference, ≥some college)	0.71 (0.40-1.24)	.23
Income (reference, ≥$50 000/y)	0.85 (0.49-1.48)	.56
Sexual orientation (reference, heterosexual)	2.66 (1.26-5.61)	.01
FTND score	0.88 (0.78-0.99)	.04
Treatment arm (reference, standard treatment)	1.70 (1.03-2.81)	.04

Week 52 abstinence

Covariate	OR (95% CI)	*P* Value
Model 2[b]		
Sex (reference, female)	0.85 (0.52-1.39)	.53
Race (reference, white)	1.48 (0.87-2.53)	.15
Adherence to patch regimen	1.68 (1.41-2.01)	<.001
Age	1.02 (0.99-1.04)	.18
Educational level (reference, ≥some college)	0.49 (0.27-0.89)	.19
Income (reference, ≥$50 000/y)	0.67 (0.38-1.20)	.18
Sexual orientation (reference, heterosexual)	2.18 (1.01-4.73)	.05
FTND score	0.86 (0.76-0.98)	.02
Treatment arm (reference, standard and extended treatment)	1.17 (0.69-1.98)	.57

Schnoll et al. JAMA. 2015

Transdermal nicotine patch

Standard vs. maintenance/extended

Days until relapse	Days of abstinence	Cigarettes per day on smoking days
72 vs. 89 days	68 vs .81 days	6.4 vs 5.8 cigarettes
$P < 0.001$	$P = 0.02$	$P = 0.02$

– No significant differences among the groups in adverse effects

Benefits and safety 24 weeks of nicotine patch

Schnoll et al. JAMA. 2015

Short acting agents

- Combination with transdermal nicotine patch
- Repeated use throughout the day
- Lead to more variable nicotine levels
- Require more instruction for correct use

Nicotine gum

- Chewing → nicotine release → absorption through the oral mucosa → peak of blood nicotine level 20 minutes

- **Chew and Park**
  - Chew until nicotine taste appears
  - Park in the buccal mucosal until taste disappears
  - Chew a few more times to release more nicotine
  - Repeat cycle for 30minutes

Nicotine gum

- Rapid and vigorous chewing
  - Nicotine release faster than it can be absorbed by buccal mucosa
  - swallowed → absorbed from GI tract → metabolized in liver : ineffective

- Dosing
  - 4mg : ≥ 25 cigarettes / day
  - 2mg : < 25 cigarettes / day

Nicotine gum

- Administration
  - One piece every 1-2 hours for 6 weeks with gradual reduction over a second six weeks (total 3 months)
  - Maximum
    - ≤ 24 pieces/day
    - No food or drink for 30 min before and during use
  - Avoid acidic beverage (coffee, carbonated drinks) → lowers oral pH → ionize nicotine and reduce absorption

Nicotine lozenge

- Place in mouth and dissolve for 30 minutes
- Dosing
  - 2 mg : first cigarette ≥ 30 min after waking
  - 4 mg : first cigarette < 30 min after waking
- Administration
  - 1 piece every 1-2 hrs
  - Maximum
    - 5 lozenges / 6 hrs
    - 20 lozenges / day
    - No food or drink for 30 min before and during use

Nicotine gum and lozenge

- Advantages
  - User controls nicotine dose
  - Oral substitute for cigarettes
  - Lozenge: smokers with poor dentition or dentures

- Disadvantages
  - Unpleasant taste
  - Gum: damage dental work and difficult for denture wearers to use

Nicotine gum and lozenge

- Common adverse effects
  - Mouth irritation
  - Jaw soreness (gum)
  - Heartburn
  - Hiccups
  - Nausea (GI side effects usually due to overly vigorous chewing gum)

Nicotine inhaler

- Mouthpiece and plastic, nicotine-containing cartridge
- Physical dependence, behavioral and sensory aspects of smoking
- Nicotine vapor: deposit in oropharynx → absorbed through oral mucosa

- Dosing
  - 10mg per cartridge

- Administration
  - Inhale as needed: every 1-2 hrs
  - Maximum: 16 cartridges/day
  - Initial administration for first 6 to 12 weeks with gradual reduction of dose over next 6 to 12 weeks

Nicotine inhaler

- Advantages
  - User controls nicotine dose
  - Oral substitute for cigarettes
- Disadvantages
  - Device visible when being used
  - Use caution in reactive airway disease, possible bronchospasm
- Common adverse effects
  - Mouth and throat irritation

Nicotine nasal spray

- Deliver aqueous solution of nicotine to nasal mucosa
- Dosing
  - 0.5mg / spray (10mg/mL)
- Administration
  - One spray to each nostril every 1-2 hrs
  - Maximum
    - 10 sprays/hr
    - 80 sprays/day

Nicotine nasal spray

- Advantages
  - User controls nicotine dose
  - Most rapid delivery of nicotine among NRT : peak 10 minutes after use

- Disadvantages
  - Common and intolerable local irritation to nasal mucosa
  - 94% during first two days
  - 81% after three weeks of therapy

Combination NRT

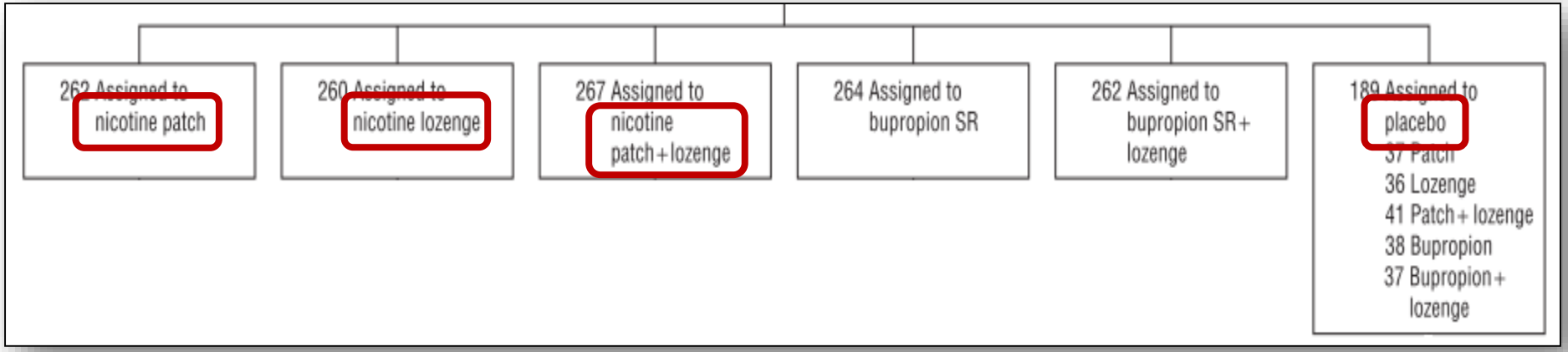


Table 2. Carbon Dioxide–Confirmed Point-Prevalent Abstinence and Initial Cessation Rates[a]

	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

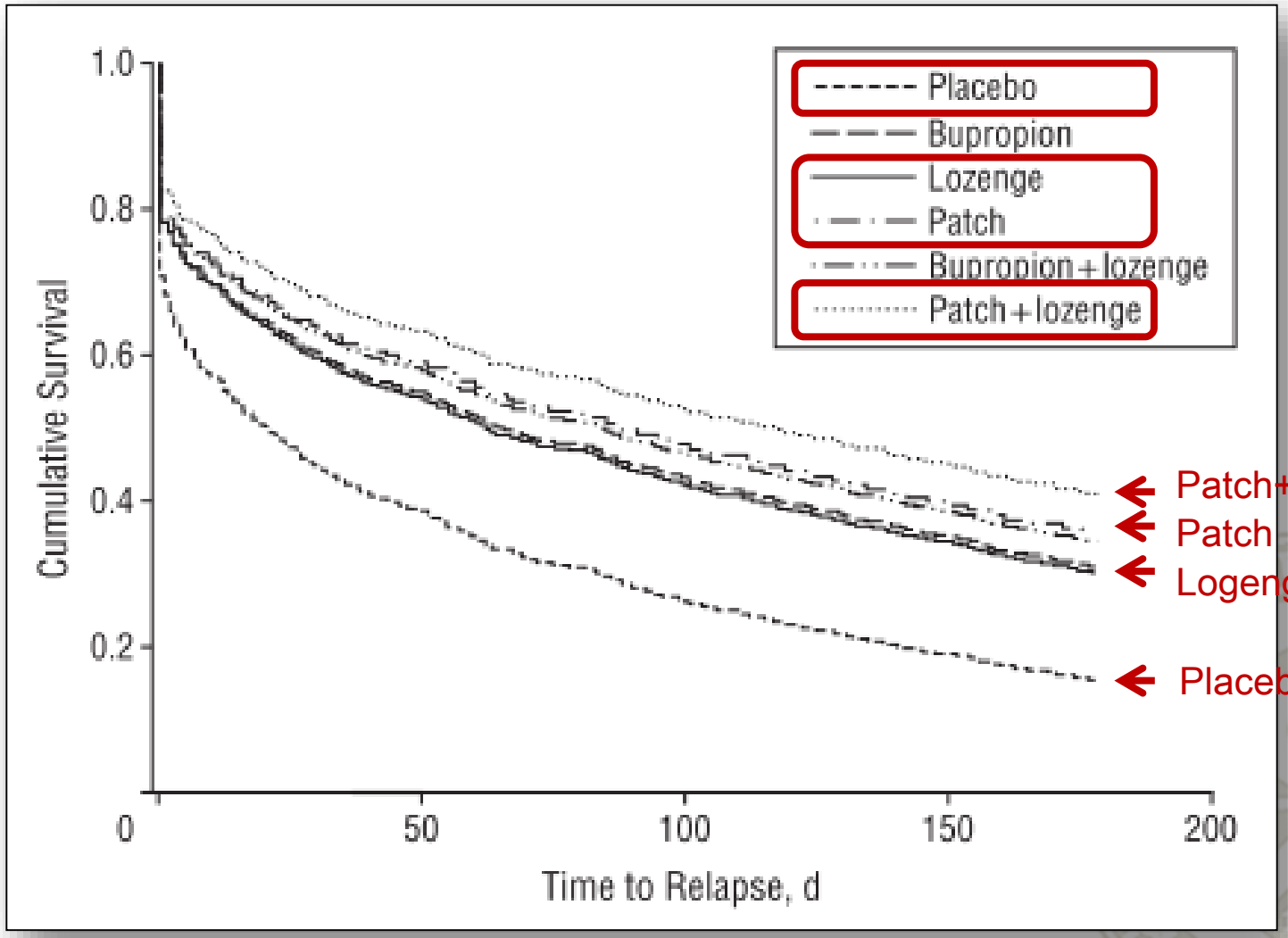
Piper et al. Arch Gen Psychiatry. 2009

Table 3. Logistic Regressions Predicting Initial Cessation and Point-Prevalent Abstinence

Treatment	Initial Cessation			1 wk Postquit		
	Wald	*P* Value	OR (95% CI)	Wald	*P* Value	OR (95% CI)
Relative to placebo						
Bupropion	9.25	.002[a]	2.04 (1.29-3.22)	6.52	.01	1.73 (1.14-2.64)
Lozenge	7.60	.006	1.91 (1.21-3.03)	1.97	.16	1.36 (.89-2.09)
Patch	20.32	<.001[a]	3.14 (1.91-5.17)	14.29	<.001[a]	2.24 (1.47-3.40)
Bupropion + lozenge	13.14	<.001[a]	2.40 (1.50-3.84)	10.00	.002[a]	1.97 (1.29-3.00)
Patch + lozenge	31.18	<.001[a]	4.73 (2.74-8.16)	19.23	<.001[a]	2.53 (1.67-3.83)
Relative to monotherapies						
Bupropion + lozenge	0.07	.79	1.05 (0.71-1.56)	0.61	.43	1.12 (0.84-1.50)
Patch + lozenge	9.01	.003[a]	2.08 (1.29-3.36)	6.46	.01	1.44 (1.09-1.92)
Monotherapies relative to each other[b]						
Patch vs lozenge	3.86	.049	0.61 (0.37-0.999)	7.20	.007	0.61 (0.42-0.88)
Bupropion vs lozenge	0.07	.78	0.94 (0.59-1.48)	1.65	.20	0.79 (0.54-1.14)
Patch vs bupropion	2.94	.09	0.65 (0.40-1.06)	2.01	.16	0.77 (0.54-1.10)
Patch + lozenge vs bupropion + lozenge	5.77	.02	0.51 (0.29-0.88)	2.00	.16	0.78 (0.55-1.10)

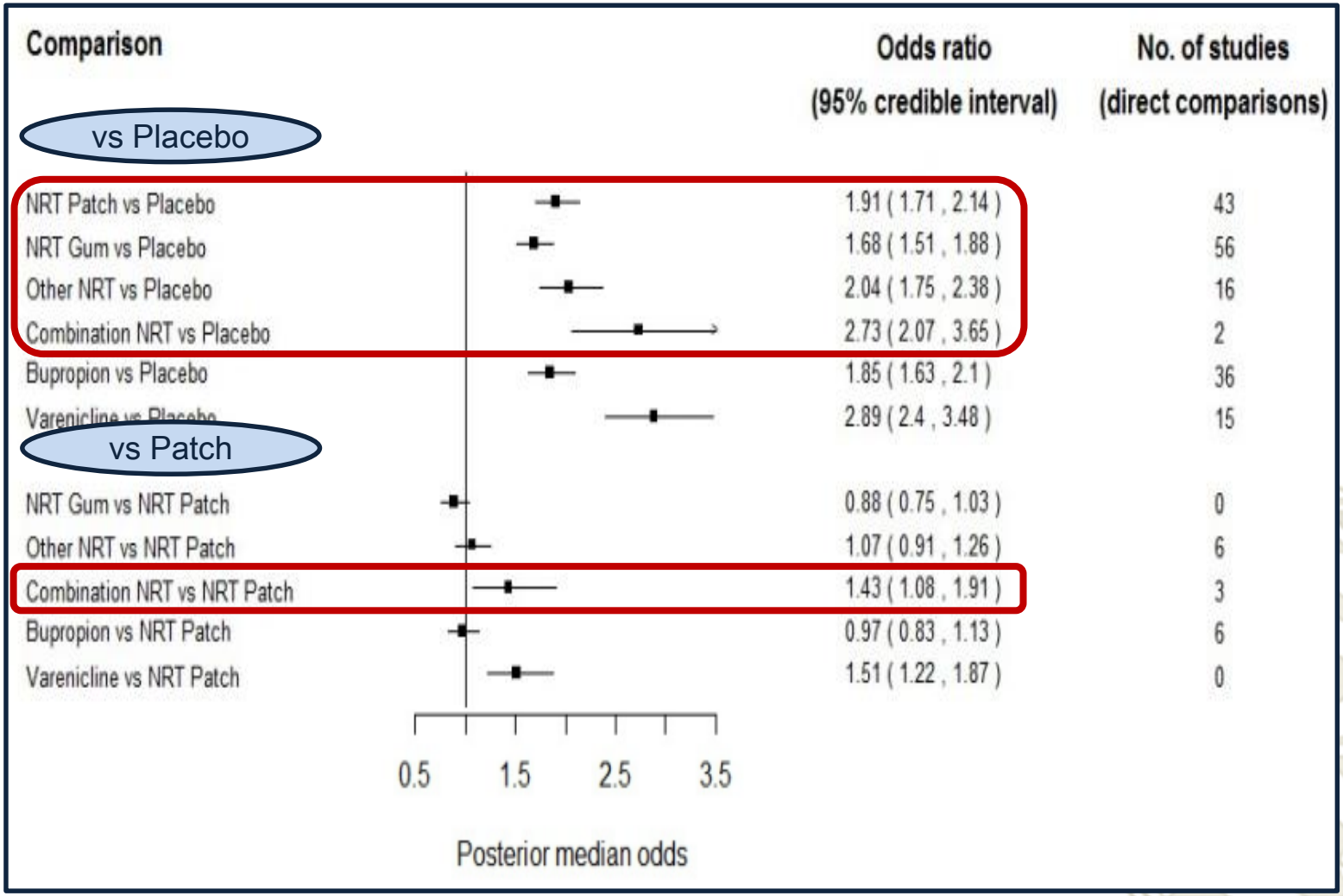
Treatment	End of Treatment, 8 wk Postquit			6 mo Postquit		
	Wald	*P* Value	OR (95% CI)	Wald	*P* Value	OR (95% CI)
Relative to placebo						
Bupropion	4.75	.03	1.55 (1.05-2.31)	5.01	.03	1.63 (1.06-2.51)
Lozenge	4.93	.03	1.57 (1.05-2.33)	6.68	.01	1.76 (1.15-2.70)
Patch	9.64	.002[a]	1.87 (1.26-2.77)	7.70	.006	1.83 (1.20-2.81)
Bupropion + lozenge	18.10	<.001[a]	2.35 (1.59-3.49)	6.42	.01	1.74 (1.13-2.67)
Patch + lozenge	24.02	<.001[a]	2.67 (1.80-3.96)	15.65	<.001[a]	2.34 (1.54-3.57)
Relative to monotherapies						
Bupropion + lozenge	5.95	.02	1.42 (1.07-1.88)	0.00	>.99	1.00 (0.74-1.35)
Patch + lozenge	11.19	.001[a]	1.61 (1.22-2.13)	4.12	.04	1.35 (1.01-1.79)
Monotherapies relative to each other[b]						
Patch vs lozenge	0.97	.32	0.84 (0.59-1.19)	0.05	.83	0.96 (0.67-1.38)
Bupropion vs lozenge	0.003	.96	1.01 (0.71-1.43)	0.38	.54	.89 (0.62-1.28)
Patch vs bupropion	1.09	.30	0.83 (0.59-1.18)	0.38	.54	.89 (0.62-1.28)
Patch + lozenge vs bupropion + lozenge	0.53	.47	0.88 (0.63-1.24)	2.68	.10	0.74 (0.52-1.06)

Combination NRT



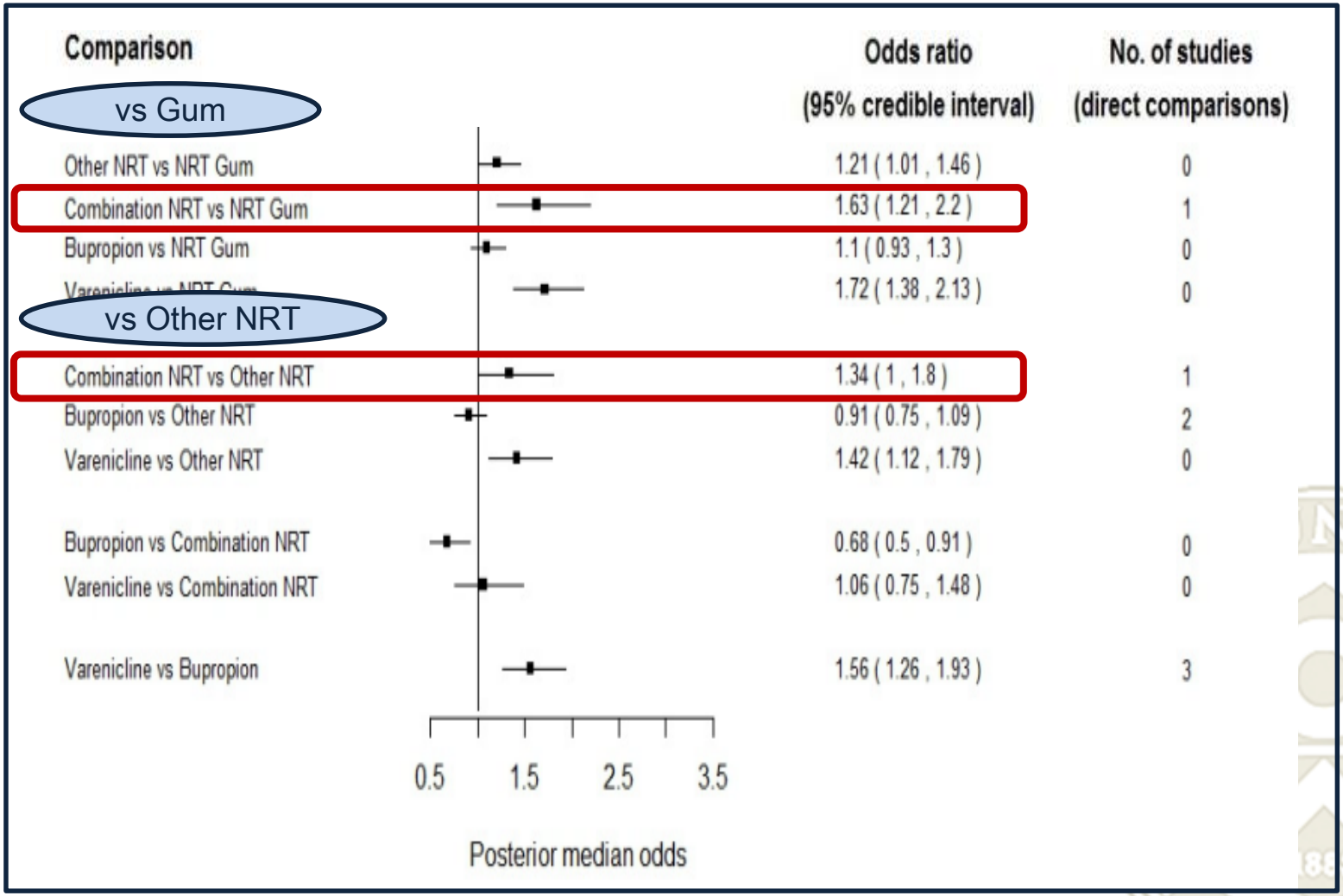
Piper et al. Arch Gen Psychiatry. 2009

Meta-analysis



Cahill et al. Cochrane. 2013

Meta-analysis



Cahill et al. Cochrane. 2013

NRT and cardiovascular disease

- Lung Health Study
- 3332 middle aged smokers with COPD; f/u for 5 yrs
- Quit with vs without nicotine gum

Table 4—*Proportional Hazards Regression* Predicting Fatal and Nonfatal Cardiovascular Events Among 3,332 Special Intervention Participants*

Covariate	Coefficient	SE	Risk Ratio	95% CI	p Value
NP use†	−1.915	1.152	0.15	(0.02, 1.41)	0.10
Current smoker†	0.473	0.150	1.61	(1.20, 2.16)	0.002
NP use by Log time†,‡	0.286	0.180			0.11
Gender (Risk=male)	0.926	0.179	2.52	(1.78, 3.59)	<0.0001
Age (Risk/decade)	0.759	0.115	2.14	(1.71, 2.68)	<0.0001
Diastolic BP (Risk/10 mm Hg)	0.186	0.078	1.20	(1.03, 1.40)	0.02

*Stratified on Lung Health Study clinic.

†Entered as a time-dependent covariate. Categories for smoking and gum use are determined at the start of each four-month interval. Data were used only from visits conducted within ±2 months of the anniversary date. Missing data were handled as follows: participants missing smoking information were assumed to be smoking, and participants missing gum information were assumed to be not using gum.

‡"Time" is entered as number of days of follow-up after the first 4-month visit.

Murray et al. Chest. 1996

NRT and cardiovascular disease

- Case-Control Network
  (Philadelphia metropolitan area)
  - Case: current smoker with MI
  - Control: current smoker without MI
  - Duration: 6 months
  - NRT: nicotine patch

Cases NRT Exposed /Total (%)	Controls NRT Exposed/Total (%)	Exact OR (95% CI)	Exact *P*-value
3/653 (0.46%)	30/2990 (1%)	0.46 (0.09-1.47)	0.26

Kimmel et al. J Am Coll Cardiol. 2001

NRT and cardiovascular disease

- RCT, 10 Veterans Affairs medical centers
- At least 1 cardiovascular disease
  - MI, CABG, angioplasty, stenosis of at least 50% in at least one major coronary artery, angina, CHF, cor pulmonale, arrhythmia, PAOD, CVD
- 10 wks course of nicotine patch
- 14 wks monitoring

Joseph et al. NEJM. 1996

NRT and cardiovascular disease

Event	Subjects with Events*			Events		
	Nicotine (N=294)	Placebo (N=290)	P value	Nicotine	Placebo	P value
	no. (%)			no.		
Primary end points						
Death	1	6		1	6	
Myocardial infarction	0	1		0	1	
Cardiac arrest	1	1		1	1	
Admission for increased severity of angina	7	10		8	12	
Admission for arrhythmia	5	3		6	6	
Admission for congestive heart failure	2	2		3	3	
Total	16 (5.4)	23 (7.9)	0.23	19	29	0.10
Secondary end points						
Admission for peripheral vascular disease	3	5		3	5	
Admission for cerebrovascular disease	4	3		5	4	
Admission for other reasons†	16	13		21	16	
Outpatient visit for increased severity of atherosclerotic cardiovascular disease	12	7		16	8	
Total	35 (11.9)	28 (9.7)	0.37	45	33	0.23
All end points	48 (16.3)	47 (16.2)	0.97	64	62	0.39

Joseph et al. NEJM. 1996

After acute coronary syndrome

- Observational study from pre-existing database
- NRT (n=184) vs none (n=479)

One-year outcomes and adjusted odds ratios (95% confidence intervals)*

Outcome	NRT	Control	OR (95% CI)
Composite†	53 (29%)	149 (31%)	0.89 (0.61–1.30)
Death	7 (4%)	24 (5%)	0.80 (0.33–1.91)
Myocardial infarction	8 (4%)	23 (5%)	0.90 (0.40–2.06)
Repeat revascularization	18 (10%)	58 (12%)	0.77 (0.44–1.36)
Hospitalization‡	41 (22%)	104 (22%)	1.01 (0.66–1.53)

OR = odds ratio; CI = confidence interval.

* Adjusted for the independent variables of dialysis status, gender, prior coronary artery bypass grafting, and race.

† Death, myocardial infarction, repeat revascularization, or hospitalization for angina, congestive heart failure, or arrhythmia.

‡ For angina, congestive heart failure, or arrhythmia.

Woolf et al. Am J Cardiol. 2012

NRT and cardiovascular disease

- Chemicals other than nicotine are responsible for the elevated risks of myocardial infarction and stroke in smokers.

- Benefits of nicotine medication far outweigh the risks of continued smoking in such patients.

NRT for Pregnancy (Nicotine Patch)

- RCT
  - 15mg (16 hrs/day) for 8 weeks then 10mg patches (16 hrs/day) for 3 week
  - Among total 77 patches
    - Nicotine: median 14 patches
    - Placebo: median 7 patches

	Nonsmokers (%)			Mean number of cigarettes/day		
	Nicotine	Placebo	*P*	Nicotine	Placebo	*P*
First prenatal visit				13.4	14.2	.78
Second prenatal visit	37	29	.15	6.7	7.2	.50
Third prenatal visit	32	26	.29	7.0	6.4	.16
Fourth prenatal visit	28	25	.52	6.7	6.5	.56
3 months postpartum	21	18	.57	7.2	7.0	.59
1 y postpartum	15	14	.92	6.8	7.3	.55

  - No difference in birth weight and preterm delivery

Wisborg et al. Obstet Gynecol. 2000

NRT for Pregnancy (Nicotine Patch)

- RCT
  - Pregnancies of 12-24 gestational weeks
  - Nicotine patches 15mg per 16 hours

Outcome	Nicotine Replacement (N=521)	Placebo (N=529)	Odds Ratio (95% CI)†	Adjusted Odds Ratio (95% CI)‡
Primary				
Abstinence from quit date to delivery, with salivary cotinine validation, with or without CO validation§	49 (9.4)	40 (7.6)	1.26 (0.82–1.96)	1.27 (0.82–1.98)
Secondary				
Abstinence from quit date to delivery without validation	65 (12.5)	49 (9.3)	1.40 (0.94–2.07)	1.41 (0.95–2.09)
Abstinence for 1 mo after quit date without validation	131 (25.1)	74 (14.0)	2.07 (1.51–2.85)	2.13 (1.54–2.95)
Abstinence for 1 mo after quit date with CO validation¶	111 (21.3)	62 (11.7)	2.05 (1.46–2.88)	2.10 (1.49–2.97)
Abstinence from quit date to delivery with validation at 1 mo and at delivery	42 (8.1)	32 (6.0)	1.36 (0.84–2.19)	1.37 (0.84–2.22)
Point-prevalence abstinence (cessation for >24 hr) at delivery with CO validation	63 (12.1)	53 (10.0)	1.23 (0.84–1.82)	1.24 (0.84–1.85)
Point-prevalence abstinence (cessation for >24 hr) at delivery without validation	104 (20.0)	89 (16.8)	1.24 (0.90–1.70)	1.25 (0.90–1.72)

Low compliance

7.2%

2.8%

Coleman et al. NEJM. 2012

NRT for Pregnancy (Nicotine Patch)

- No significantly different birth outcomes
  - Mean birth weight
  - Rates of preterm birth
  - Low birth weight
  - Congenital abnormalities

  - Cesarean section
    (20.7% in NRT vs 15.3% in placebo)

Coleman et al. NEJM. 2012

NRT for Pregnancy

- If abstinence from nicotine is not possible
  - NRT is less hazardous than cigarette smoking

- Safety of NRT during pregnancy
  - Limited
  - More clinical trials
  - More post-marketing surveillance studies

Tobacco Advisory Group of Royal College of Physicians. 2007

Summary for NRT

- Licensed nicotine-containing products:
  Safe
- Risk to health from NRT use < risk from continued smoking
- Long acting and short acting NRT
  Combination
- Risk of cardiovascular disease
  Safe
- In pregnancy
  More study is needed

Thank U