Smoking & Depression: What Every Clinician Should Know

Robert M. Anthenelli, M.D.

Professor and Executive Vice Chair
Director, Pacific Treatment and Research Center
Department of Psychiatry
University of California, San Diego, Health Sciences
ranthenelli@ucsd.edu
www.pac-tarc.org
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- *Discussion of Off-Label Drug Use*: combination treatments, nortriptyline

- The opinions expressed in this talk are Dr. Anthenelli’s own and do not necessarily reflect the views of the University of California
Objectives

- Recognize that depression is over-represented in smokers

- Implement a treatment plan for smoking cessation modified for use in smokers with depression
  - Highlight studies we’ve conducted

- Briefly discuss smoking and risk for suicide
Patients with Psychiatric & Substance Use Disorders (PSUD) Smoke at Rates 2-4 Times Higher Than the General Population and Consume Nearly 1 in 2 Cigarettes Sold

SZ=schizophrenia, BPD=bipolar disorder, MDD= major depressive disorder, PD=panic disorder, OCD=obsessive-compulsive disorder, PTSD=post-traumatic stress disorder.

Depression and Smoking Are Major Global Public Health Problems

- Estimated ~1 billion smokers worldwide
  - leading preventable cause of death in adults

- Depression affects roughly 350 million people
  - leading cause of disability worldwide

- Roughly half of smokers seeking treatment have history of depression
What is Meant By “Depression”? 

“The difference between the almost right word & the right word is really a large matter - - it’s the difference between the lightning bug and the lightning.”
Mark Twain, 1888

- Definitions and measurements used matter
  - history of depression vs. current depression
  - negative affect vs. tobacco withdrawal
  - depressive symptoms vs. syndrome
Clinical Characteristics of Smokers With Depression (Compared with Non-Mentally Ill Smokers)

- Initiate daily smoking earlier
- Smoke more heavily
- More likely to be nicotine dependent
- Experience more severe and prolonged tobacco withdrawal symptoms
- Experience more severe mood disruption during initial abstinence; Women > Men

Gaalema DE et al. Tobacco Regulatory Science, 2015
Treating Smokers With Depression: Still Use The “5 As” Brief Intervention

1. **ASK** - Systematically identify all tobacco users at every visit.

2. **ADVISE** - Strongly urge all tobacco users to quit.

3. **ASSESS** - Determine willingness to make a quit attempt.

4. **ASSIST** - Aid the patient in quitting.

5. **ARRANGE** - Schedule follow-up contact.
PLUS -- Screen & MONITOR Smokers for Depression and Suicidality

- Use a depression screening questionnaire – PHQ-2, PHQ-9, CES-D, others

- Ask screening questions: 1) Have you been depressed or down most of the day, nearly every day, for the past two weeks? 2) In the past two weeks, have you been less interested in most things or less able to enjoy the things you used to enjoy most of the time?

- Use a suicide screening questionnaire – SBQ-R, C-SSRS, others

When Is The Best Time For a Depressed Smoker To Try To Quit?

- When motivated to do so
  - About 25% of smokers with current depression motivated to try to quit
- Psychiatically stable
- Not in crisis or suicidal
- Has no recent or planned psychiatric medication changes

Anthenelli RM Current Psychiatry 2005; 4: 77 - 87
Consider Whether Single Episode versus Recurrent Major Depressive Disorder

- Approx. 75% of depressives have multiple depressive episodes
- Distinction matters: recurrent = poorer prognosis; Require longer, more intensive treatment and monitoring
- Cognitive Behavioral Therapy (CBT) more effective in recurrent MDD smokers
- Depressive symptoms during smoking cessation portend poorer outcomes
Tailoring Treatment In Smokers With Depression

- Lower your expectations; depressed smokers have a harder time quitting smoking
  - Major Depression ↓ 20%; Anxiety Disorders ↓ 20 – 40 %
- Are at greater risk for adverse events – ongoing monitoring
- Consider flexible quit date or reduce to quit strategies to minimize pre-quit anxiety, withdrawal and cessation fatigue*
- Consider greater use of nortriptyline, combination treatments, varenicline, and enhanced intra-treatment psychosocial support*
- Maintain success by using longer term treatment options*

*Opinions expressed by Dr. Anthenelli and not those recommended on the package inserts of the FDA-approved smoking cessation aids
Combine Medications With Behavioral Counseling

<table>
<thead>
<tr>
<th>Medication Condition</th>
<th>Behavioral Therapy Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Therapy</td>
</tr>
<tr>
<td>Medication</td>
<td>10%</td>
</tr>
<tr>
<td>No Medication or Placebo</td>
<td>5%</td>
</tr>
</tbody>
</table>

*Brief therapy = approx. 2-3 minutes; Intensive therapy ≥ 10 minutes
Medications evaluated included only NRT and Bupropion SR

Hughes JR; *CA Cancer J Clin.* 2000, 50:143-151
Behavioral Treatments in Smokers with Depression

- Meta-analyses find that adding a psychosocial mood management component to a standard smoking cessation intervention enhances long-term abstinence \(^1,^2\)

- Other promising treatments
  - Behavioral Activation Treatment for Smoking (BATS)
  - Acceptance and Commitment Therapy (ACT)

Pharmacotherapies for Nicotine Dependence in Smokers with Depression

1. Nicotine Replacement Therapy (i.e., gum, patches, inhaler, nasal spray, lozenge)
2. Bupropion SR (sustained-release)
3. Varenicline tartrate
4. Nortriptyline
5. Combination Treatments
# NRT for Smoking Cessation Results from Cochrane Meta-Analysis

<table>
<thead>
<tr>
<th>Formulation</th>
<th>RR for Abstinence</th>
<th># Clinical Trials in Meta-Analysis</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gum</td>
<td>1.43</td>
<td>53</td>
<td>1.33-1.53</td>
</tr>
<tr>
<td>Patch</td>
<td>1.66</td>
<td>41</td>
<td>1.53-1.81</td>
</tr>
<tr>
<td>Inhaler</td>
<td>1.90</td>
<td>4</td>
<td>1.36-2.67</td>
</tr>
<tr>
<td>Lozenge/tablets(^a)</td>
<td>2.00</td>
<td>6</td>
<td>1.63-2.45</td>
</tr>
<tr>
<td>Spray</td>
<td>2.02</td>
<td>4</td>
<td>1.49-3.73</td>
</tr>
</tbody>
</table>

Overall RR of abstinence for any form of NRT vs. control = 1.58 (95% CI = 1.50-1.66)

RR = Risk Ratio for abstinence compared with control (placebo or no NRT)
CI = Confidence Interval
\(^a\)Only lozenges are FDA-approved in U.S.

adapted from Stead LF et al. *Cochrane Database of Systematic Reviews* 2008
Mechanism of Action
Bupropion SR

- Antidepressant approved as an aid to smoking cessation in 1997
- Blocks neural reuptake of dopamine and norepinephrine, decreasing craving and withdrawal symptoms
- May work primarily as a non-selective nAChR antagonist
- Effective in smokers with history of depression
Subtype-Selective $\alpha_4\beta_2$ nicotinic Acetylcholine Receptor (nAChR) Partial Agonists

- Partial agonism $\rightarrow$ nAChRs occupied - ameliorates withdrawal
- Partial antagonism $\rightarrow$ nicotine can’t bind to nAChRs - blocks nicotine’s reinforcing effects
- Prototype agent: Varenicline
- Other compounds in this class:
  - Dianicline – Tonstad S. et al. 2011
  - Cytisine -- Walker N. et al. 2014
### Cochrane Database Network Meta-Analysis on the Efficacies of Smoking Cessation Aids

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio Compared With</th>
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<tbody>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td>NRT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.84^a</td>
</tr>
<tr>
<td>Patch Only</td>
<td></td>
</tr>
<tr>
<td>Gum Only</td>
<td></td>
</tr>
<tr>
<td>Other Only</td>
<td></td>
</tr>
<tr>
<td>Bupropion</td>
<td>1.82^b</td>
</tr>
<tr>
<td>Varenicline</td>
<td>2.88^c</td>
</tr>
</tbody>
</table>

Adapted from Cahill K et al. Cochrane Database Syst Rev. 2013; May 31; 5:CD009329

^a-h: 95% CIs > 1 (see article for details)
Non-FDA-Approved (Off-Label) Medication for Tobacco Dependence: Nortriptyline

- A “second-line” pharmacotherapy
- Precautions in pregnancy, cardiovascular disease
- Side effects include sedation, dry mouth (64-78%), blurred vision (16%), urinary retention, lightheadedness (49%), tremor (23%). Risk of overdose and cardiotoxicity
- Instructions: Initiate therapy 10-28 days before the quit date to reach steady state levels at target dose.
  - Initial dosage: 25 mg/day increasing gradually to 75-100 mg/day
- Duration of treatment: At least 12 weeks
Varenicline & Bupropion SR Post-Approval Surveillance Safety Warnings

- Observe patients for serious neuropsychiatric symptoms including changes in behavior, agitation, depressed mood, suicidal and homicidal thoughts and/or behavior. These symptoms as well as worsening of pre-existing psychiatric illness have been reported in patients attempting to quit smoking with varenicline and bupropion.
Why the Concerns About Neuropsychiatric Adverse Events?

- Affects benefit-risk ratio
  - Only 3 first-line medication classes; 2 carry boxed warnings
- Influences medication acceptance & adherence
- Affects prescribing practices and medication utilization
- Some are particularly worrisome (e.g., suicide)
Study #1 -- A Randomized Controlled Trial of Varenicline in Stably Depressed Smokers: Rationale & Objectives


- Case reports, and post-marketing surveillance data raised concerns about varenicline’s neuropsychiatric safety profile in psychiatric patients

- Are clinicians reluctant to prescribe varenicline to depressed smokers?

- This study evaluated smoking abstinence and changes in mood and anxiety levels in smokers with stable current or past depression treated with varenicline vs. placebo
Depressed Smokers Trial --Participant Disposition

- 646 screened
- 525 randomized

256 assigned to receive varenicline
- 256 received varenicline
  - 40 (15.6%) discontinued study during treatment phase*
  - 55 (21.5%) discontinued varenicline treatment*
  - 216 (84.4%) completed treatment phase of study
  - 41 (16.0%) discontinued study during post-treatment follow-up phase*
  - 175 (68.4%) completed study
  - 256 (100%) included in the efficacy and safety analyses

269 assigned to receive placebo
- 269 received placebo
  - 83 (30.9%) discontinued placebo treatment*
  - 59 (21.9%) discontinued study during treatment phase*
  - 210 (78.1%) completed treatment phase of study
  - 31 (11.5%) discontinued study during post-treatment follow-up phase*
  - 179 (66.5%) completed study
  - 269 (100%) included in the efficacy and safety analyses
## Baseline Demographic, Smoking, and Psychiatric Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Varenicline N = 256</th>
<th>Placebo N = 269</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>159 (62.1)</td>
<td>170 (63.2)</td>
</tr>
<tr>
<td><strong>Age, years Mean (SD)</strong></td>
<td>45.4 (10.9)</td>
<td>47.1 (10.8)</td>
</tr>
<tr>
<td><strong>Body mass index (kg/m²) Mean (SD)</strong></td>
<td>26.8 (4.6)</td>
<td>27.3 (5.0)</td>
</tr>
<tr>
<td><strong>Smoking characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fagerström Test for Nicotine Dependence total score Mean (SD)</td>
<td>5.9 (1.9)</td>
<td>5.9 (2.0)</td>
</tr>
<tr>
<td>Total number of years of smoking Mean (SD)</td>
<td>26.0 (11.7)</td>
<td>27.3 (11.8)</td>
</tr>
<tr>
<td><strong>Psychiatric characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline MADRS total score Mean (SD)</td>
<td>7.6 (7.4)</td>
<td>7.9 (7.5)</td>
</tr>
<tr>
<td>Participants with MADRS total score &gt;11, n</td>
<td>60 (23.4%)</td>
<td>76 (28.3%)</td>
</tr>
<tr>
<td>Baseline HAM-A total score Mean (SD)</td>
<td>6.1 (5.2)</td>
<td>6.4 (5.2)</td>
</tr>
<tr>
<td>Participants taking any antidepressant medication, n (%)</td>
<td>181 (70.7)</td>
<td>197 (73.2)</td>
</tr>
</tbody>
</table>
Varenicline Increases Smoking Cessation in Adults with Stably Treated Current or Past Major Depression

Varenicline- and placebo-treated participants had similar change of scores over time and trajectories of ratings trended toward slight improvement in mood and anxiety ratings across time in both treatment groups.

Vertical bars show 95% CIs; HAM-A 95% CIs for quitters only.
Study # 2: Evaluating Adverse Events in a GLobal Smoking CESsation (EAGLES) Trial

(Anthenelli RM et al. The Lancet 2016;387:2507-2520)

- Multicenter, double-blind, randomized, controlled trial – 140 centers; Post-marketing requirement
- Psychiatric (PC) and non-psychiatric (NPC) cohorts
- Varenicline vs bupropion vs transdermal nicotine patch (nicotine replacement therapy [NRT]) vs placebo – triple dummy
- 1000 subjects per treatment arm and cohort
- Balanced by diagnostic group within PC
- Brief smoking cessation counseling at all visits/contacts
EAGLES Study Design

(Anthenelli RM et al. The Lancet, 2016)
EAGLES Participants

- Ages 18–75 years with ≥10 cigarettes per day and exhaled carbon monoxide (CO) >10 parts per million (ppm)
- In the PC, DSM-IV-TR:
  - Unipolar or bipolar mood disorders
  - Anxiety disorders
  - Psychotic disorders
  - Borderline personality disorder
- Psychiatric co-morbidity not excluded
- Clinically stable for 6 months; stable medication for 3 months

# EAGLES Demographics and Smoking Characteristics

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>NPC (N = 3984)</th>
<th>PC (N = 4074)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, no. (%)</td>
<td>1999 (50.2)</td>
<td>1550 (38.0)</td>
</tr>
<tr>
<td>Age, years (SD)</td>
<td>46.0 (12.9)</td>
<td>47.1 (11.7)</td>
</tr>
<tr>
<td>Weight, kg (SD)</td>
<td>80.7 (19.7)</td>
<td>82.2 (21.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Smoking characteristics</th>
<th>NPC (N = 3984)</th>
<th>PC (N = 4074)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTCD score, mean (SD)</td>
<td>5.5 (2.0)</td>
<td>6.0 (2.0)</td>
</tr>
<tr>
<td>Duration of smoking, years (SD)</td>
<td>28.1 (12.8)</td>
<td>28.6 (11.9)</td>
</tr>
<tr>
<td>Cigarettes per day in past month, no. (SD)</td>
<td>20.7 (8.0)</td>
<td>20.7 (8.4)</td>
</tr>
<tr>
<td>Previous quit attempts, no. (SD)</td>
<td>3.2 (9.6)</td>
<td>3.5 (8.0)</td>
</tr>
<tr>
<td>Participants with $\geq 1$ previous quit attempt, no. (%)</td>
<td>3244 (81.4)</td>
<td>3403 (83.5)</td>
</tr>
</tbody>
</table>

FTCD, Fagerström Test for Cigarette Dependence.
Primary Psychiatric Diagnoses

PC (N = 4074)

- 70.7% Personality disorders
- 19.2% Anxiety disorders
- 9.5% Psychotic disorders
- 0.6% Unipolar and bipolar mood disorders

Primary diagnosis as per SCID (Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Axis I or II Disorders).
**EAGLES Primary Safety Endpoint**

- Comparison of varenicline and bupropion vs placebo for number (%) of patients reporting the following composite endpoint:

<table>
<thead>
<tr>
<th>≥1 “severe” AE of:</th>
<th>Feeling Abnormal</th>
<th>Hostility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>Depression</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>And/or ≥1 “moderate” or “severe” AE of:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitation</td>
<td>Aggression</td>
</tr>
<tr>
<td>Homicidal Ideation</td>
<td>Mania</td>
</tr>
<tr>
<td>Psychosis</td>
<td>Suicidal Ideation</td>
</tr>
</tbody>
</table>
## EAGLES Subject Disposition

<table>
<thead>
<tr>
<th></th>
<th>Number (%) of subjects</th>
<th>Varenicline</th>
<th>Bupropion</th>
<th>NRT</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NPC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All randomized (ITT)</td>
<td>1005</td>
<td>1001</td>
<td>1013</td>
<td>1009</td>
<td></td>
</tr>
<tr>
<td>All treated (safety)</td>
<td>990</td>
<td>989</td>
<td>1006</td>
<td>999</td>
<td></td>
</tr>
<tr>
<td>Completed treatment</td>
<td>793 (80.1)</td>
<td>772 (78.1)</td>
<td>777 (77.2)</td>
<td>803 (80.4)</td>
<td></td>
</tr>
<tr>
<td>Completed study</td>
<td>787 (79.5)</td>
<td>783 (79.2)</td>
<td>767 (76.2)</td>
<td>787 (78.8)</td>
<td></td>
</tr>
<tr>
<td><strong>PC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All randomized (ITT)</td>
<td>1032</td>
<td>1033</td>
<td>1025</td>
<td>1026</td>
<td></td>
</tr>
<tr>
<td>All treated (safety)</td>
<td>1026</td>
<td>1017</td>
<td>1016</td>
<td>1015</td>
<td></td>
</tr>
<tr>
<td>Completed treatment</td>
<td>772 (75.2)</td>
<td>765 (75.2)</td>
<td>761 (74.9)</td>
<td>725 (71.4)</td>
<td></td>
</tr>
<tr>
<td>Completed study</td>
<td>811 (79.0)</td>
<td>803 (79.0)</td>
<td>790 (77.8)</td>
<td>765 (75.4)</td>
<td></td>
</tr>
</tbody>
</table>
### Primary NPS Composite Safety Endpoint – Risk Differences Between Treatment Groups

#### Risk difference (95% CI)

<table>
<thead>
<tr>
<th>Treatment Comparison</th>
<th>Risk Difference (95% CI)</th>
</tr>
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<tbody>
<tr>
<td><strong>NPC</strong></td>
<td></td>
</tr>
<tr>
<td>Varenicline vs placebo</td>
<td>$-1.28 (-2.40, -0.15)$</td>
</tr>
<tr>
<td>Bupropion vs placebo</td>
<td>$-0.08 (-1.37, 1.21)$</td>
</tr>
<tr>
<td>NRT vs placebo</td>
<td>$-0.21 (-1.54, 1.12)$</td>
</tr>
<tr>
<td><strong>PC</strong></td>
<td></td>
</tr>
<tr>
<td>Varenicline vs placebo</td>
<td>$1.59 (-0.42, 3.59)$</td>
</tr>
<tr>
<td>Bupropion vs placebo</td>
<td>$1.78 (-0.24, 3.81)$</td>
</tr>
<tr>
<td>NRT vs placebo</td>
<td>$0.37 (-1.53, 2.26)$</td>
</tr>
</tbody>
</table>

AEs reported during treatment and ≤30 days after last dose (All treated population).
## Relative Efficacy of First-Line SC Aids

### Primary Comparisons

<table>
<thead>
<tr>
<th></th>
<th>NPC (N = 4028)</th>
<th>PC (N = 4116)</th>
<th>Overall (N = 8144)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OR (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Varenicline vs. placebo</strong></td>
<td>4.00 (3.20, 5.00)</td>
<td>2.99 (2.33, 3.83)</td>
<td>2.74 (2.28, 3.30)</td>
</tr>
<tr>
<td><strong>Bupropion vs. placebo</strong></td>
<td>2.26 (1.80, 2.85)</td>
<td>2.00 (1.54, 2.59)</td>
<td>1.89 (1.56, 2.29)</td>
</tr>
<tr>
<td><strong>Secondary Comparisons</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NRT vs. placebo</strong></td>
<td>2.30 (1.83, 2.90)</td>
<td>1.96 (1.51, 2.54)</td>
<td>1.81 (1.49, 2.19)</td>
</tr>
<tr>
<td><strong>Varenicline vs. NRT</strong></td>
<td>1.74 (1.43, 2.10)</td>
<td>1.52 (1.23, 1.89)</td>
<td>1.52 (1.29, 1.78)</td>
</tr>
<tr>
<td><strong>Bupropion vs. NRT</strong></td>
<td>0.98 (0.80, 1.20)</td>
<td>1.02 (0.81, 1.28)</td>
<td>1.04 (0.88, 1.24)</td>
</tr>
<tr>
<td><strong>Varenicline vs. bupropion</strong></td>
<td>1.77 (1.46, 2.14)</td>
<td>1.49 (1.20, 1.85)</td>
<td>1.45 (1.24, 1.70)</td>
</tr>
</tbody>
</table>
CARs Weeks 9-12 and 9-24 By Treatment in Smokers with Unipolar (90%) and Bipolar Mood Disorders

CAR, continuous abstinence rate; NRT, transdermal nicotine patch
Smoking is Independently Associated With Suicide

- Regardless of the use of smoking cessation aids, and after controlling for potential confounders (e.g., demographics, heavier drinking, less education), cigarette smoking is reliably associated with suicide.

- Association appears dose dependent:
  
  Smokers of > 20 cigarettes/day more than twice as likely than non-smokers to commit suicide.

Plausible Explanations for the Relationship Between Smoking and Suicide

- Smokers have pre-existing conditions that increase their risk for suicide
  - Psychiatric comorbidity hypothesis
- Smoking causes painful and debilitating conditions that might lead to suicide
  - Medical comorbidity hypothesis
- Smoking changes multiple aspects of brain function
  - Brain dysregulation hypothesis

Adapted from: Hughes JR. *Drug Alcohol Depend* 2008.
EAGLES -- Lifetime Rates of SI – C-SSRS

NPC overall vs PC overall: 4.8% vs 33.8% (~7 times greater)

C-SSRS, Columbia Suicide Severity Rating Scale; SI, suicide ideation.
NPC overall vs PC overall: 0.7% vs 12.6% (~18 times greater)

NPC (N = 3984): 0.6, 0.9, 0.7, 0.6

PC (N = 4074): 13.4, 14.1, 10.9, 12.1

C-SSRS, Columbia Suicide Severity Rating Scale; SB, suicide behavior.
Rates of SI and/or SB During Treatment – C-SSRS

<table>
<thead>
<tr>
<th></th>
<th>SI (%)</th>
<th>SB (%)</th>
<th>SI and/or SB (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPC (N = 3984)</td>
<td>0.7</td>
<td>0.3</td>
<td>0.6</td>
</tr>
<tr>
<td>PC (N = 4074)</td>
<td>2.7</td>
<td>2.0</td>
<td>2.5</td>
</tr>
</tbody>
</table>

NPC overall vs PC overall: 0.5% vs 2.0% (~4 times greater)

C-SSRS, Columbia Suicide Severity Rating Scale; SI, suicide ideation; SB, suicide behavior.
EAGLES Study Limitations

- Findings may not generalize to smokers with untreated or unstable psychiatric disease
- Light smokers not included
- Smokers with imminent suicidality risk and active substance use disorders were excluded
- Low power for rare NPS adverse events
Summary of EAGLES Findings

- Higher rates of NPS AEs seen in smokers with psychiatric disease including depressives
- Neither varenicline nor bupropion increased serious NPS AEs compared with NRT or placebo in smokers with or without psychiatric disease
- Varenicline, bupropion, and NRT transdermal patches are more effective than placebo in aiding smoking cessation in patients with and without a history of psychiatric disorder
- Varenicline is more effective than bupropion and NRT in psychiatric (including smokers with mood disorders) and non-psychiatric cohorts
Summary & Conclusions

- Tobacco cessation specialists play an important role in helping patients with histories of or current depression quit smoking.

- Screening, advising, assessing patients’ readiness to quit, and then acting (assist OR refer) is our standard of care – also screen for depression and suicidality.

- NRT, bupropion, varenicline, and nortriptyline are effective in smokers with stable or history of depression.

- These medications work best when combined with counseling; consider disease-specific modifications as well.

- Clinicians should remain vigilant when treating depressed smokers with more complex psychiatric presentations for smoking cessation and consult mental health professionals.