Smokeless Tobacco Cessation: Review of the evidence

> Raymond Boyle, PhD Tobacco Summit 2007 MDQuit.org

Previous Reviews of ST evidence

- Hatsukami and Boyle (1997)
 - Evidence base is limited by small sample sizes and lack of control groups

- Ebbert et al. (2007)
 - A Cochrane review www.thecochranelibrary.com
 - Behavioural treatments may help people stop using ST

Presentation Goals

 To review the current status of ST use in the United States

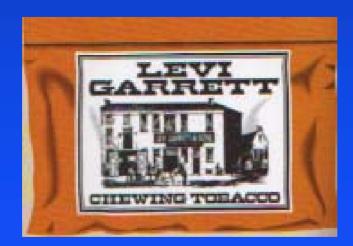
 To review the behavioral and pharmacologic evidence for ST cessation

 To discuss the debate of ST as a method for smoking cessation

Smokeless Tobacco (ST) Products

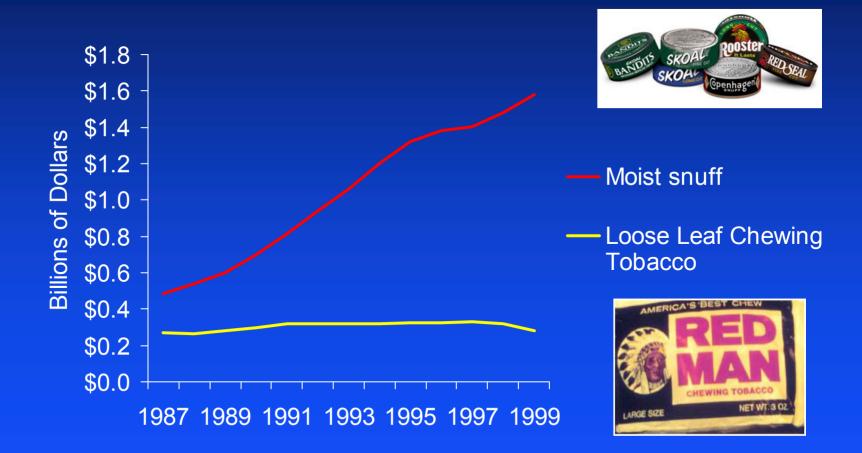








Sales of Smokeless Tobacco in Dollars United States, 1987-1999

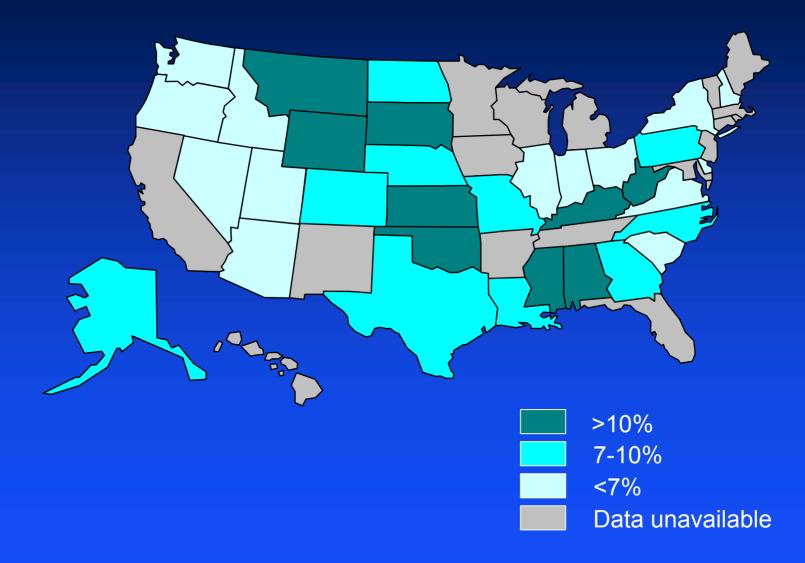


Source: FTC Report to Congress, 2001

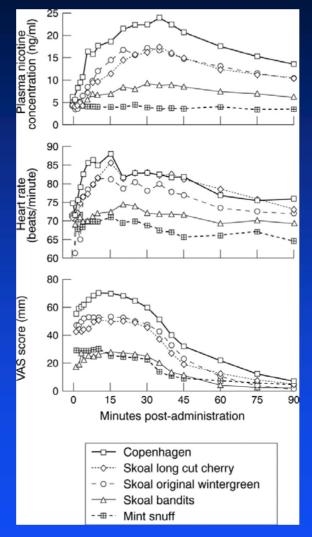
Adverse Health Effects of ST Use

- Oral and pharyngeal cancer
- Smokeless tobacco keratosis / leukoplakia
- Gingival recession
- Dental caries
- Cardiovascular diseases
- Nicotine addiction

Current ST Use by Males Aged 18+ Yrs BRFSS, 1995-1999



Nicotine plasma concentrations, HR, and subjective ratings of drug strength



Fant, R. V et al. Tob Control 1999;8:387-392



Pharmacotherapy for ST Use:

What is Known

Goals of Pharmacotherapy

Increase abstinence (quit rates)

Control symptoms
 Craving

Withdrawal

Medications Tried for ST Use

Nicotine gum

Nicotine patch

Bupropion SR

Nicotine lozenge

Efficacy

Analysis 02.01. Comparison 02 Pharmocotherapy: NRT versus placebo, Outcome 01 6 months or greater abstinence, strictest criteria

Review: Interventions for smokeless tobacco use cessation

Comparison: 02 Pharmocotherapy: NRT versus placebo

Outcome: 01 6 months or greater abstinence, strictest criteria

| Study | Nicotine replacement | Placebo | Odds Ratio (Fixed) | Weight | Odds Ratio (Fixed) |
|--------------------------------|---------------------------------|---------|-----------------------------|--------|---------------------|
| | n/N | n/N | 95% CI | (%) | 95% CI |
| 01 Nicotine Patch | | | | | |
| Hatsukami 2000 | 62/201 | 49/201 | - | 38.1 | 1.38 [0.89, 2.15] |
| Howard-Pitney 1999 | 78/206 | 69/204 | - | 48.4 | 1.19 [0.80, 1.79] |
| Stotts 2003 | 6/98 | 13/100 | | 13.6 | 0.44 [0.16, 1.20] |
| Subtotal (95% Cl) | 505 | 505 | * | 100.0 | 1.16 [0.88, 1.54] |
| Total events: 146 (Nicotine re | eplacement), 131 (Placebo) | | | | |
| Test for heterogeneity chi-squ | ıare=4.23 df=2 p=0.12 l² =52.7% | | | | |
| Test for overall effect z=1.04 | p=0.3 | | | | |
| 02 Nicotine Gum | | | | | |
| Boyle 1992 | 13/50 | I 3/50 | _ | 31.6 | 1.00 [0.41, 2.44] |
| Hatsukami 1996 | 28/106 | 28/104 | | 68.4 | 0.97 [0.53, 1.80] |
| Subtotal (95% CI) | 156 | 154 | • | 100.0 | 0.98 [0.59, 1.63] |
| Total events: 41 (Nicotine rep | blacement), 41 (Placebo) | | | | |
| Test for heterogeneity chi-squ | uare=0.00 df=1 p=0.96 l² =0.0% | | | | |
| Test for overall effect z=0.07 | р=0.9 | | | | |
| | | | | | |
| | | | 0.1 0.2 0.5 1 2 5 10 | | |
| | | | Favours Placebo Favours NRT | | |

Ebbert. Cochrane Database Syst Rev, 2007

Symptom Control: Craving & Withdrawal

- Nicotine gum (2 mg/d)
 - Reduces craving^A
 - Reduces withdrawal symptoms^A

- Nicotine patch (21 mg/d)
 - Reduces craving^B
 - Reduces withdrawal symptoms^B

^A Hatsukami et al. J Consult Clin Psychol. Feb 1996;64(1):153-161.

^B Hatsukami et al. J. Consult. Clin. Psychol. 2000;68(2):241-249.

Medications Tried for ST Use

Nicotine gum

Nicotine patch

Bupropion SR

Nicotine lozenge

Efficacy

Analysis 01.01. Comparison 01 Pharmacotherapy: Buproprion versus placebo, Outcome 01 All tobacco abstinence at longest follow-up

Review: Interventions for smokeless tobacco use cessation

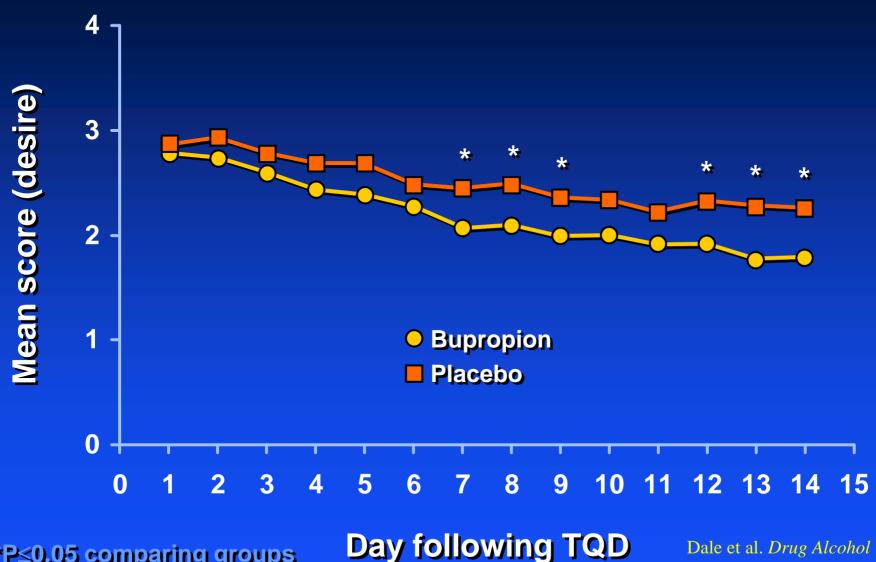
Comparison: 01 Pharmacotherapy: Buproprion versus placebo

Outcome: 01 All tobacco abstinence at longest follow-up

| Study | Buproprion | Placebo | Odds Ratio (Fixed) | Weight | Odds Ratio (Fixed) |
|----------------------------|---------------------------|------------|-----------------------------------|--------|---------------------|
| | n/N | n/N | 95% CI | (%) | 95% CI |
| 01 6 months or greater | continous abstinence | | | | |
| Dale 2002 | 4/34 | 4/34 | | 15.2 | 1.00 [0.23, 4.37] |
| Dale 2007 | 21/113 | 24/112 | | 84.8 | 0.84 [0.43, 1.61] |
| Subtotal (95% CI) | 147 | 146 | - | 100.0 | 0.86 [0.47, 1.57] |
| Total events: 25 (Buprop | rion), 28 (Placebo) | | | | |
| Test for heterogeneity cl | ni-square=0.05 df=1 p=0.8 | 3 l² =0.0% | | | |
| Test for overall effect z= | 0.49 p=0.6 | | | | |
| | | | <u> </u> | | |
| | | | 0.1 0.2 0.5 1 2 5 10 | | |
| | | | Favours Placebo Favours Bupropion | | |

Ebbert. Cochrane Database Syst Rev, 2007

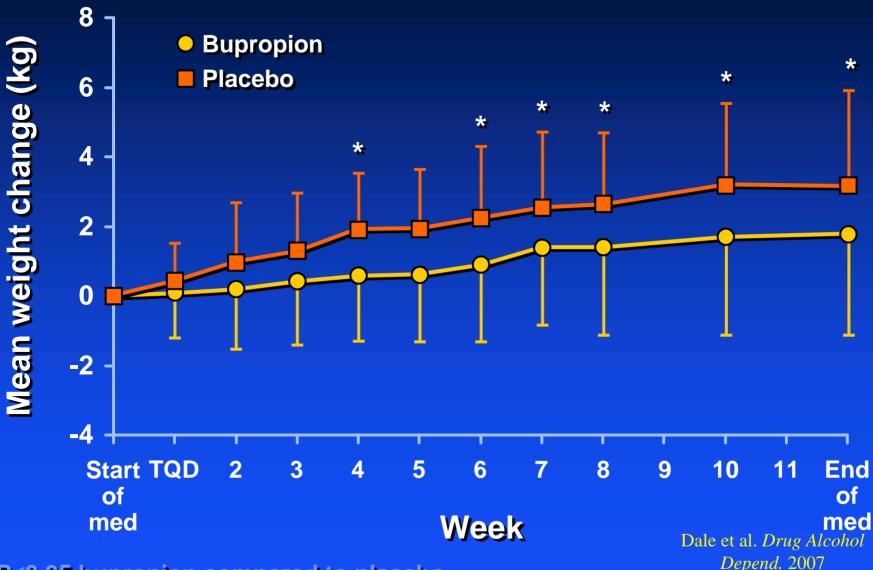
Desire to Use Tobacco



Dale et al. *Drug Alcohol* Depend. 2007

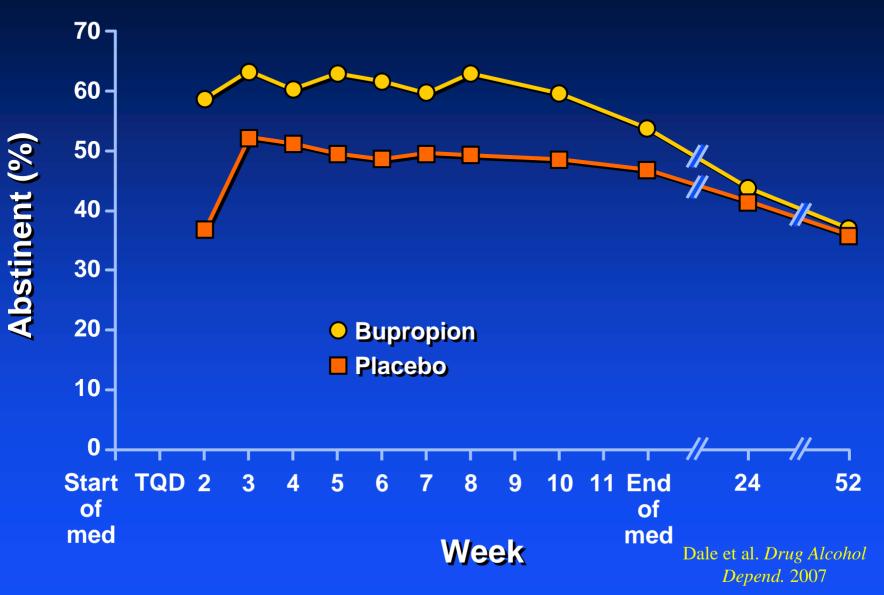
*P≤0.05 comparing groups

Weight Change During Medication Phase



*P≤0.05 bupropion compared to placebo

7-Day Point Prevalence Abstinence



Bupropion SR Study Conclusions

- Bupropion SR is effective for:
 - Decreasing craving
 - Attenuating weight gain
- Bupropion SR is not effective for:
 - Increasing long-term ST abstinence rates
 - Decreasing withdrawal symptoms

Nicotine Lozenges for ST Users

Nicotine Lozenge Study

| | Goal lozenges/day | Max lozenges/day |
|-------------|-------------------|---------------------|
| Weeks 1-6 | 20 | 20 |
| Weeks 7-9 | 8 | 20 |
| Weeks 10-12 | 4 | 20 |

Ebbert JO, et al.. Nicotine Tob Res. Feb 2007

Nicotine Lozenge Study

- ST users:
 ≥18 years of age
 Daily use for the 6 months
- 4 mg nicotine lozenge

30 subjects

Ebbert JO, et al.. Nicotine Tob Res. Feb 2007

Nicotine Lozenge Study Conclusions

- Nicotine lozenge <u>may be</u> effective for addressing:
 - Craving
 - Withdrawal
- Conclusions must be interpreted with caution
 About 47% quit
 - Placebo-controlled study is ongoing

ST Behavioral interventions randomized by organization

Analysis 03.01. Comparison 03 Behavioral interventions, Outcome 01 Abstinence from all tobacco use (where reported) at 6 months or more

Review: Interventions for smokeless tobacco use cessation

Comparison: 03 Behavioral interventions

Outcome: 01 Abstinence from all tobacco use (where reported) at 6 months or more

| Study | Treatment | Control | Odds Ratio (Fixed) | Weight | Odds Ratio (Fixed) |
|--|-----------|---------|---------------------------------------|--------|---------------------|
| | n/N | n/N | 95% CI | (%) | 95% CI |
| 01 Randomisation by org | anisation | | | | |
| Cummings 1995 | 76/316 | 102/417 | + | 16.6 | 0.98 [0.70, 1.38] |
| Gansky 2005 | 103/285 | 130/352 | + | 18.4 | 0.97 [0.70, 1.34] |
| Severson 1998 | 40/394 | 8/239 | — — — — — — — — — — — — — — — — — — — | 2.2 | 3.26 [1.50, 7.10] |
| Walsh 1999 | 60/171 | 30/189 | | 4.6 | 2.86 [1.74, 4.73] |
| Walsh 2003 | 38/141 | 23/166 | | 3.8 | 2.29 [1.29, 4.08] |
| Subtotal (95% CI) | 1307 | 1363 | • | 45.7 | 1.38 [1.15, 1.67] |
| Total events: 317 (Treatment), 293 (Control) | | | | | |
| Test for heterogeneity chi-square=24.43 df=4 p=<0.0001 l² =83.6% | | | | | |
| Test for overall effect z=3 | | | | | |

ST behavioral interventions randomized by individual

| 02 Individual randomisation | 1 | | | | |
|-----------------------------|-------------------------|------------------|-------------------------------------|-------|----------------------|
| Boyle 2004 | 44/109 | 28/112 | | 4.1 | 2.03 [1.14, 3.60] |
| Cigrang 2002 | 7/31 | 3/29 | | 0.6 | 2.53 [0.59, 10.90] |
| Severson 2006 | 119/393 | 60/392 | - | 10.4 | 2.40 [1.69, 3.41] |
| Severson 2007a | 69/535 | 52/534 | - | 11.3 | 1.37 [0.94, 2.01] |
| | | | | | |
| | | | 0.1 0.2 0.5 1 2 5 10 |) | |
| Severson 2007b | 159/1260 | 100/1263 | - | 21.7 | 1.68 [1.29, 2.19] |
| Stevens 1995 | 25/245 | 19/273 | | 4.0 | 1.52 [0.81, 2.83] |
| Stotts 2003 | 19/198 | 8/105 | | 2.3 | 1.29 [0.54, 3.05] |
| Subtotal (95% CI) | 2771 | 2708 | • | 54.3 | 1.76 [1.49, 2.08] |
| Total events: 442 (Treatm | nent), 270 (Control) | | | | |
| Test for heterogeneity ch | i-square=6.00 df=6 p=0. | 42 l² =0.1% | | | |
| Test for overall effect z=6 | 6.75 p<0.00001 | | | | |
| Total (95% CI) | 4078 | 407 I | • | 100.0 | 1.59 [1.40, 1.80] |
| Total events: 759 (Treatm | nent), 563 (Control) | | | | |
| Test for heterogeneity ch | i-square=34.44 df=11 p= | =0.0003 P =68.1% | | | |
| Test for overall effect z=7 | 7.34 p<0.00001 | | | | |
| | | | <u> </u> | | |
| | | | 0.1 0.2 0.5 1 2 5 10 | | |
| | | | Favours control Favours interventio | n | |
| | | | | | |

Ebbert. Cochrane Database Syst Rev, 2007

ST Behavioral Interventions: Evidence Summary

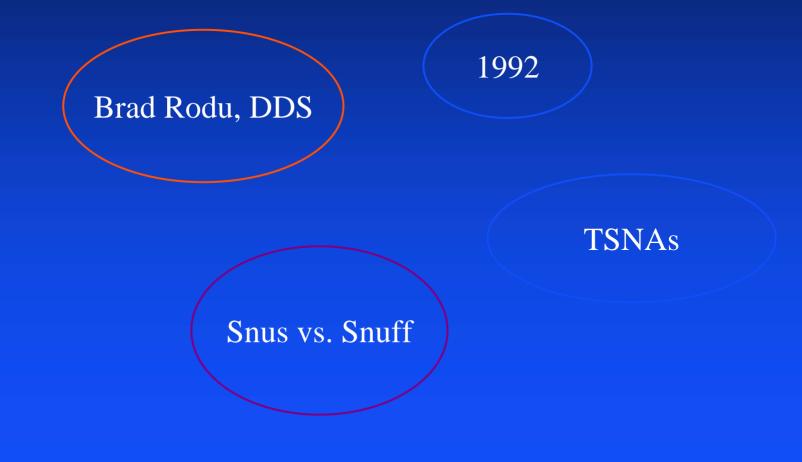
- The Cochrane review identified 8 RCTs
- Positive, strong effects are seen for
 - Telephone counseling
 - Dental team advice
 - Self-help materials (web, video, manual)
 - Interventions with athletic teams

Recommended Treatment Approach

- 1. Behavioral treatment
 - Oral examination
 - Oral replacement products
 - Reducing/blending
 - Telephone based CBT
- 2. Consider tailored nicotine therapy
 - Patch/gum/lozenge for self-titration

The ST harm reduction debate

A product is harm reducing if it lowers total tobacco-related mortality and morbidity even though continued use may involve exposure to tobacco toxins (Stratton et al. 2001)



Cigarette companies enter the market

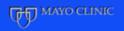




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