



Pharmacotherapy for Smokeless Tobacco Use



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Disclosures

- Research has been supported by:
 - National Cancer Institute
 - Mayo Clinic College of Medicine
 - Pfizer
 - Varenicline supplied for drug trial
- Opinions expressed do not necessarily reflect the official views of the funding institutions
- Off-Label Use: Varenicline, bupropion, NRT not approved for the treatment of ST use



Goals & Objectives

- Provide a brief overview of smokeless tobacco (ST)
- Review what we know about the pharmacologic treatment of ST use
 - Nicotine replacement therapy (NRT)
 - Patch/Gum/Lozenge
 - Bupropion SR
 - Varenicline



Smokeless Tobacco: United States

- Chewing tobacco
 - Loose leaf (i.e., Redman)
 - Plugs
 - Twists
- Snuff
 - Moist (Copenhagen, Skoal)
 - Dry (Honest, Honey bee, Navy, Square)



Scandinavian Snus

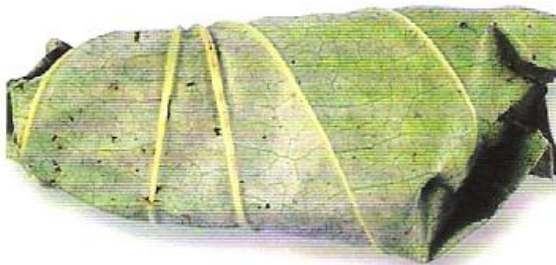




Pan Masala (Betel quid)



Handmade



Manufactured





A street vendor in Mumbai makes paan, a South Asian chewing tobacco product made from the leaf of the Betel tree packed with a lime paste and spices, decorated with coconut shavings and cherries on top. MCT

Toombak



Toombak wholesale advertisement



RJ Reynolds's



Phillip Morris (Altria)



“Dissolvables”



Tobacco-less Nicotine Product - Altria

“VERVE discs are a new kind of tobacco product designed to appeal to adult smokers interested in innovative types of spit-free tobacco product alternatives to cigarettes. Adult tobacco product consumers put the product in their mouth, chew on it and should properly dispose of it when they are done.”



Package of 16 discs, each containing about 1.5 milligrams of nicotine = \$3

Virginia test market

Tobacco-Related Oral Disease



Health Effects: Cancers - U.S. Data

<u>Location</u>	<u>OR (95% CI)</u>
Cancer, Mouth and Gum	11.2 (4.1-30.7) ^A
Gum & Buccal Mucosa	4.2 (2.6-6.7) ^B
Larynx	7.3 (2.9-18.3) ^A
Salivary gland	5.3 (1.2-23.4) ^A
Kidney cancer	4.0 (1.2-12.9) ^C
Pancreatic cancer	3.5 (1.1-11) ^D

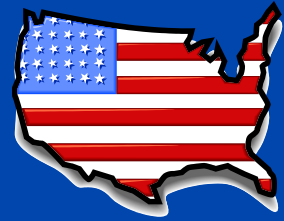
A - Stockwell HG, et al. Head Neck Surg. 1986 Nov-Dec;9(2):104-10.

B - Winn DM, et al. N Engl J Med. 1981 Mar 26;304(13):745-9.

C - Goodman MT, et al. Am J Epidemiol. 1986 Dec;124(6):926-41.

D - Alguacil J, et al. Cancer Epidemiol Biomarkers Prev. 2004 Jan;13(1):55-8.





ST Health Effects: CV Disease

- CPS-II

- **Current ST use vs. never* associated with death from:
 - All causes: HR 1.18 (95% CI: 1.08-1.29)
 - CHD: HR 1.26 (95% CI: 1.08-1.47)
 - Cerebrovascular dz: HR 1.40 (95% CI: 1.10-1.79)
- No difference between snuff and chewing tobacco
 - *Multivariate-adjusted

Henley et al., *Canc Cause Control*. 2005; 16: 347-358.

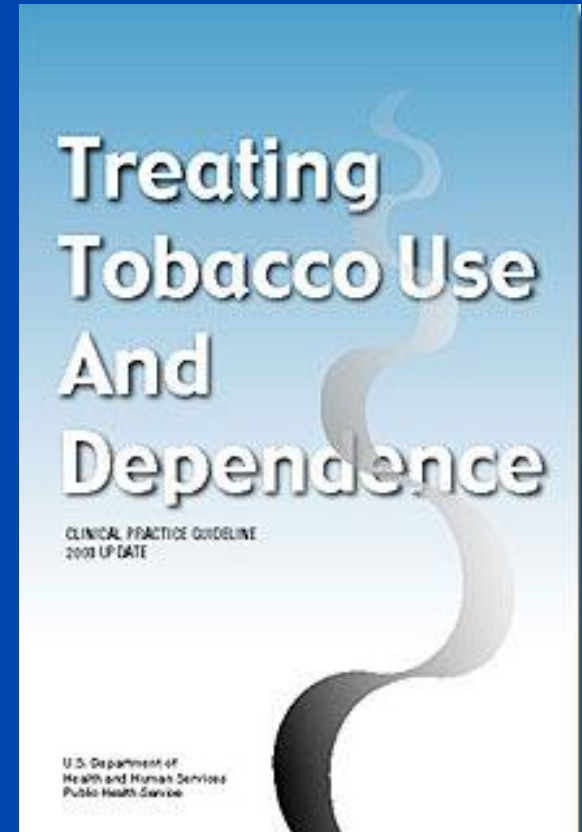


What do we know about ST treatment?



USPHS Guideline Recommendations

- **First-Line**
 - **Nicotine Replacement Therapy**
 - Gum
 - Patch
 - Inhaler
 - Nasal Spray
 - Lozenge
 - **Non-NRT**
 - Bupropion SR
 - Varenicline



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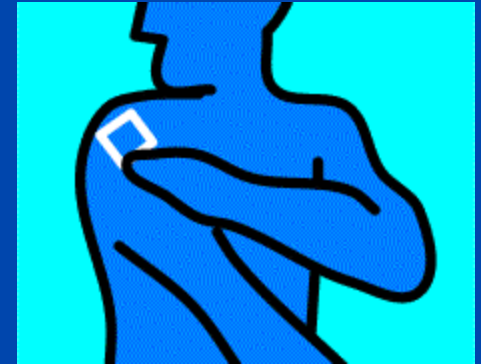
Nicotine Gum (2 mg)

- 210 ST users
 - Group Tx + 2 mg gum
 - Group Tx + placebo
 - Min. contact + 2 mg gum
 - Min. contact + placebo
- 2 mg gum: 8 weeks
- Groups involving group therapy or placebo were equally effective and superior to minimal contact + 2 mg group
- Withdrawal symptoms were reduced



Hatsukami DK, et al. *J Consult Clin Psychol.* Feb 1996;64(1):153-161.

Nicotine Patch



- 402 ST users
 - Active Patch + Mint Snuff
 - Active Patch + \emptyset Snuff
 - Placebo Patch + Mint Snuff
 - Placebo Patch + \emptyset Snuff
- Patch: 21 mg x 6 weeks; 14 mg x 2 weeks; 7 mg x 2 weeks
- Nicotine patch increased continuous abstinence rates compared to placebo at 10 weeks but not at 23 weeks
- Nicotine patch decreased craving and withdrawal
 - But so did the mint snuff

Hatsukami DK, et al. *J Consult Clin Psychol.* 2000;68(2):241-249.

Bupropion SR for ST Users Study

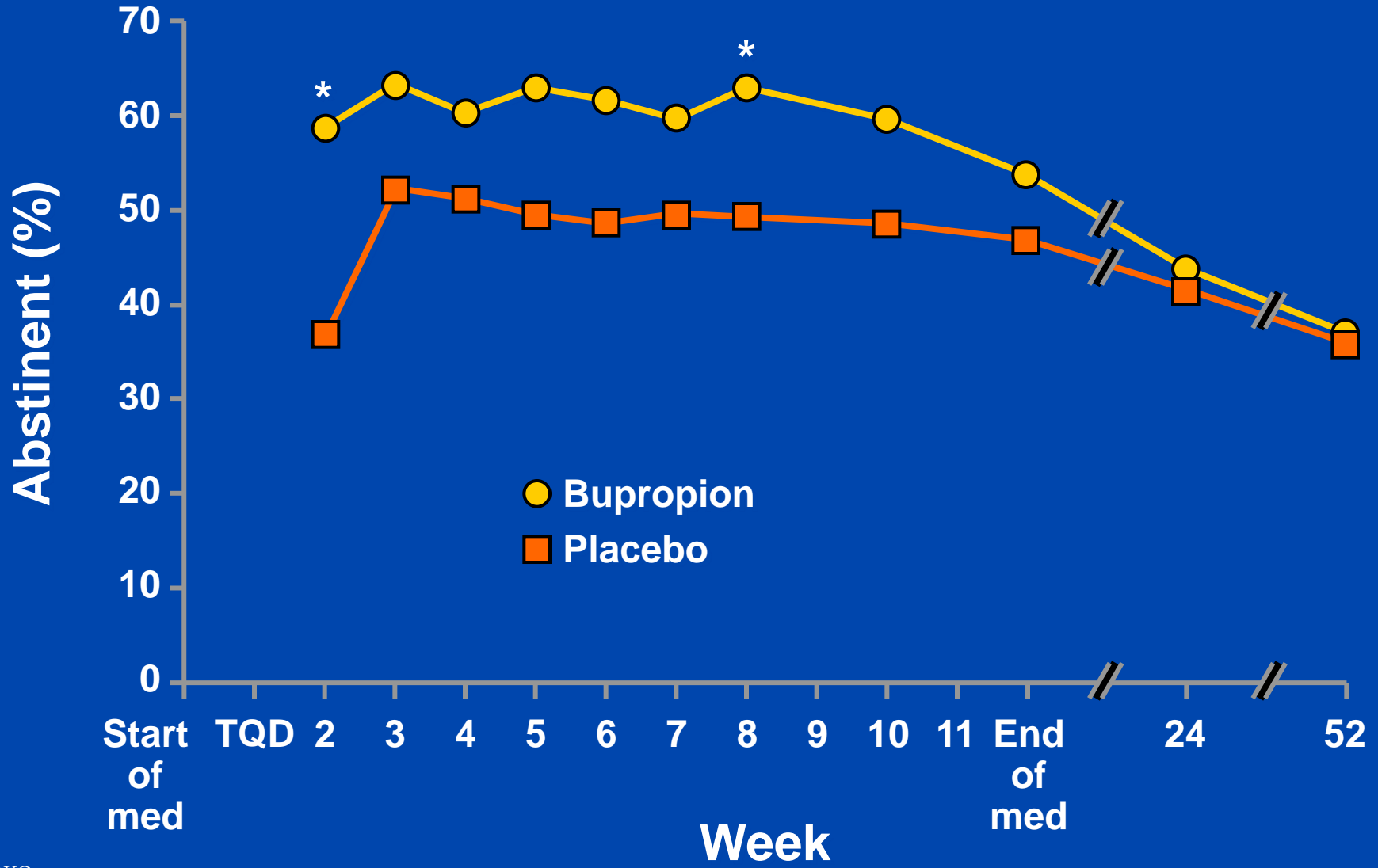
- NCI R01 9088
- Randomized 225 ST users to:
 - Bupropion SR (N = 113)
 - 150 mg twice daily x 12 weeks
 - Placebo (N = 112)



Dale LC, et al. *Drug Alcohol Depend.* Sep 6 2007;90(1):56-63.

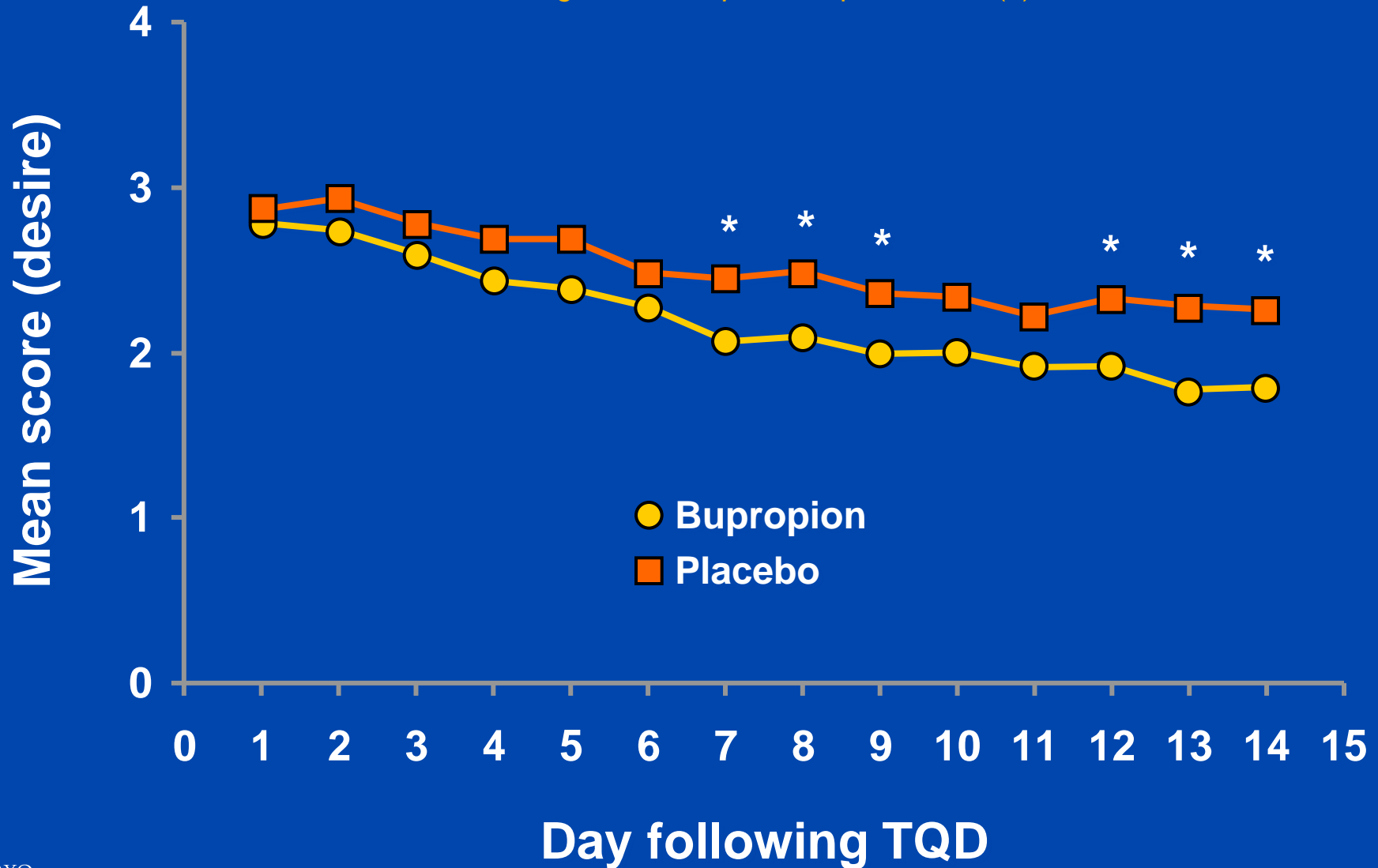
7-Day Point Prevalence Abstinence

Dale LC, et al. *Drug Alcohol Depend.* Sep 6 2007;90(1):56-63.



Desire (Craving) to Use Tobacco

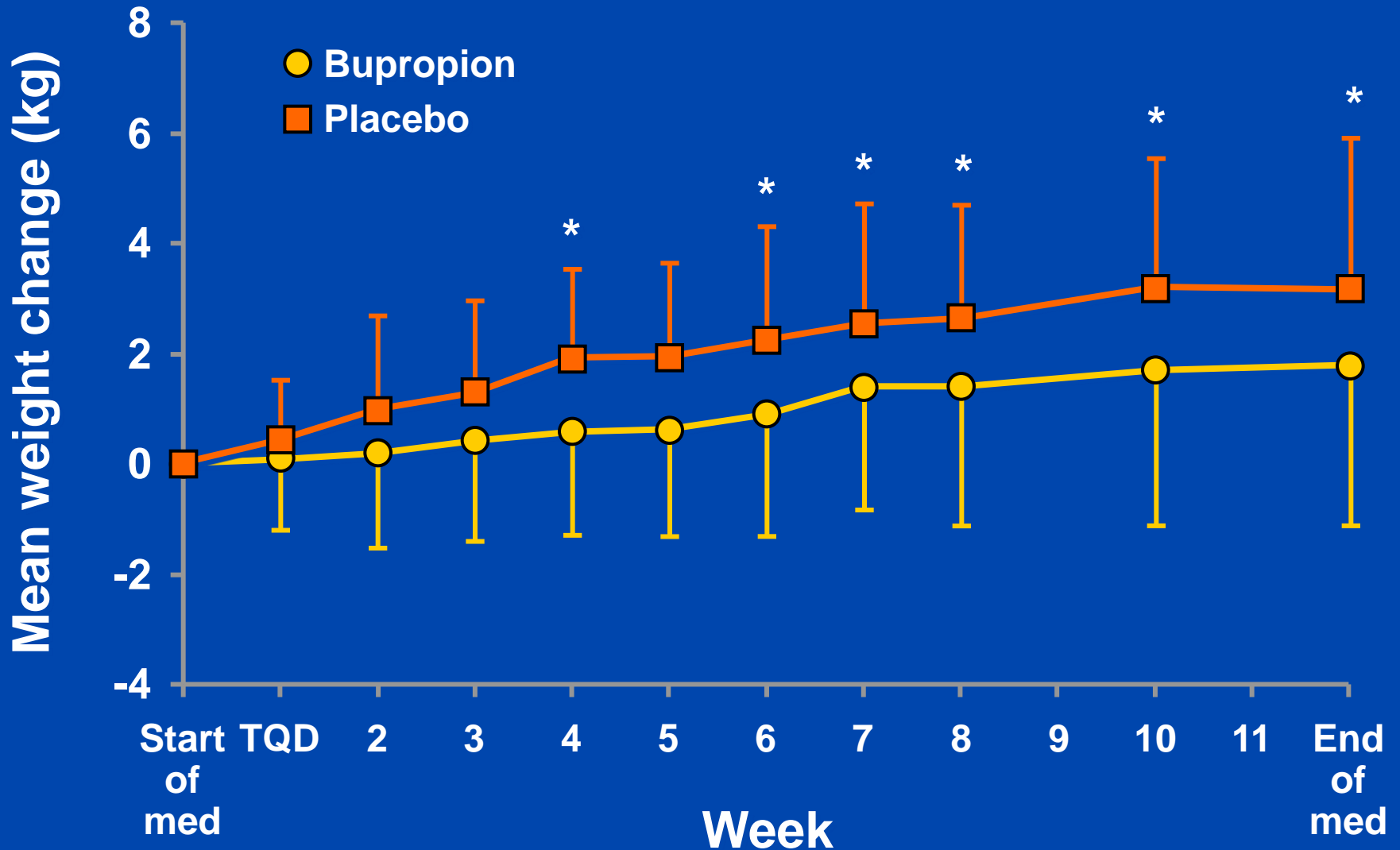
Dale LC, et al. *Drug Alcohol Depend.* Sep 6 2007;90(1):56-63.



* $P \leq 0.05$ comparing groups

Weight Change During Medication Phase

Dale LC, et al. *Drug Alcohol Depend.* Sep 6 2007;90(1):56-63.



* $P \leq 0.05$ bupropion compared to placebo

Nicotine Lozenge for ST Users

- NCI RO1 CA121165
- 270 ST users
- Randomized to:
 - Placebo
 - 4-mg nicotine lozenge



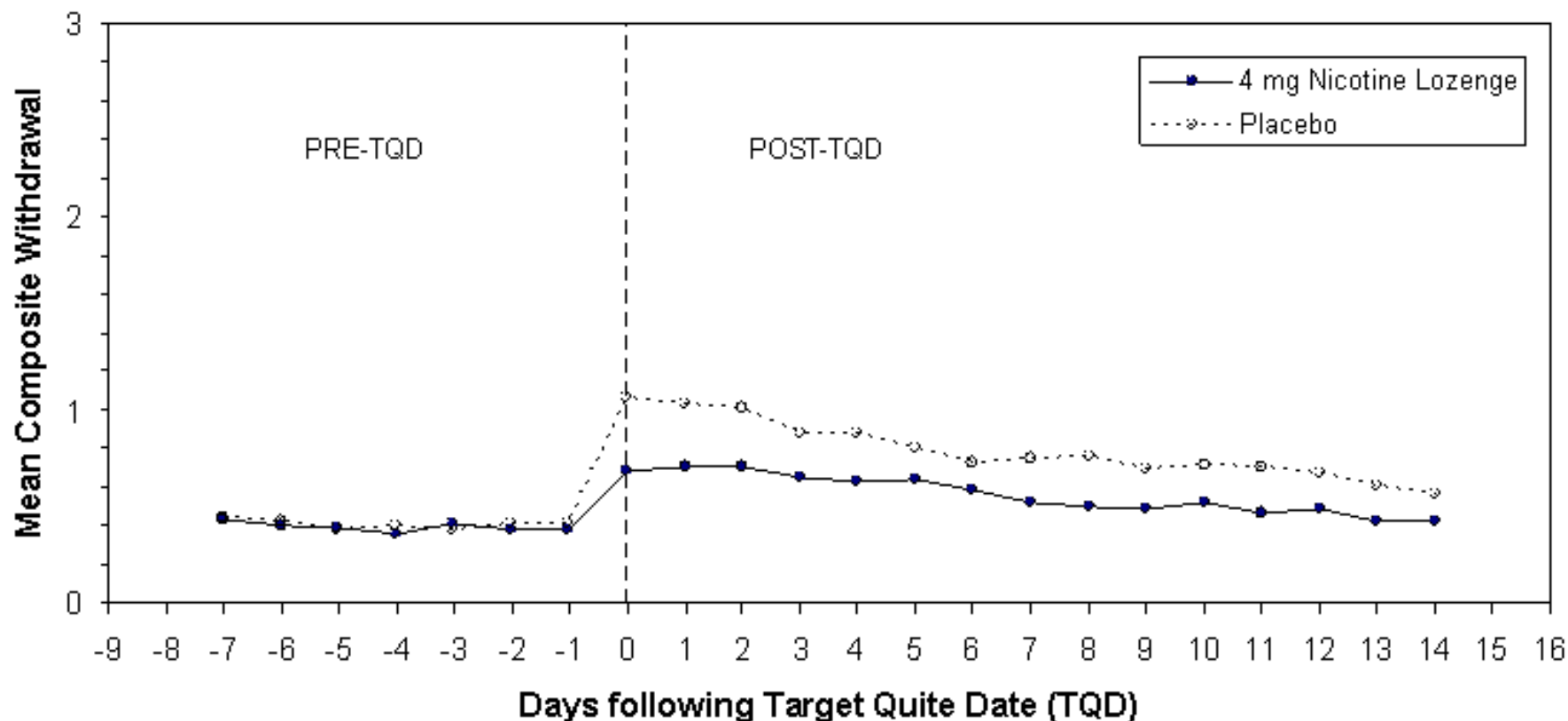
Self-reported 7-day point prevalence abstinence with 4-mg nicotine lozenge

Abstinence Definition*	4 mg nicotine lozenge (N=136)		Placebo (N=134)		Logistic Regression Result†		
	No.	(%)	No.	(%)	OR	95% C.I.	P-value
Week 12 (end-of-medication)							
Point Prevalence							
Smokeless tobacco abstinence	69	50.7	46	34.3	2.0	1.2 to 3.2	0.013
All tobacco abstinence	60	44.1	39	29.1	1.9	1.2 to 3.2	0.011
Prolonged							
Smokeless tobacco abstinence	65	47.8	41	30.6	2.1	1.3 to 3.4	0.004
Week 24							
Point Prevalence							
Smokeless tobacco abstinence	43	31.6	35	26.1	1.3	0.8 to 2.2	0.319
All tobacco abstinence	36	26.5	29	21.6	1.3	0.7 to 2.3	0.345
Prolonged							
Smokeless tobacco abstinence	41	30.2	31	23.1	1.4	0.8 to 2.5	0.194

*Abstinence is based upon self-reported 7-day point prevalence defined as no use within the past 7 days. In all cases, subjects that missed a visit were assumed to be using tobacco.

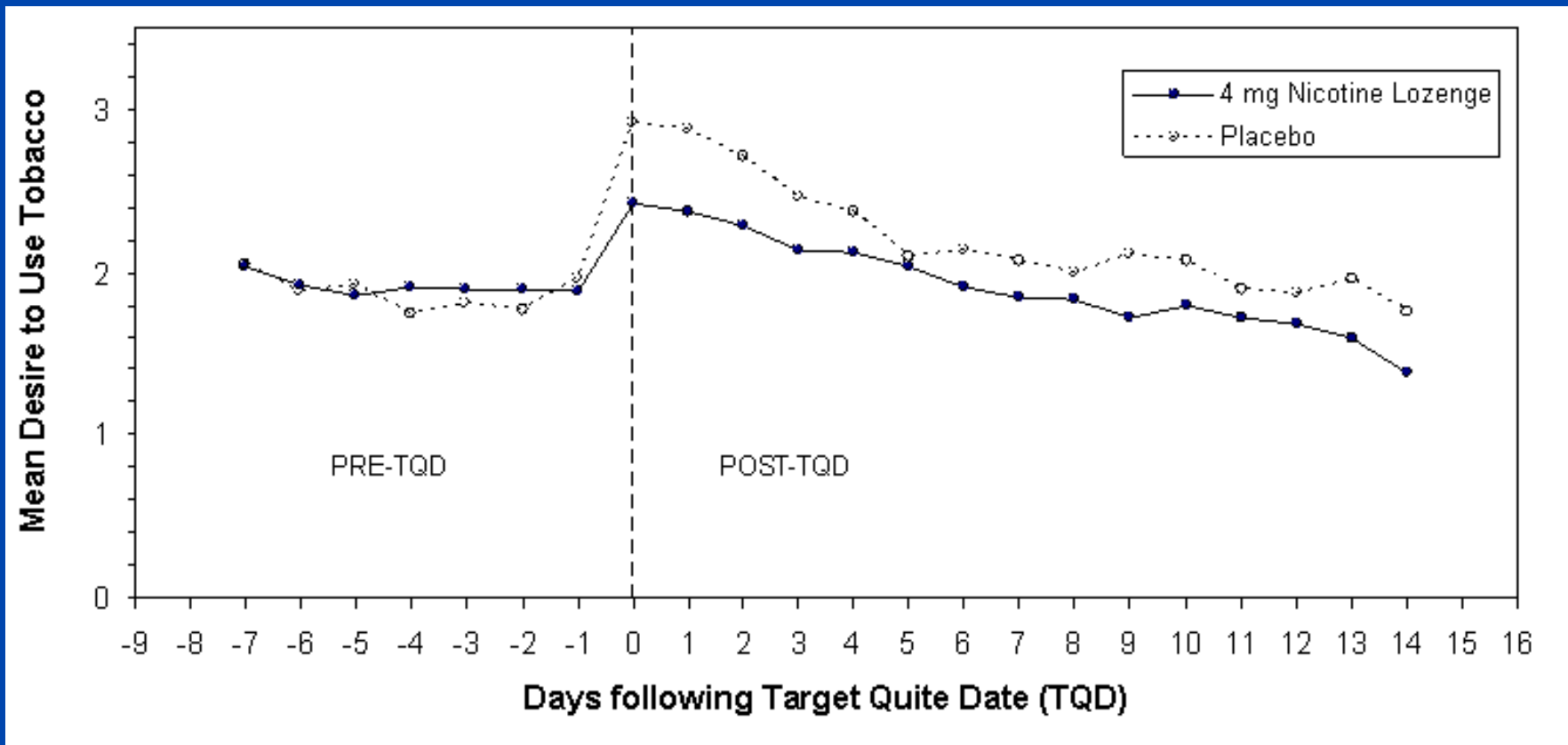
† In addition to treatment (nicotine vs. placebo) the logistic regression analysis included a covariate for study site. Odds ratios > 1.0 indicate an increased likelihood of abstinence for active nicotine lozenge compared to placebo.

Mean Composite Withdrawal



4-mg nicotine lozenge vs. placebo (treatment effect = -0.213, SE=0.071; $p=0.003$).

Mean Craving



4-mg nicotine lozenge vs. placebo (treatment effect = -0.452, SE=0.164; $p=0.006$)



Pharmacotherapy may decrease craving & withdrawal among ST users trying to achieve ST abstinence

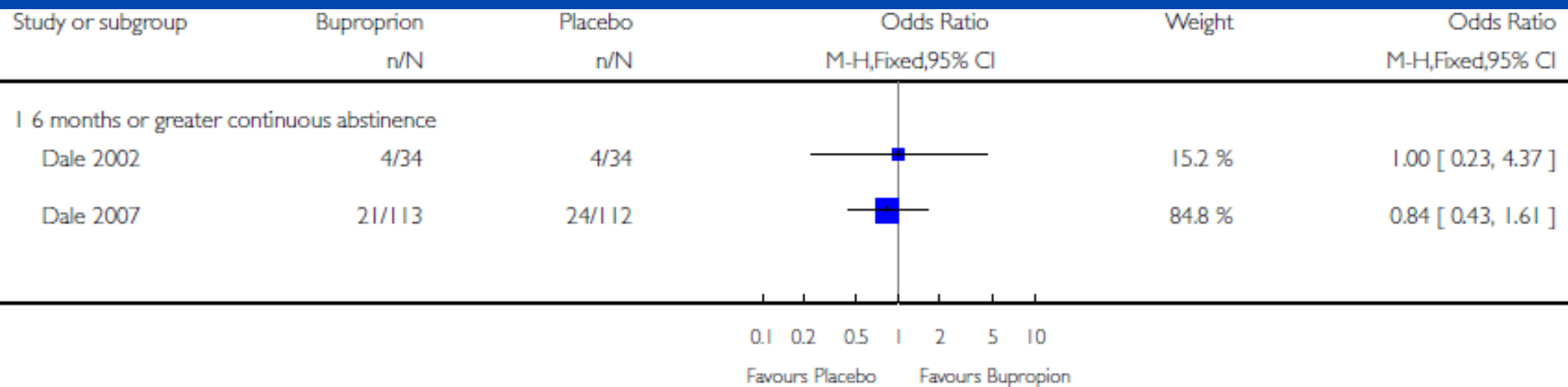
but....

What's the overall effect of pharmacotherapy on long-term (≥ 6 months) abstinence rates?

Long-term (abstinence ≥ 6 months) for ST Users

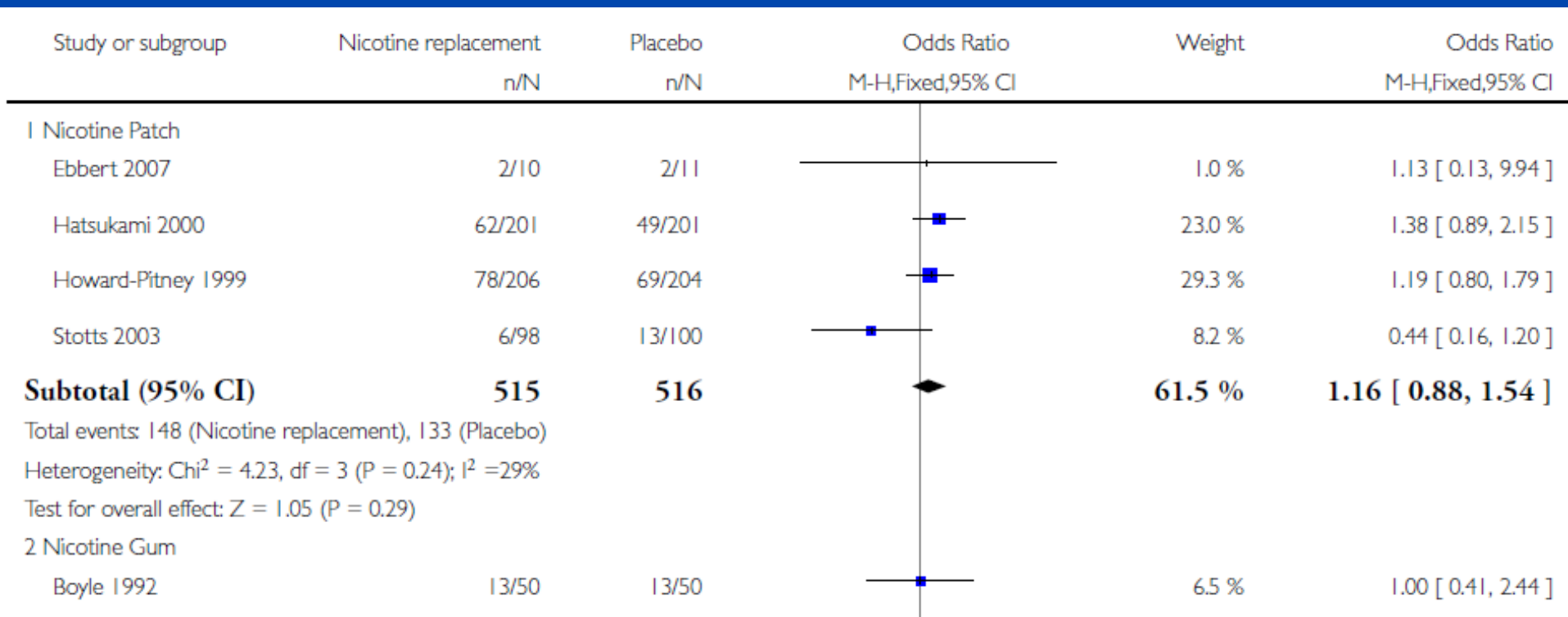


Bupropion: Effect at ≥ 6 months



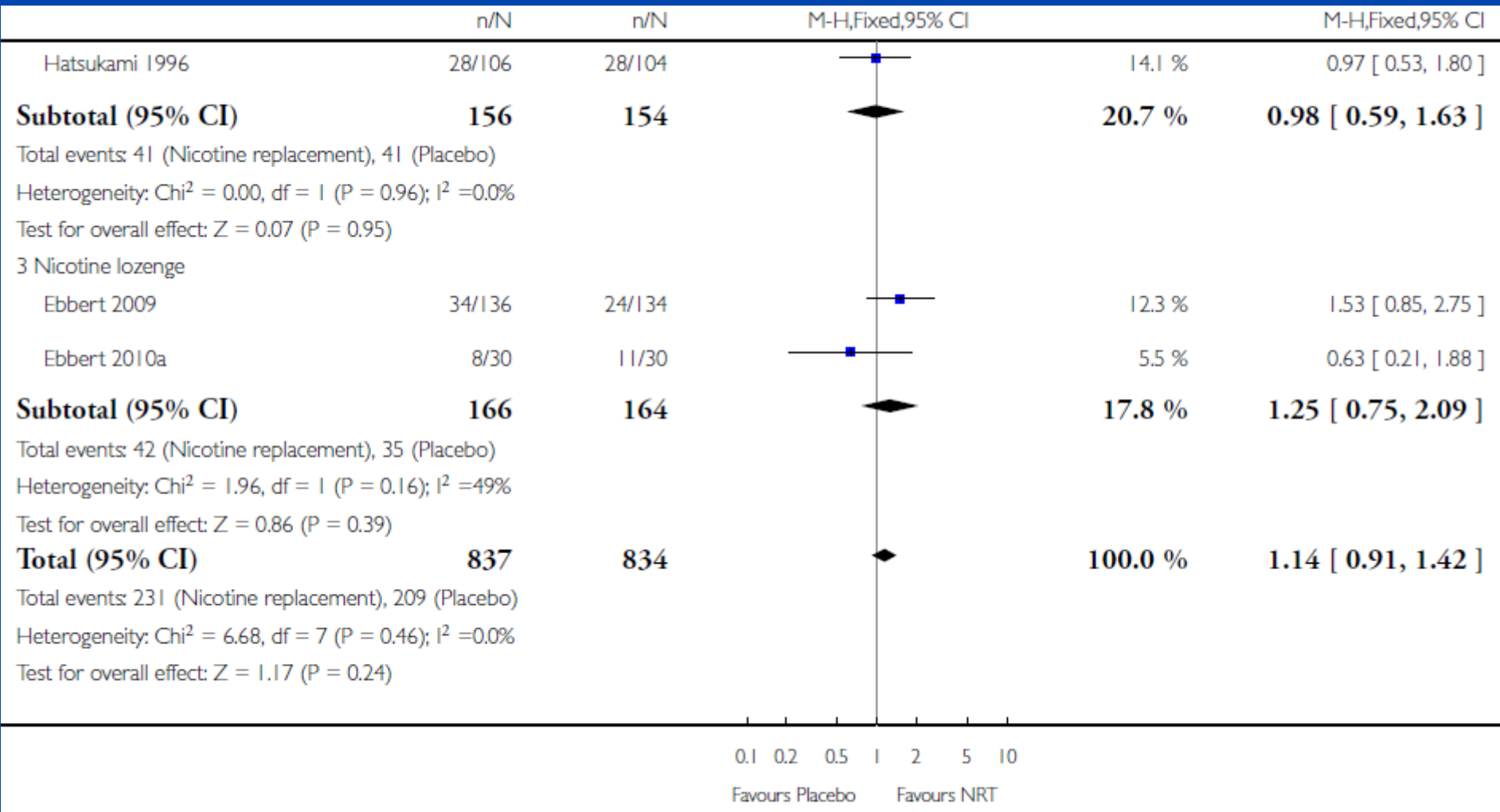
Ebbert J, Montori VM, Erwin PJ, Stead LF. Interventions for smokeless tobacco use cessation. *Cochrane Database Syst Rev.* 2011 Feb 16;(2):CD004306. PubMed PMID: 21328266.

NRT: Effect at ≥ 6 months



Ebbert J, Montori VM, Erwin PJ, Stead LF. Interventions for smokeless tobacco use cessation. *Cochrane Database Syst Rev.* 2011 Feb 16;(2):CD004306. PubMed PMID: 21328266.

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Why is NRT Not Effective?

- Under-replacement of nicotine with standard NRT dosing
- Similarities between ST and certain nicotine replacement products (i.e., nicotine gum)
- Treatment-naïve ST users
- High control condition abstinence rates in clinical trials of ST users



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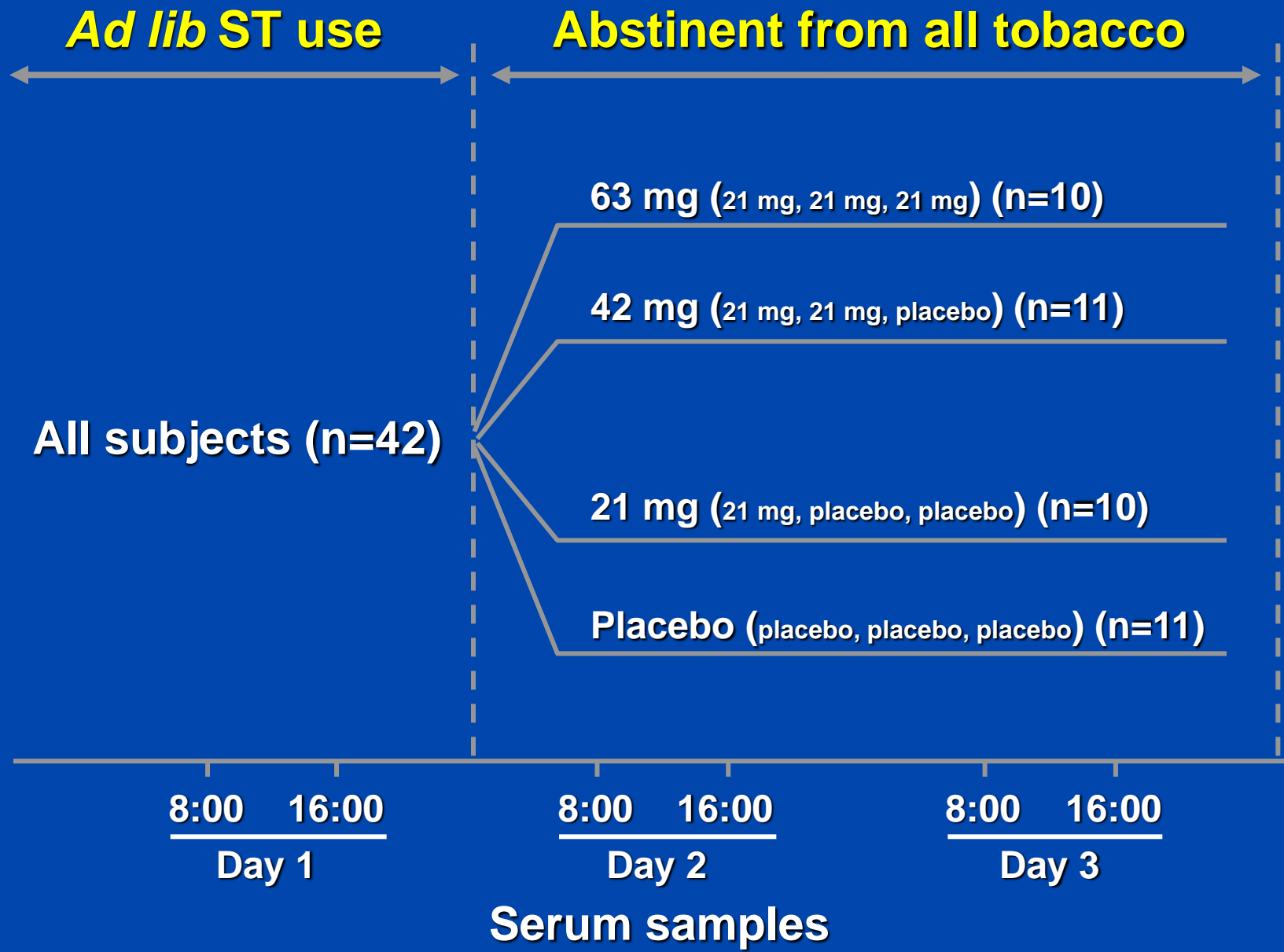


Nicotine Patch for ST Users

- NCI RO1 96881
- 42 ST users
- Randomized to:
 - Placebo
 - 21 mg/day
 - 42 mg/day
 - 63 mg/day

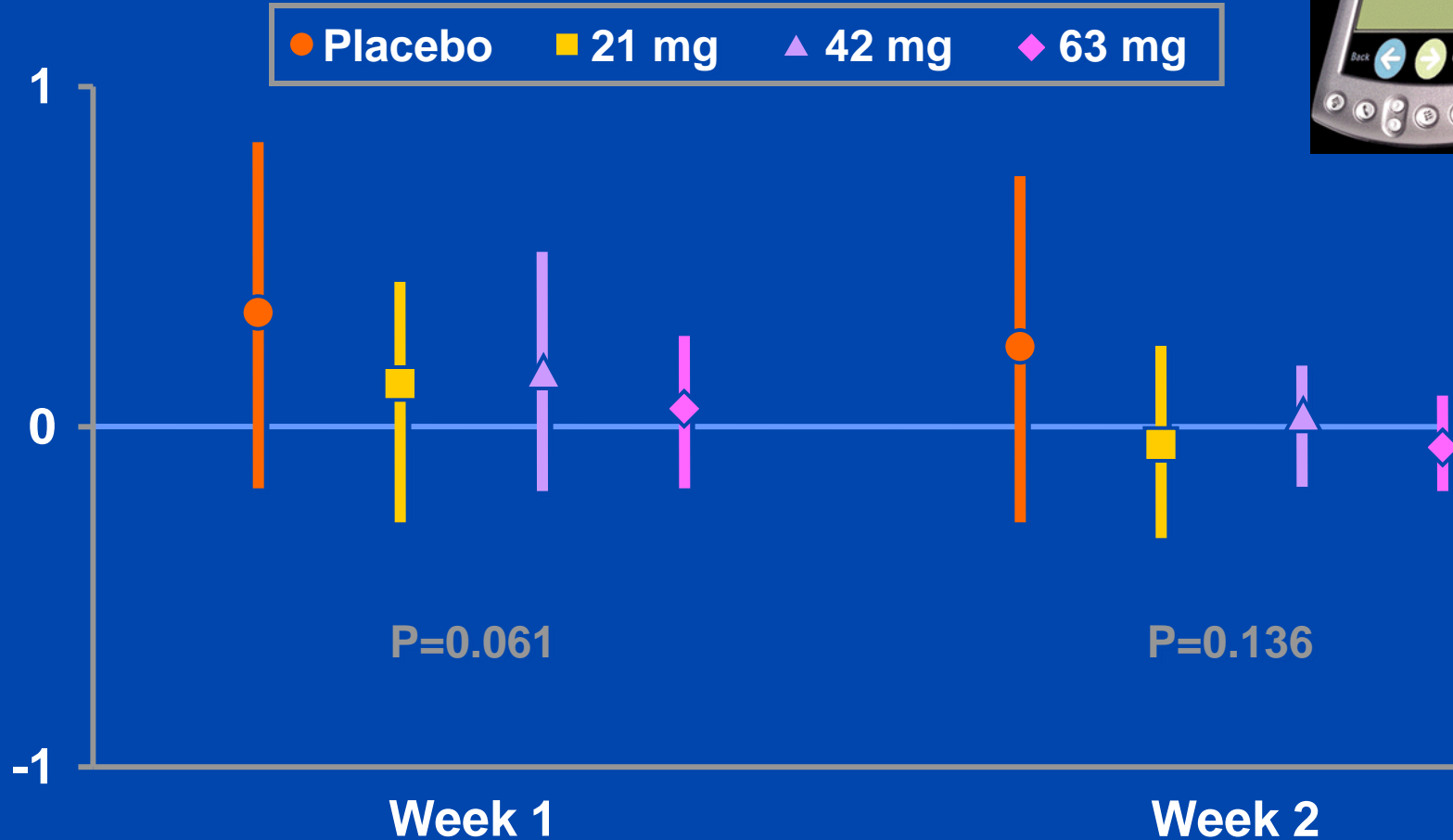


Ebbert JO, et al. *Nicotine Tob Res.* 2007;9(1):43-52.

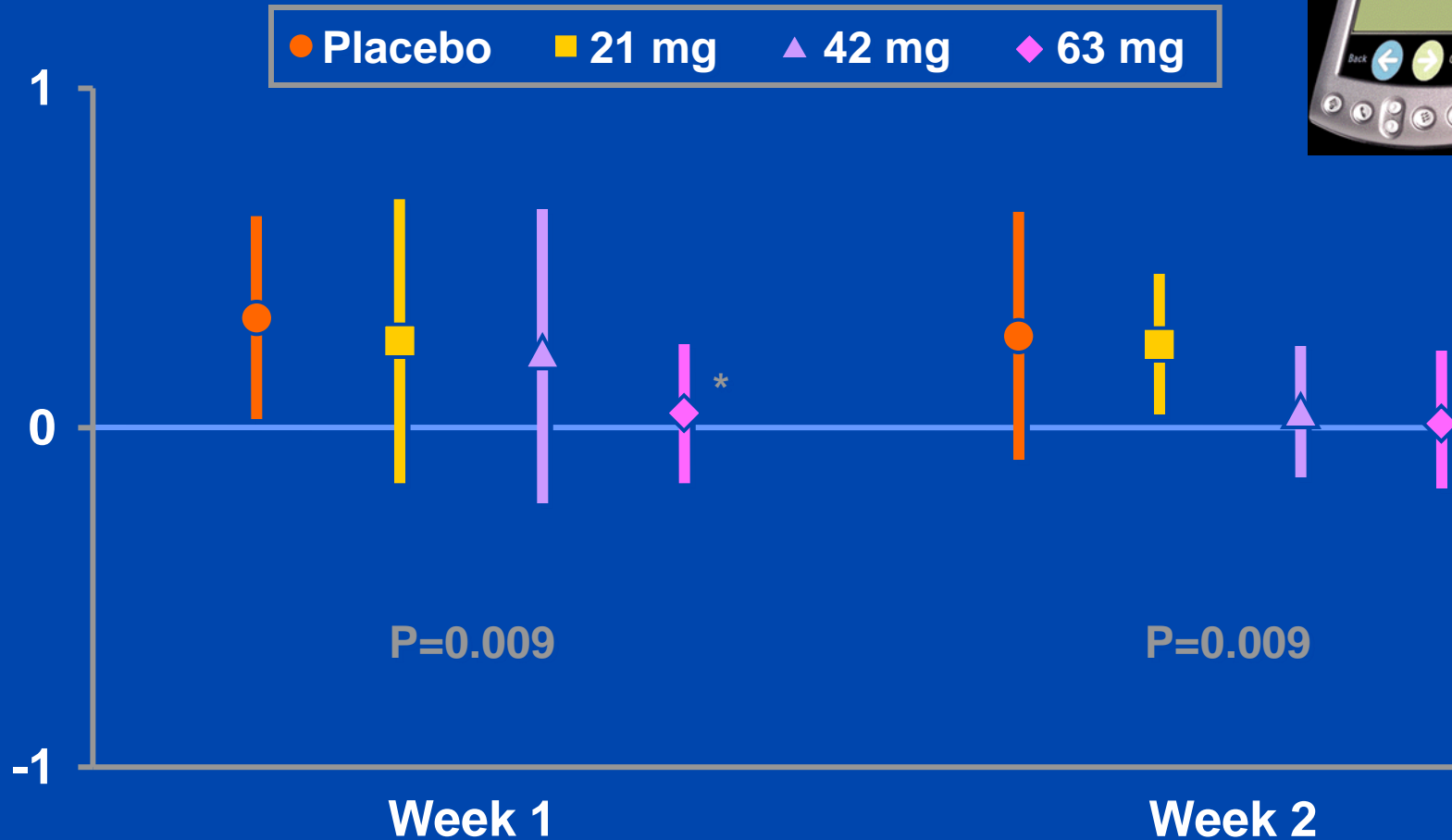


Ebbert JO, et al. *Nicotine Tob Res.* 2007;9(1):43-52.

Attention Disturbance

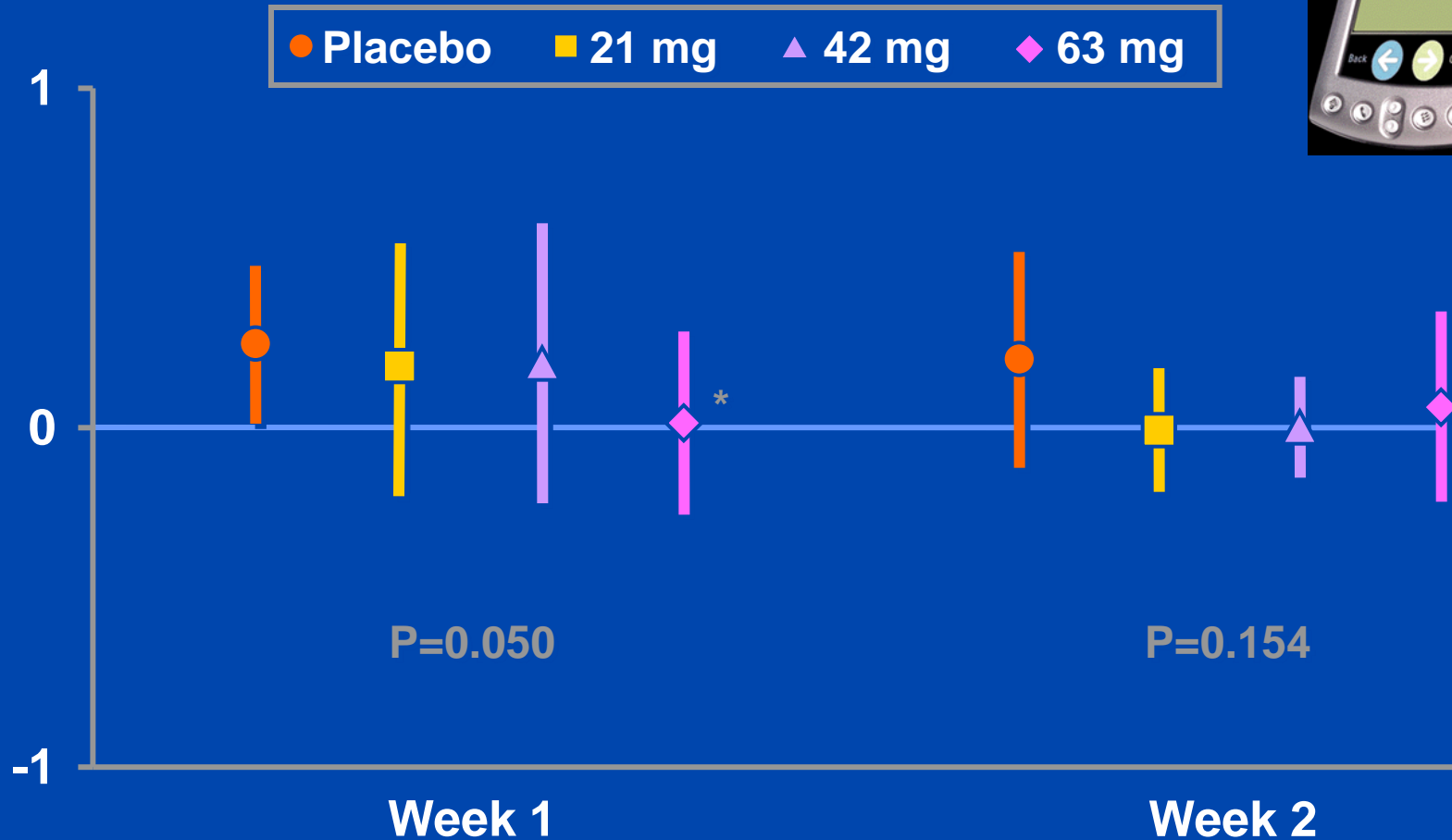


Decreased Arousal



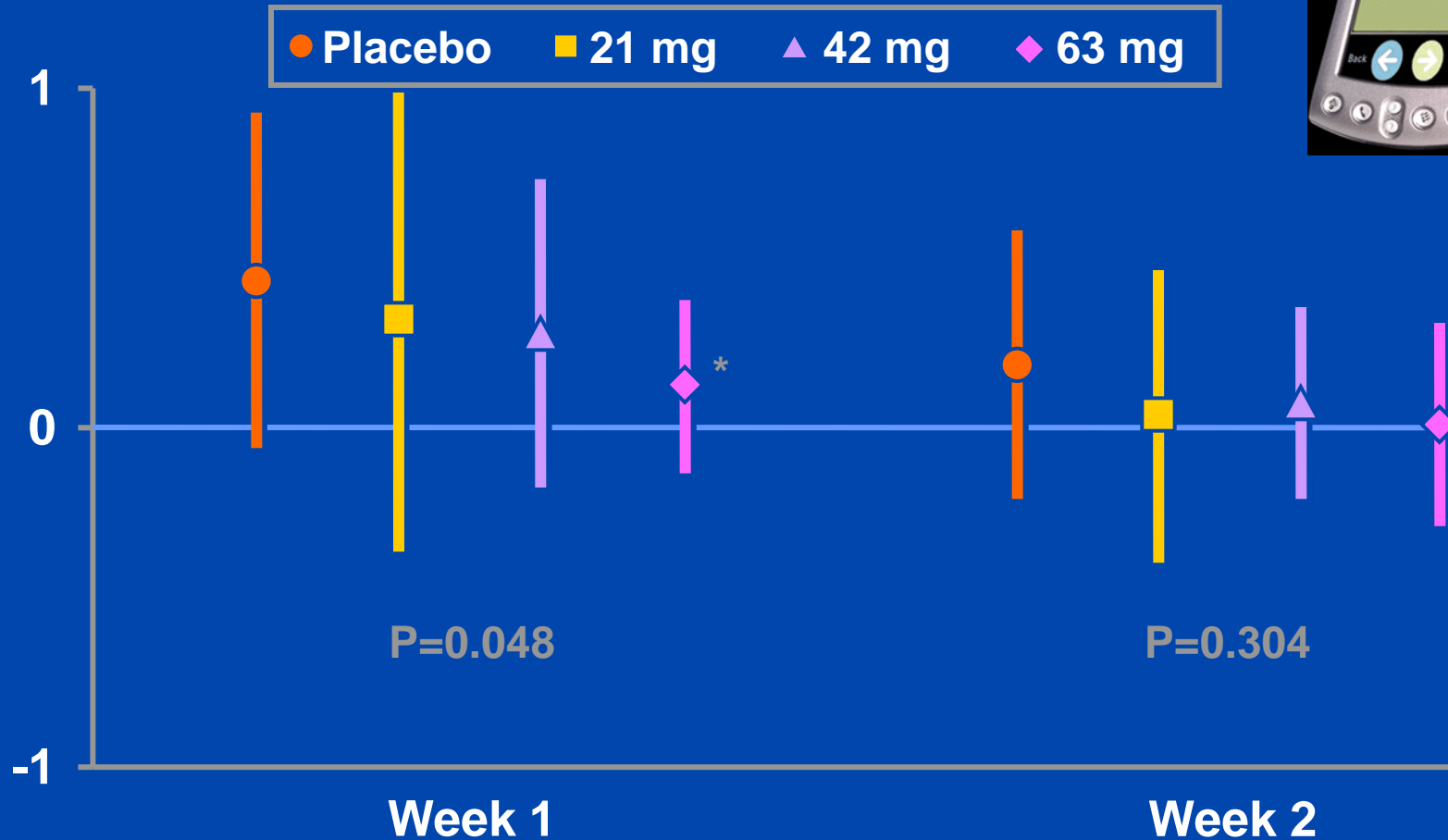
Ebbert JO, et al. *Nicotine Tob Res.* 2007;9(1):43-52.

Negative Affect



Ebbert JO, et al. *Nicotine Tob Res.* 2007;9(1):43-52.

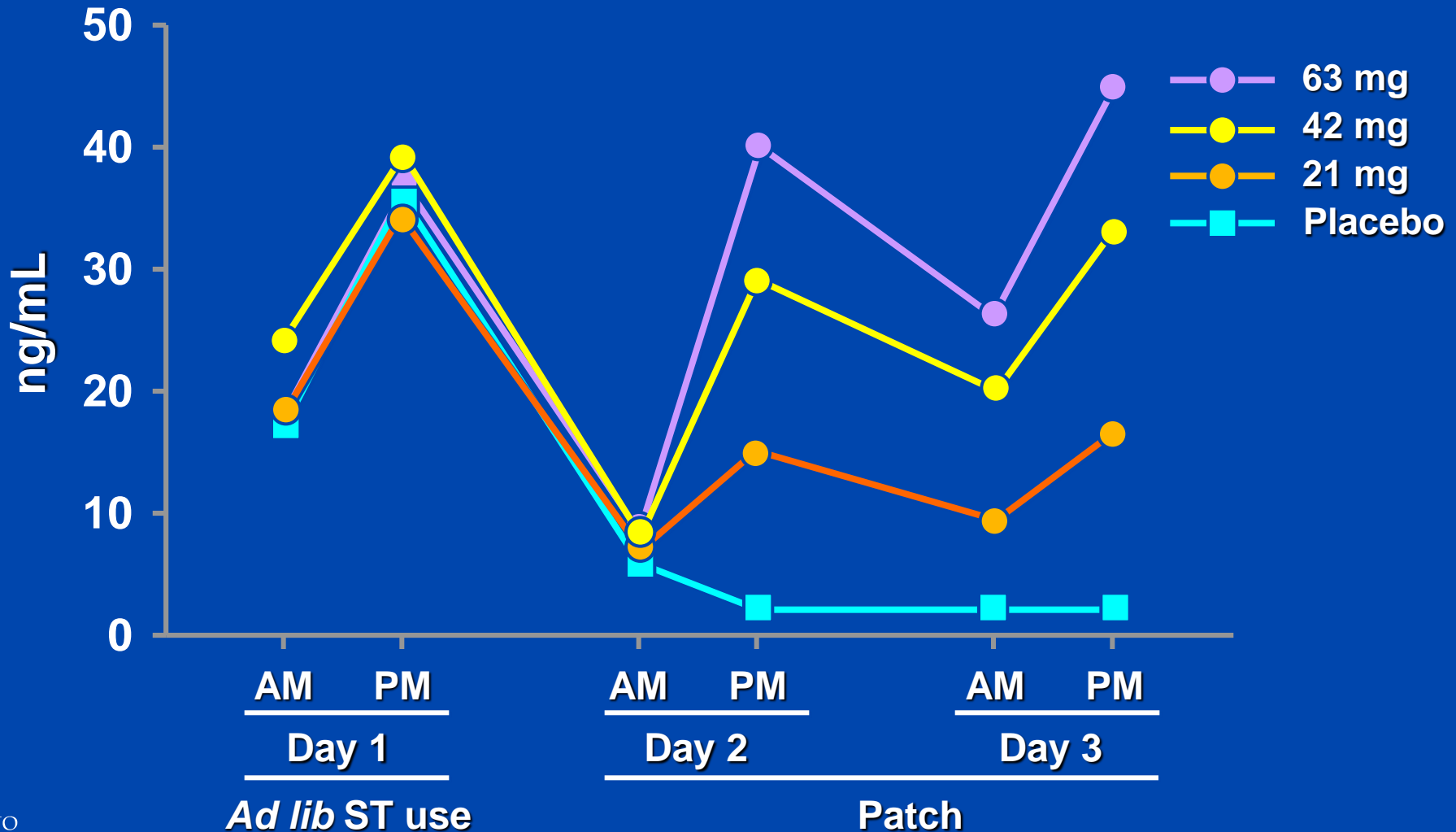
Restlessness



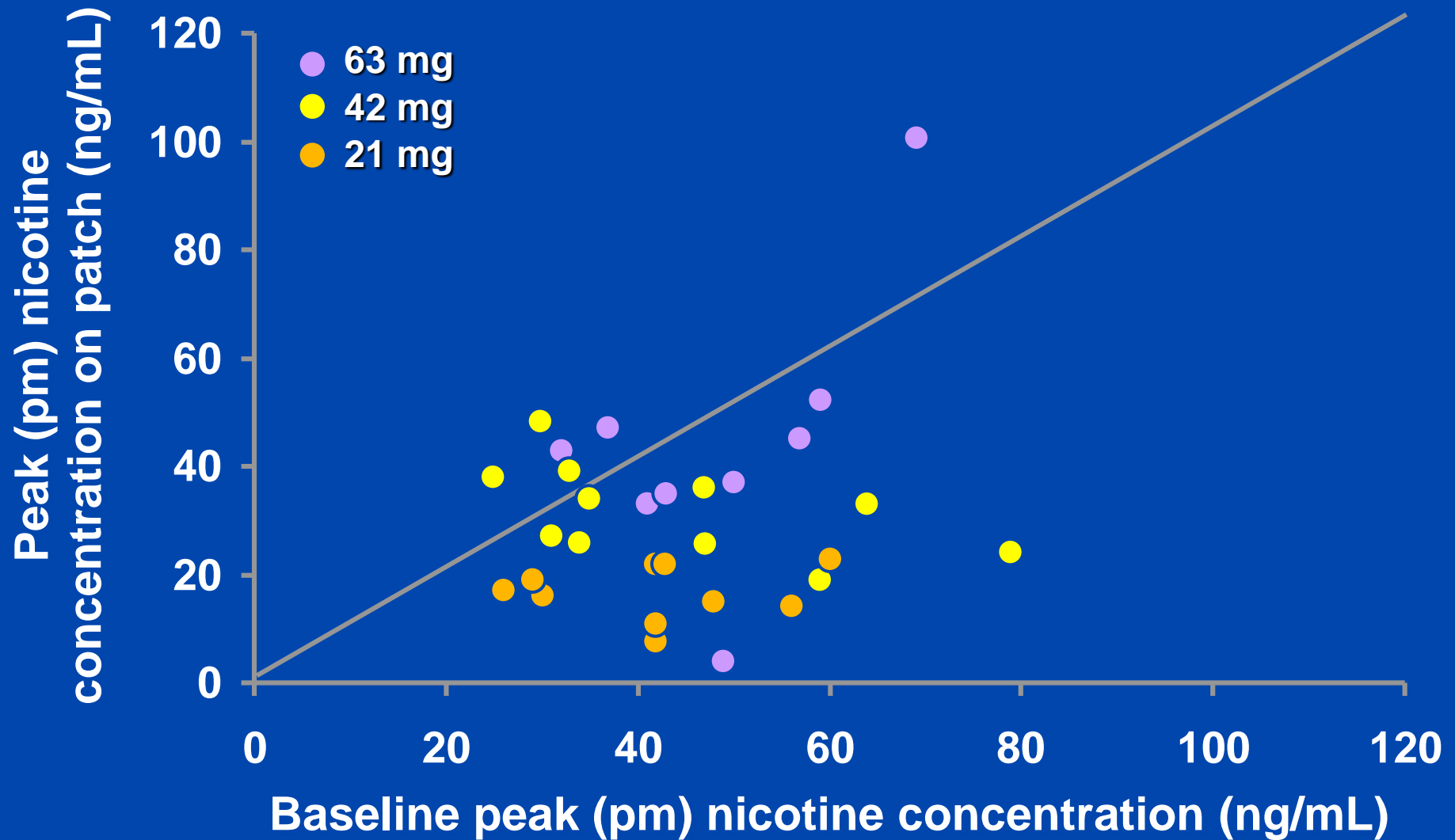
Ebbert JO, et al. *Nicotine Tob Res.* 2007;9(1):43-52.

Median Serum Nicotine Concentration

Ebbert JO, et al. *Drug Alcohol Depend.* Feb 12 2007.



Ebbert JO, et al. *Drug Alcohol Depend.* Feb 12 2007.



High Dose Patch Therapy: Adverse Events

- No difference in overall adverse events
- 63 mg/day
 - 1 subject with nausea/vomiting
 - Completed study on 2 patches
 - 1 subject with nausea
 - Completed study on 2 patches
- 42 mg/day
 - Vomiting – possibly unrelated
 - Completed study on 3 patches



Nicotine Patch for ST Users

- NCI R21 CA140125
- 52 ST users
- Randomized to:
 - Placebo
 - 42 mg/day
- 8 weeks of therapy



Ebbert JO, et al. *Nicotine Tob Res.* 2007;9(1):43-52.

Abstinence Rates: Self-Reported

	42 mg Nicotine Patch N=25	Placebo Patch N=27	p†
End of treatment (week 8)			
Point prevalence abstinence	13 (52%)	8 (30%)	0.050
Prolonged abstinence	13 (52%)	7 (26%)	0.027
6-months			
Point prevalence abstinence	13 (52%)	8 (30%)	0.050
Prolonged abstinence	10 (40%)	7 (26%)	0.140

* Subjects met criteria for point-prevalence all tobacco abstinence if they reported not using any tobacco in the last 7 days. To meet criteria for prolonged abstinence, subjects had to meet criteria for 7-day point prevalence abstinence and also report not using tobacco for 7 consecutive days or at least once each week on 2 consecutive weeks, since 2 weeks following their target quit date. In all cases, subjects with missing information were assumed to be using tobacco.

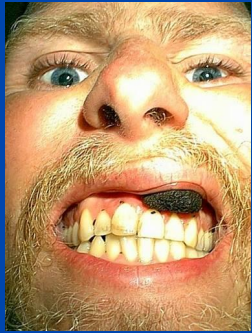
† One-tailed, Chi-square test.

Summary of NRT Studies for ST Users

- NRT increases short-term (3 month) ST abstinence
- Decreases craving & withdrawal
- Does not increase long-term (≥ 6 month) abstinence



Scandinavian Snus



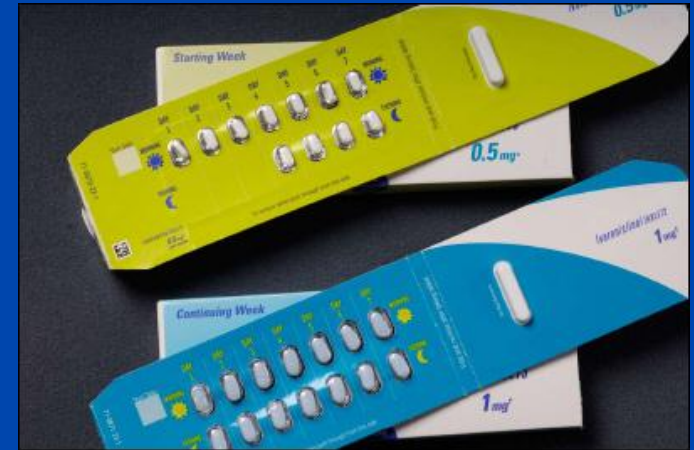
32% of men aged 16-35 use snus daily

19% adult snus use prevalence

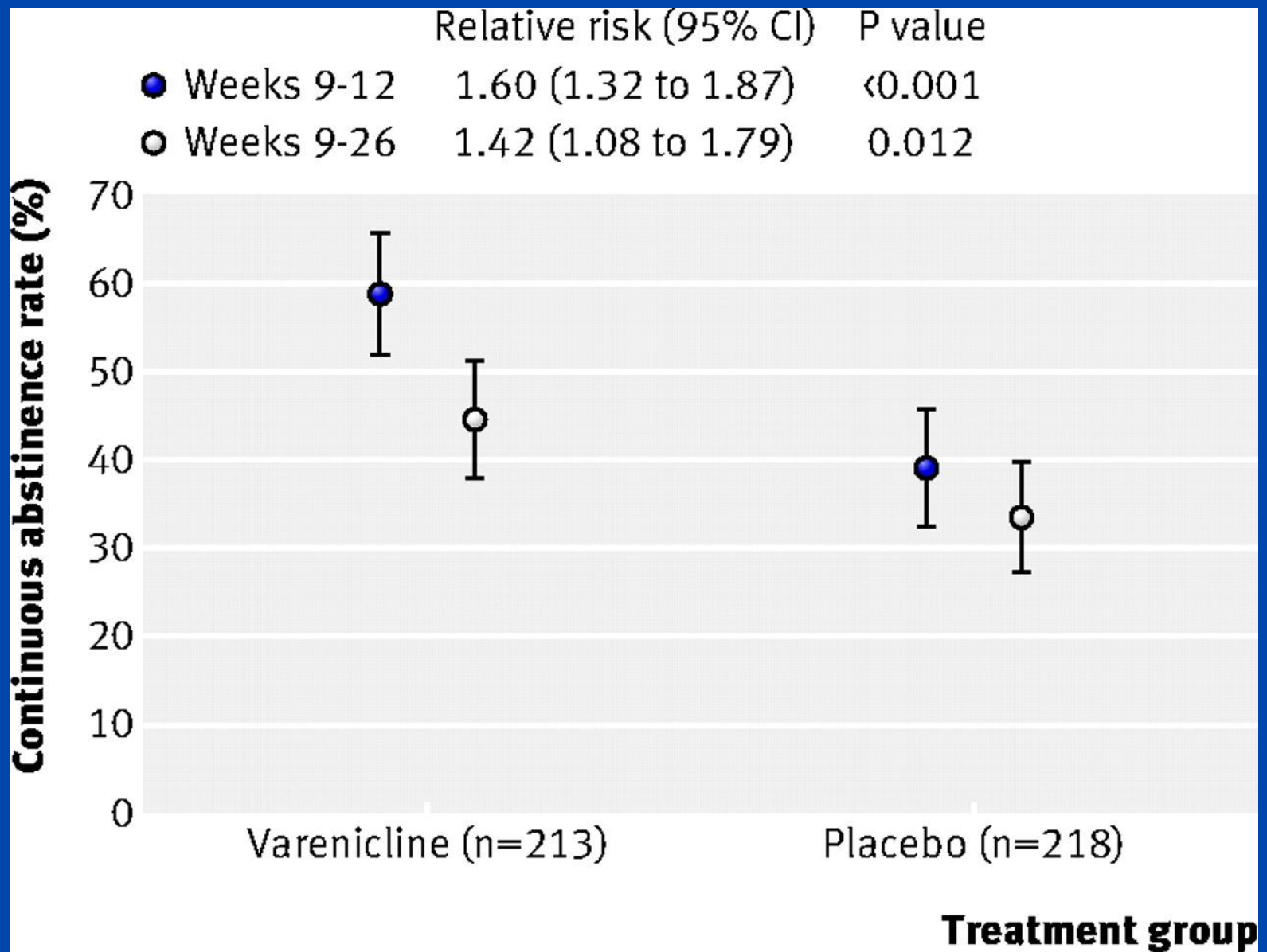


Varenicline for Snus Users

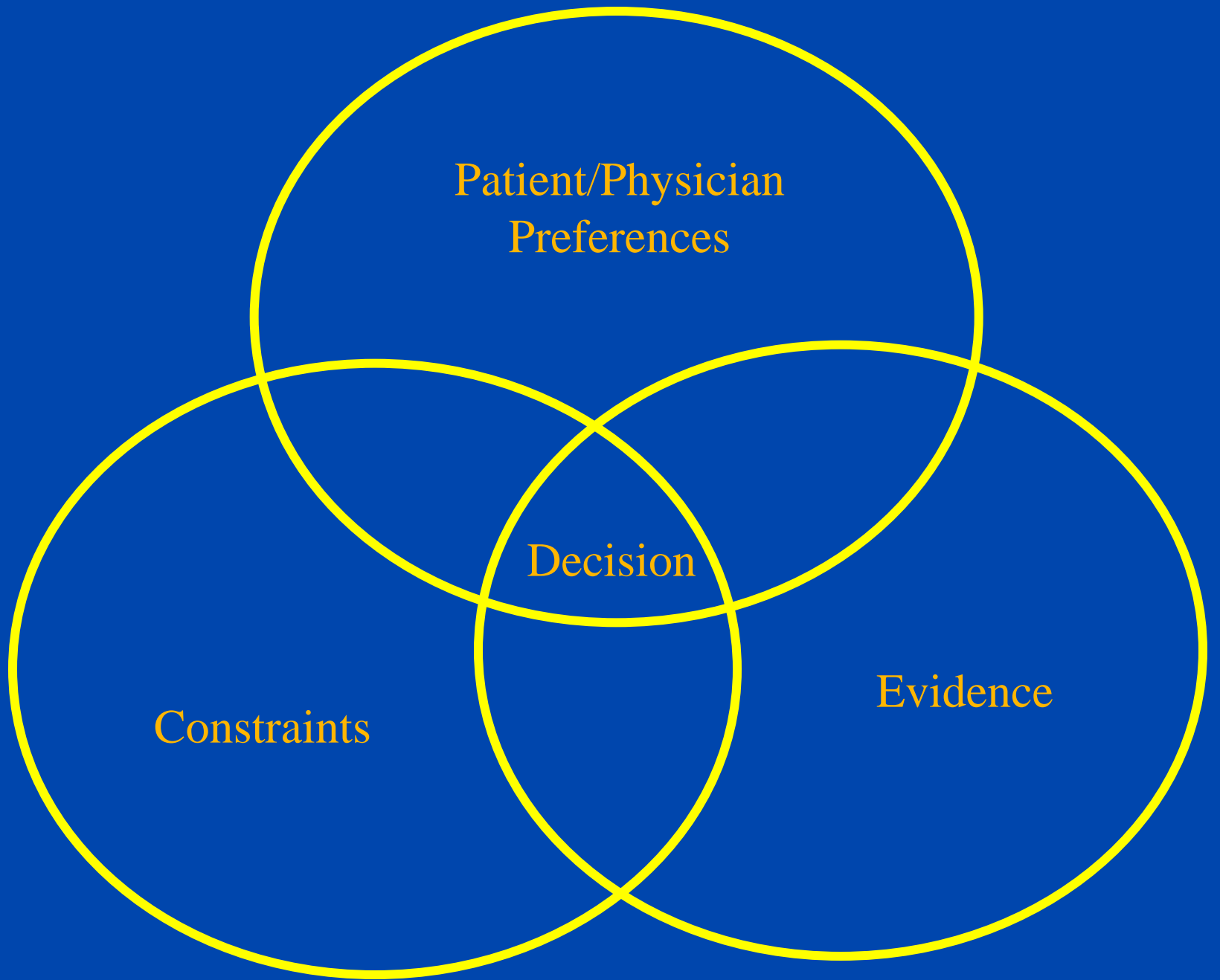
- Norway (7 sites) & Sweden (9 sites)
- Male/female daily ST users
 - Use at least 8 times/day
- Randomized to:
 - Varenicline for 12 weeks
 - Placebo
- Biochemical confirmation of abstinence
 - Salivary cotinine > 15 ng/mL



Fagerström K, et al. BMJ. 2010 Dec 6;341.

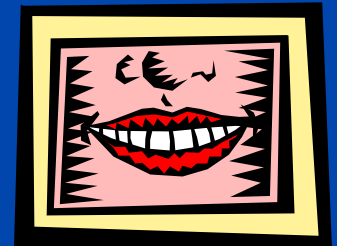


Fagerström K, et al. Stopping smokeless tobacco with varenicline: randomised double blind placebo controlled trial. *BMJ*. 2010 Dec 6;341.



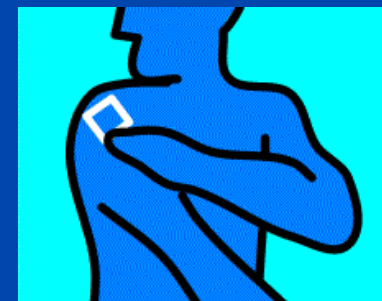
Recommended ST Treatment Approach

- Bupropion SR
 - Weight gain prevention
 - Craving reduction
- Tailored nicotine patch therapy
 - Craving reduction
 - Short-term (end-of-treatment) abstinence
- Nicotine lozenge (short-term abstinence)
- Nicotine gum (craving reduction)
- Varenicline



Nicotine Patch Dosing Algorithm for ST Users

	Peak serum nicotine concentrations (ng/mL)	Cans or pouches per week	Patch dose
Low	0-10	< 2	14 mg/d
Intermediate	11-20	2-3	21mg/d
High	> 20	> 3	42 mg/d



Ebbert JO, et al. *J. Subst. Abuse Treat.* Jul 2004;26(4):261-267.

Question #1:

Which medication has been shown to increase ST abstinence rates at 6 months?

1. Nicotine patch
2. Nicotine lozenge
3. Bupropion
4. Varenicline



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Question #2:

If a ST user uses 4 cans/week, what dose of nicotine patch should they be placed on?

1. 7 mg
2. 14 mg
3. 21 mg
4. 42 mg



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References

- Dale LC, Ebbert JO, Glover ED, et al. Bupropion SR for the treatment of smokeless tobacco use. *Drug Alcohol Depend.* Sep 6 2007;90(1):56-63.
- Ebbert JO, Dale LC, Patten CA, et al. Effect of high-dose nicotine patch therapy on tobacco withdrawal symptoms among smokeless tobacco users. *Nicotine Tob. Res.* Jan 2007;9(1):43-52.
- Ebbert JO, Dale LC, Severson HH, et al. Nicotine lozenges for the treatment of smokeless tobacco use. *Nicotine Tob. Res.* Feb 2007;9(2):233-240.
- Ebbert J, Montori VM, Erwin PJ, Stead LF. Interventions for smokeless tobacco use cessation. *Cochrane Database Syst Rev.* 2011 Feb 16;(2):CD004306. PubMed PMID: 21328266.
- Fagerstrom K, Gilljam H, Metcalfe M, Tonstad S, Messig M. Stopping smokeless tobacco with varenicline: randomised double blind placebo controlled trial. *BMJ.* 2010;341:c6549.

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