# Introducing the *EAGLES* Trial: Its Purpose, Findings & Implications

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# Disclosure

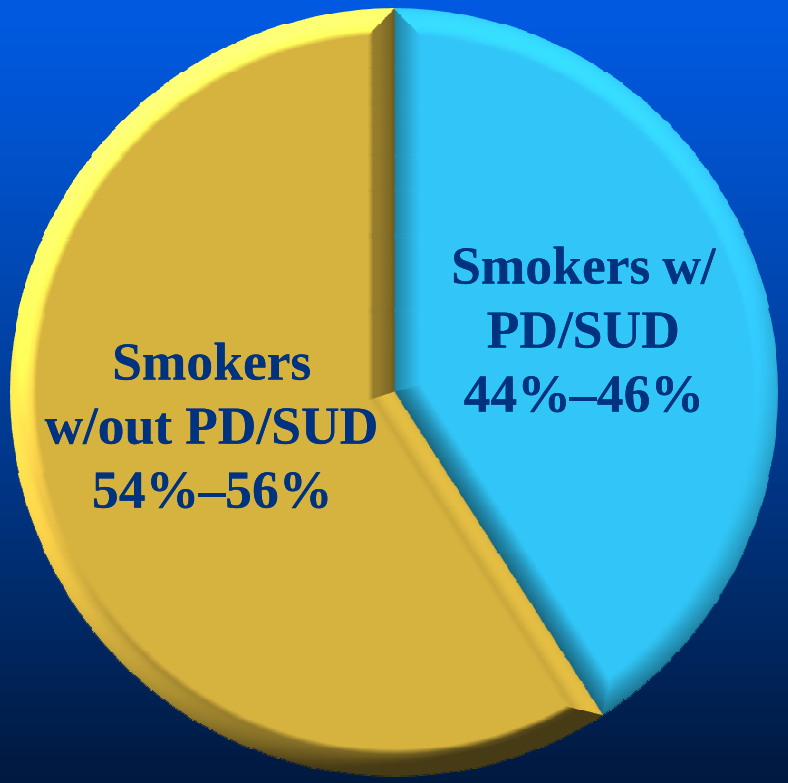
- *Other Research Funding:* Pfizer, Alkermes
- *Current Consulting Agreements:* Pfizer; Arena Pharmaceuticals; Cerecor
- *Discussion of Off-Label Drug Use:* Some 1st-line smoking cessation aids in psychiatric patients (e.g., bupropion in bipolar smokers)
- The opinions expressed in this talk are Dr. Anthenelli's own and do not necessarily reflect the views of the University of California

# Objectives

- Explain why the *EAGLES* trial was conducted
- Describe the study's design and main findings
- Discuss how the *EAGLES* trial results extend findings from observational cohort studies and meta-analyses
- Discuss the implications of these findings from a clinical and regulatory perspective

# Individuals with Psychiatric and Substance Use Disorders Comprise an Important Segment of Smokers & Consume Nearly 1 in 2 Cigarettes Sold

## Cigarette Consumption[1-2]



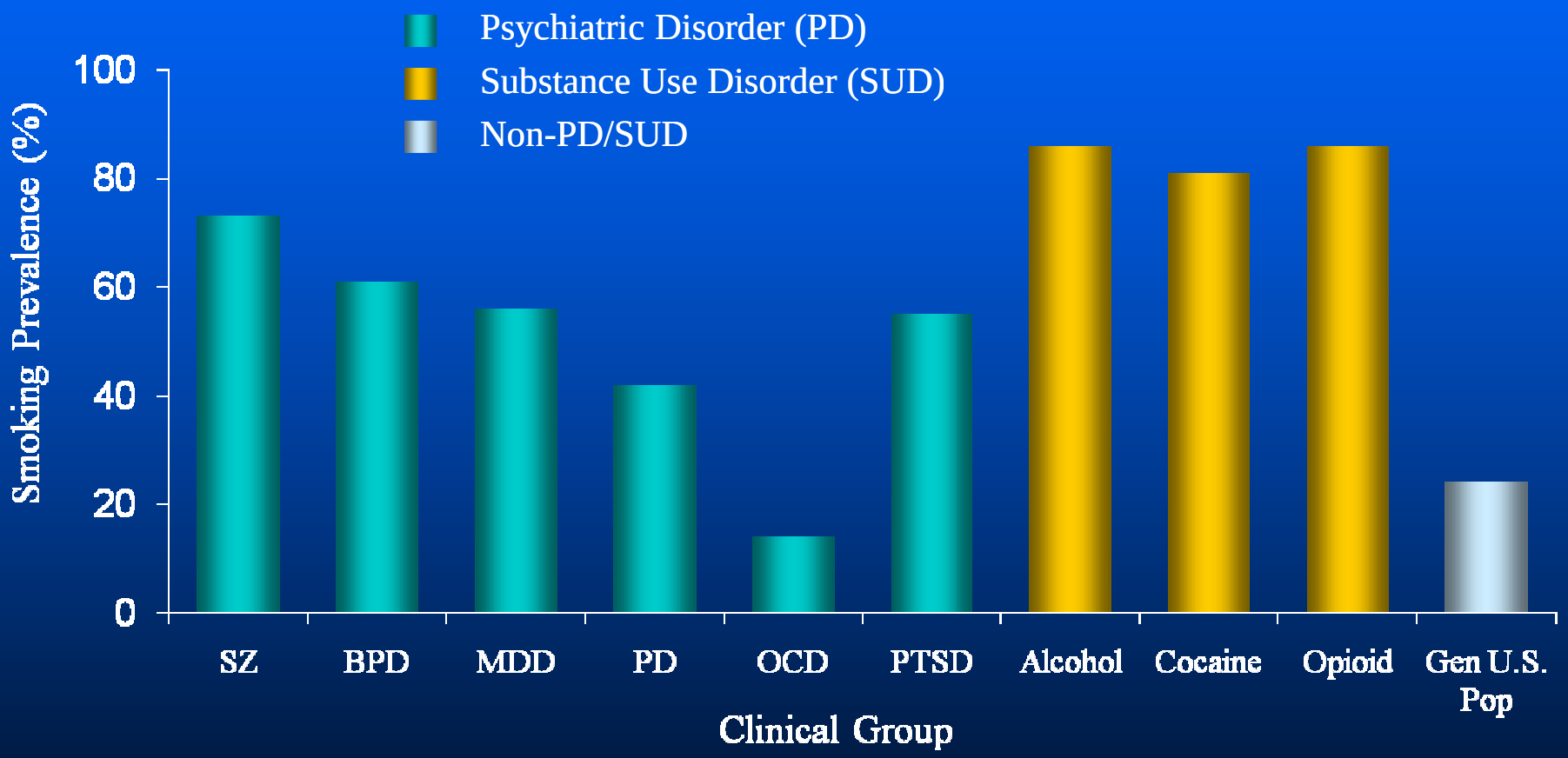

= 175 billion cigarettes[3]

= $39 billion in annual sales[3]

PD=psychiatric disorder, SC=smoking cessation, SUD=substance use disorder.

**1.** Lasser K et al. *JAMA* 2000;284:2606-10. **2.** Grant BF et al. *Arch Gen Psychiatry* 2004; 61:1107-15. **3.** *Federal Trade Commission Cigarette Report for 2003*. 2005. Washington, DC: FTC.

# Patients with Psychiatric & Substance Use Disorders (PSUD) Smoke at Rates 2-4 Times Higher Than the General Population




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

Adapted from Kalman D et al. *Am J Addict.* 2005;14:106-123.

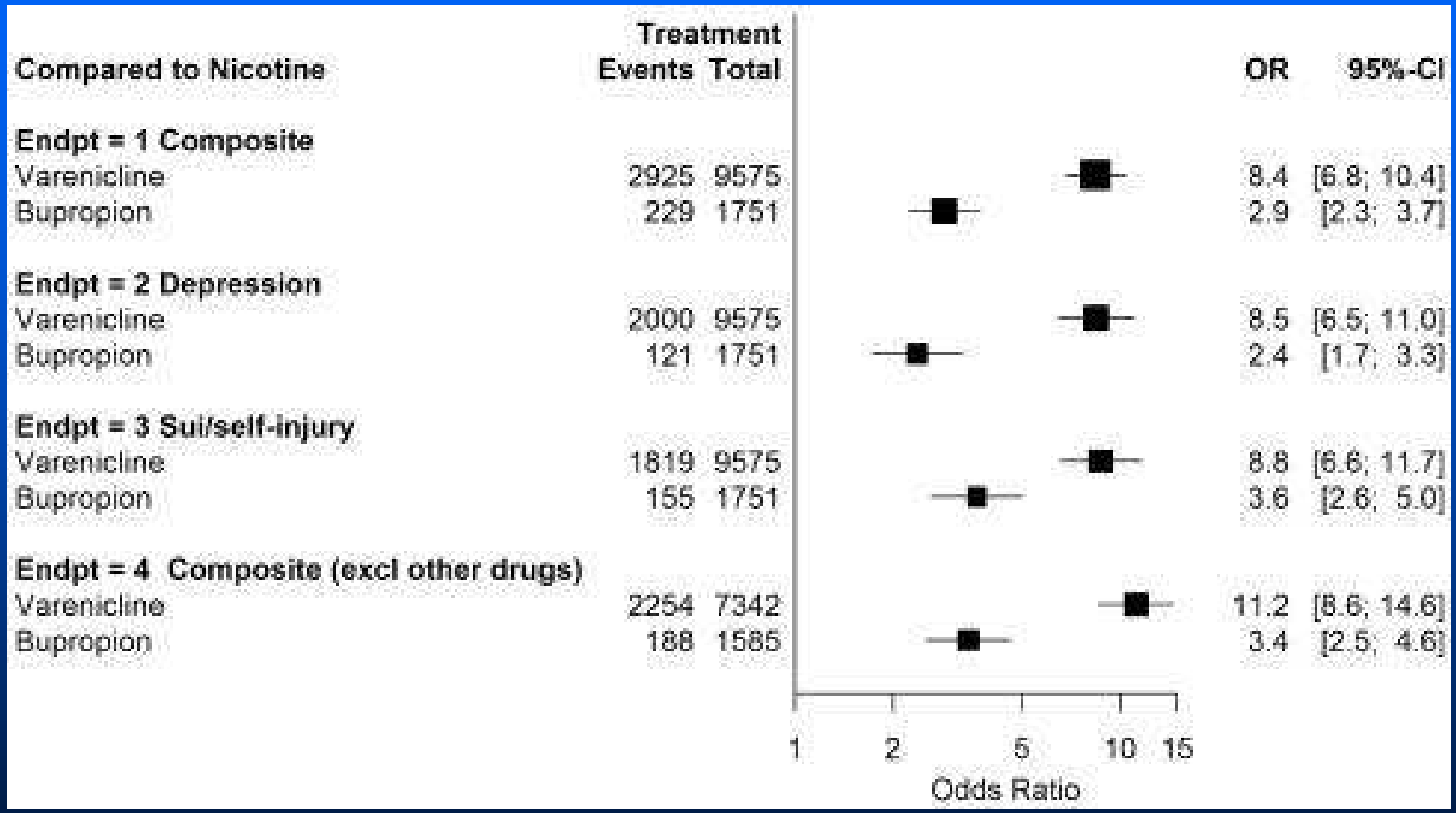
# US FDA AERS Report: Summary of Suicidal Ideation (SI) and Behavior (SB) for Varenicline and Bupropion

| Variables | Varenicline | | | Bupropion | | |
|---|---|---|---|---|---|---|
| | **SI** | **SB** | **Total** | **SI** | **SB** | **Total** |
| Total Cases | n = 116 | n = 37 | n = 153 | n = 46 | n = 29 | n = 75 |
| Median Age[a] | 44.5 | 46.3 | ----- | 46 | 35 | ----- |
| Sex (% Female) [b] | 74% | 50% | ----- | 60% | 41% | ----- |
| Psych History | 54% | 38% | 50% | 26% | 21% | 24% |
| Unknown Psych History | 21% | 32% | 24% | 39% | 52% | 44% |
| Concomitant Psych Meds | 42% | 30% | 39% | 20% | 17% | 19% |
| Unknown Concom. Psych Meds | 38% | 46% | 40% | 39% | 62% | 48% |
| Serious (cases reporting) | n = 110 | n = 37 | n = 147 | n = 30 | n = 29 | n = 59 |

[a] 87% of sample reported; [b] 97% of sample reported

Adapted from US Food and Drug Administration (FDA) Drug Safety newsletter 2009; 2(1): 1-4. Data as of 11/27/2007

# Secondary Analyses of AERS Data: Cases of Suicidality and Depression




Serious AEs reported from 1998 through September 2010
Contrasts versus NRT

Moore TJ et al. PLoS One 2011; 6(11):e27016

# 2009 --Varenicline & Bupropion Receive Post-Approval Boxed 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.

# FDA Also Issues a Post-Marketing Requirement (PMR) to Makers of Varenicline and Bupropion

- Assess risk of clinically significant neuropsychiatric (NPS) adverse events (AEs) in subjects using varenicline, bupropion, nicotine replacement therapy (NRT), or placebo
- Determine whether subjects with prior history of psychiatric disorders are at greater risk for development of clinically significant NPS AEs compared to subjects without such history while using varenicline or bupropion as aids to smoking cessation

# Why the Concerns About Neuropsychiatric Adverse Events?

- Affects benefit-risk ratio
  - Only 3 first-line medication classes; 2 carry boxed warnings in the US
- Influences medication acceptance & adherence
- Affects prescribing practices and medication utilization
- Some are particularly worrisome (e.g., suicide)

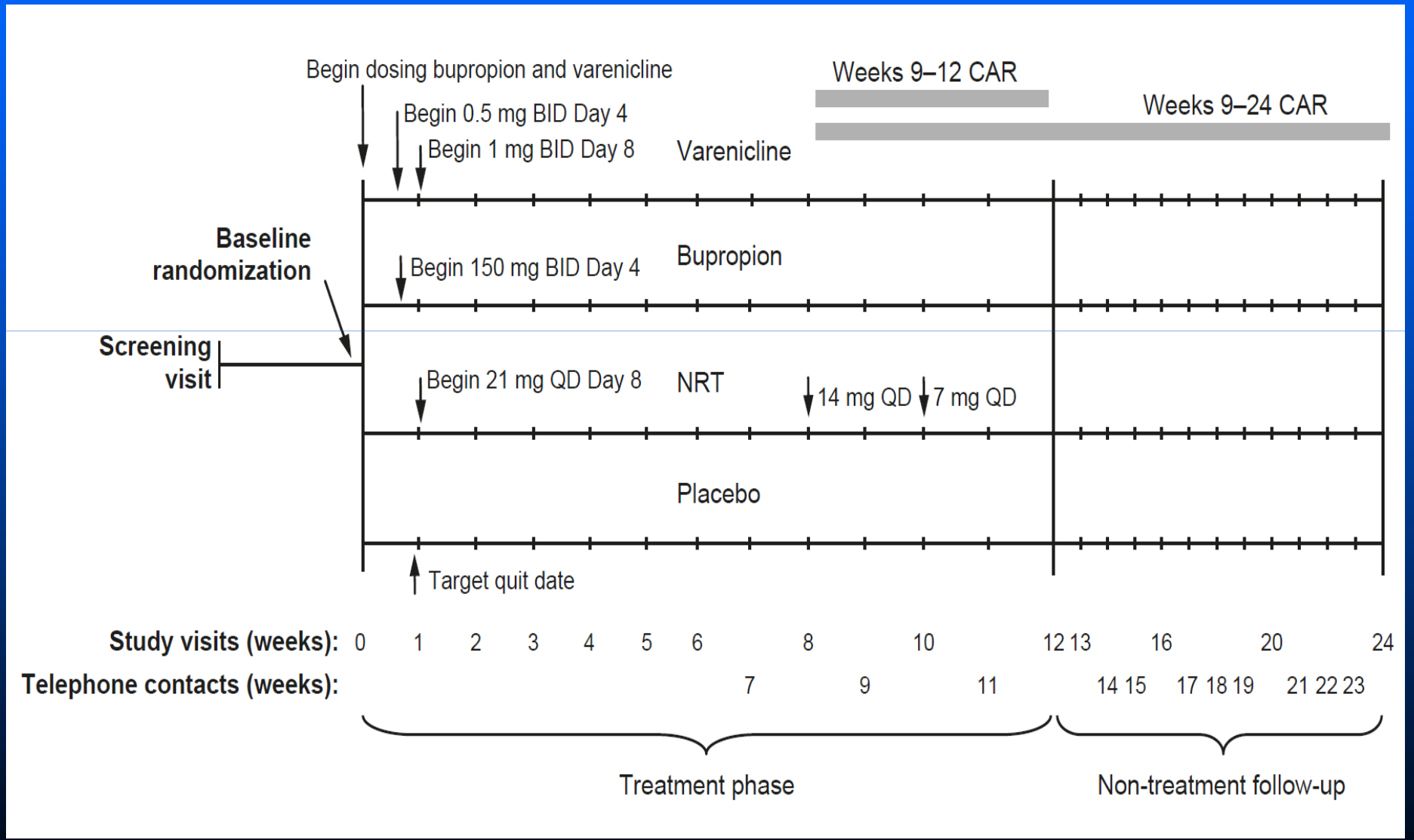
# Evaluating Adverse Events in a GlobaL Smoking CEssation Study (*EAGLES*) Trial

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

- Multicenter, double-blind, randomized, controlled trial – 140 centers; 16 countries
- 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 (Total N = >8000)
- 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

DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision.

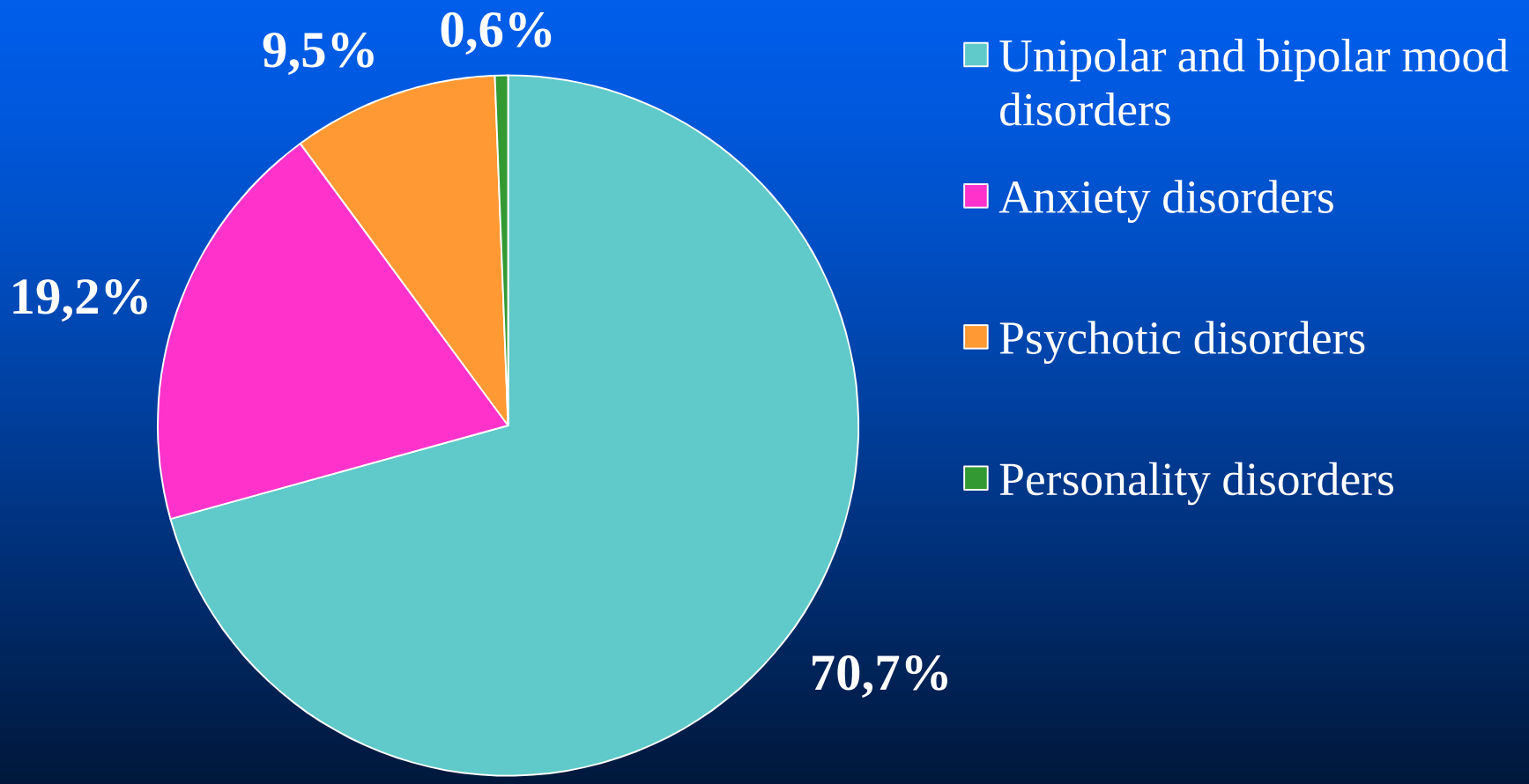
# *EAGLES* Demographics and Smoking Characteristics

| | NPC (N = 3984) | PC (N = 4074) |
|---|---|---|
| **Demographic characteristics** | | |
| Male, no. (%) | 1999 (50.2) | 1550 (38.0) |
| Age, years (SD) | 46.0 (12.9) | 47.1 (11.7) |
| Weight, kg (SD) | 80.7 (19.7) | 82.2 (21.0) |
| **Smoking characteristics** | | |
| FTCD score, mean (SD) | 5.5 (2.0) | 6.0 (2.0) |
| Duration of smoking, years (SD) | 28.1 (12.8) | 28.6 (11.9) |
| Cigarettes per day in past month, no. (SD) | 20.7 (8.0) | 20.7 (8.4) |
| Previous quit attempts, no. (SD) | 3.2 (9.6) | 3.5 (8.0) |
| Participants with ≥1 previous quit attempt, no. (%) | 3244 (81.4) | 3403 (83.5) |

FTCD, Fagerström Test for Cigarette Dependence.

# Distribution of Primary Psychiatric Diagnoses in the Psychiatric Cohort (PC)

**PC (N = 4074)**




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 participants reporting the following composite neuropsychiatric adverse event (AE) endpoint:

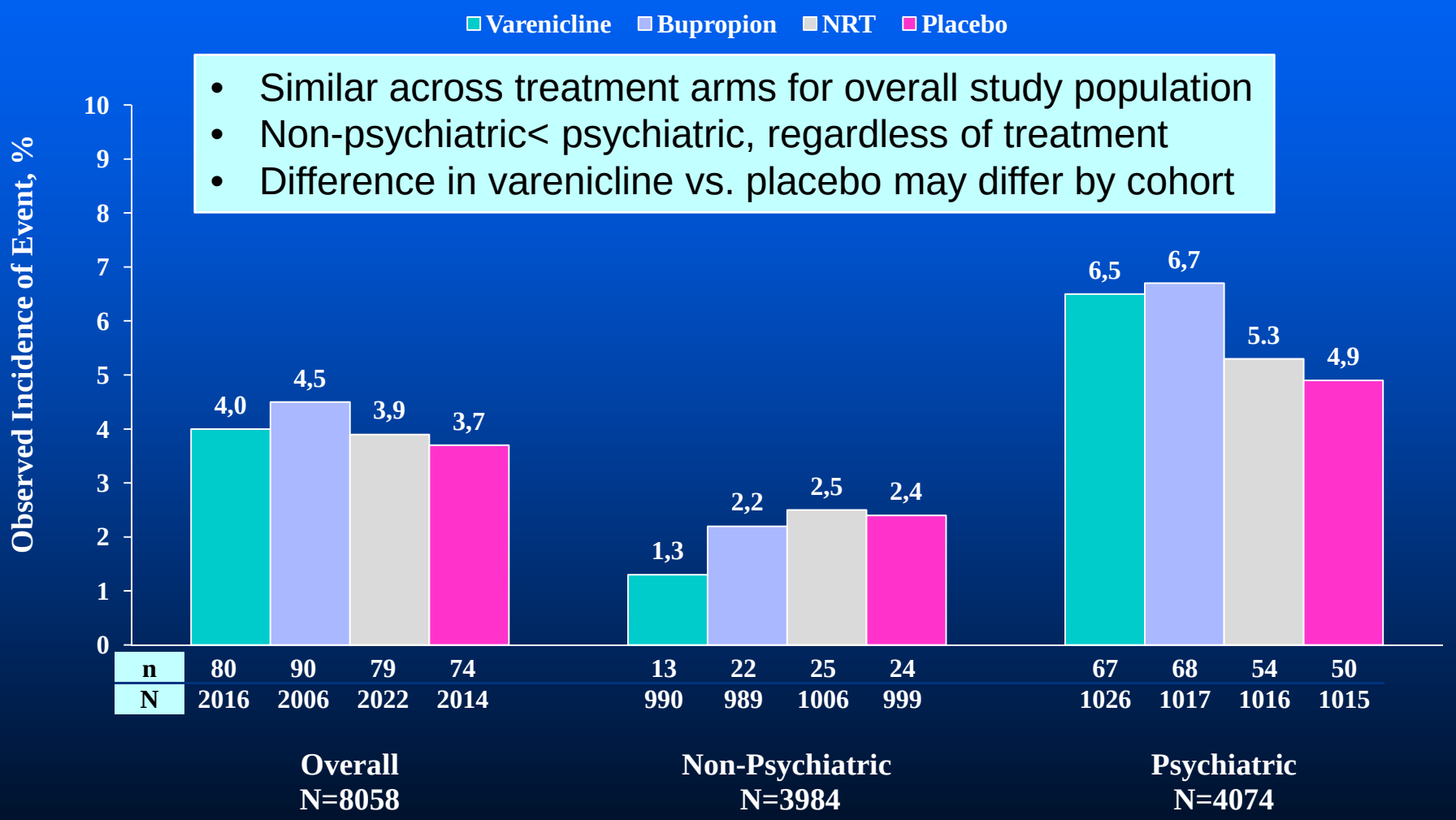
| | | | |
|---|---|---|---|
| **≥1 "severe" AE of:** | | | |
| Anxiety | Depression | Feeling Abnormal | Hostility |
| **And/or ≥1 "moderate" or "severe" AE of:** | | | |
| Agitation | Aggression | Delusions | Hallucinations |
| Homicidal Ideation | Mania | Panic | Paranoia |
| Psychosis | Suicidal Ideation | Suicidal Behavior | Completed Suicide |

# *EAGLES* Subject Disposition

| | Number (%) of subjects | | | |
|---|---|---|---|---|
| | **Varenicline** | **Bupropion** | **NRT** | **Placebo** |
| **NPC** | | | | |
| All randomized (ITT) | 1005 | 1001 | 1013 | 1009 |
| All treated (safety) | 990 | 989 | 1006 | 999 |
| Completed treatment | 793 (80.1) | 772 (78.1) | 777 (77.2) | 803 (80.4) |
| Completed study | 787 (79.5) | 783 (79.2) | 767 (76.2) | 787 (78.8) |
| **PC** | | | | |
| All randomized (ITT) | 1032 | 1033 | 1025 | 1026 |
| All treated (safety) | 1026 | 1017 | 1016 | 1015 |
| Completed treatment | 772 (75.2) | 765 (75.2) | 761 (74.9) | 725 (71.4) |
| Completed study | 811 (79.0) | 803 (79.0) | 790 (77.8) | 765 (75.4) |

# Primary Neuropsychiatric AE Composite Endpoint

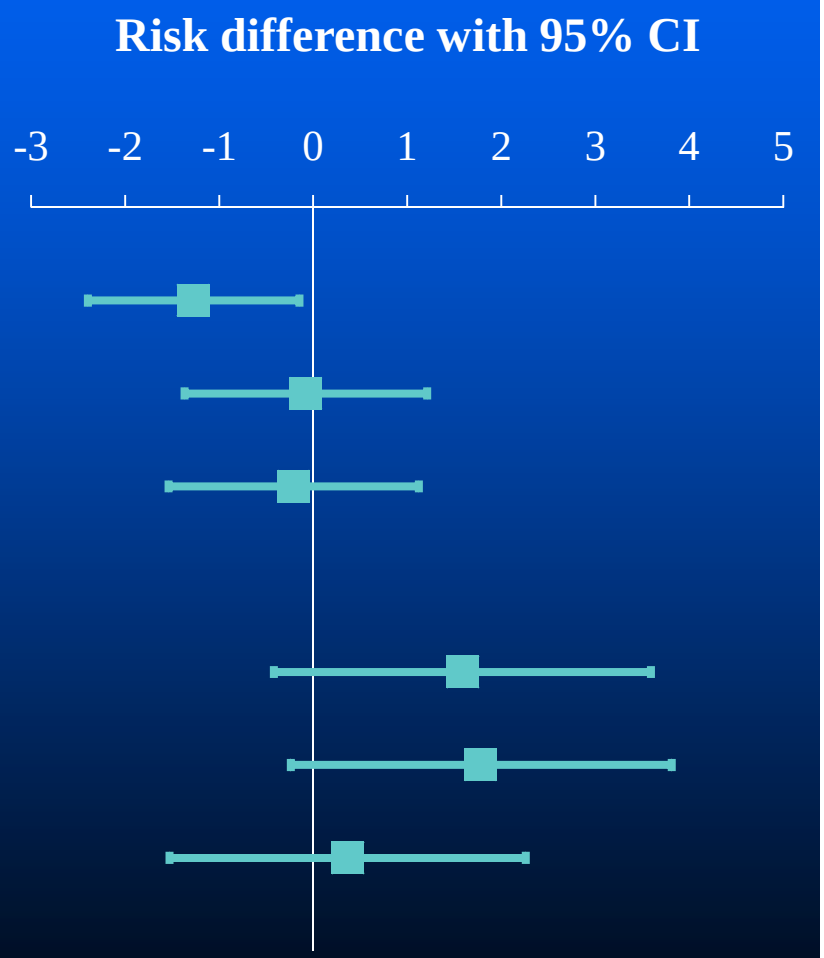
## Observed incidence




Treatment + 30 days

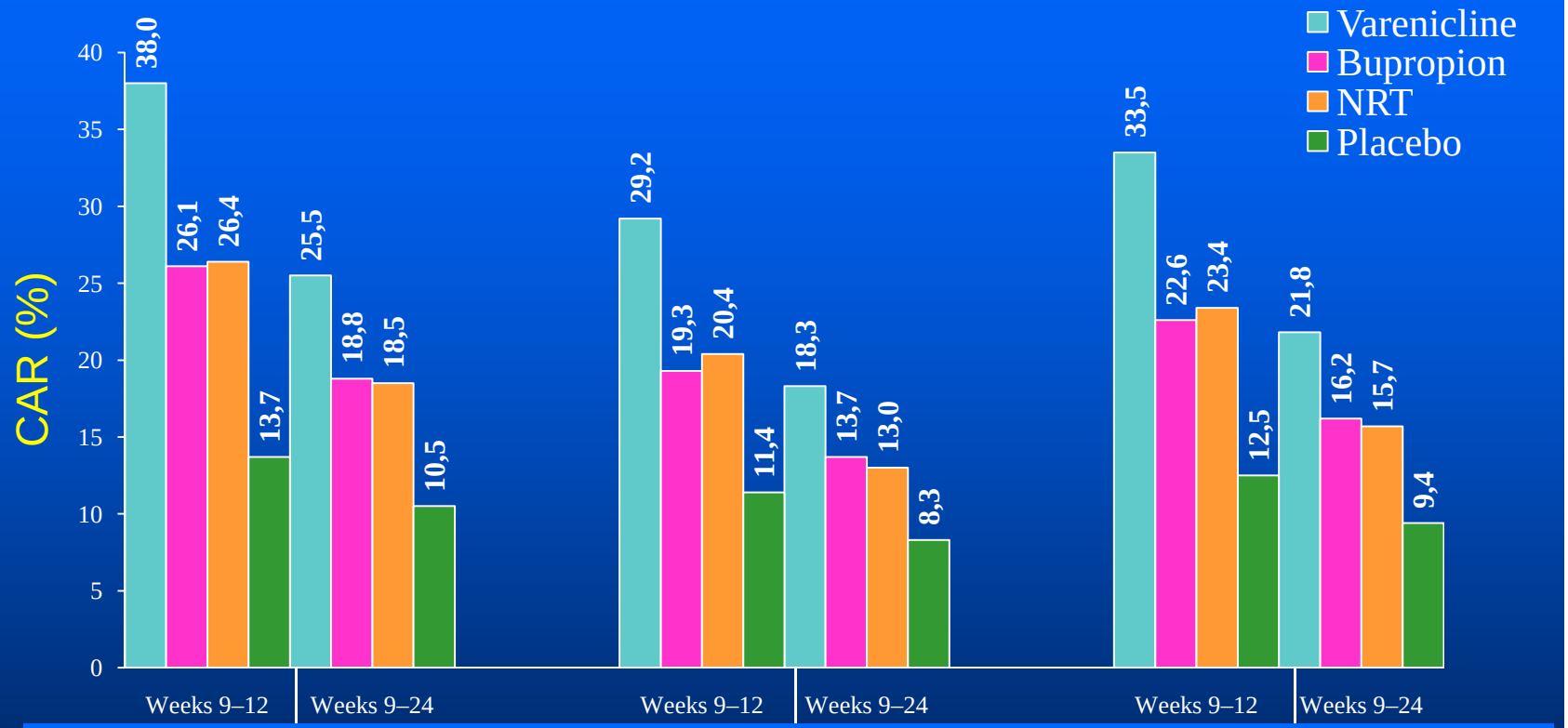
# Primary NPS Composite Safety Endpoint: Risk Differences Between Treatment Groups

| | Risk difference (95% CI) |
|---|---|
| **NPC** | |
| Varenicline vs placebo | **−1.28 (−2.40, −0.15)** |
| Bupropion vs placebo | −0.08 (−1.37, 1.21) |
| NRT vs placebo | −0.21 (−1.54, 1.12) |
| **PC** | |
| Varenicline vs placebo | 1.59 (−0.42, 3.59) |
| Bupropion vs placebo | 1.78 (−0.24, 3.81) |
| NRT vs placebo | 0.37 (−1.53, 2.26) |




AEs reported during treatment and ≤30 days after last dose (All treated population).

# Relative Efficacy of 1st–Line Smoking Cessation Aids



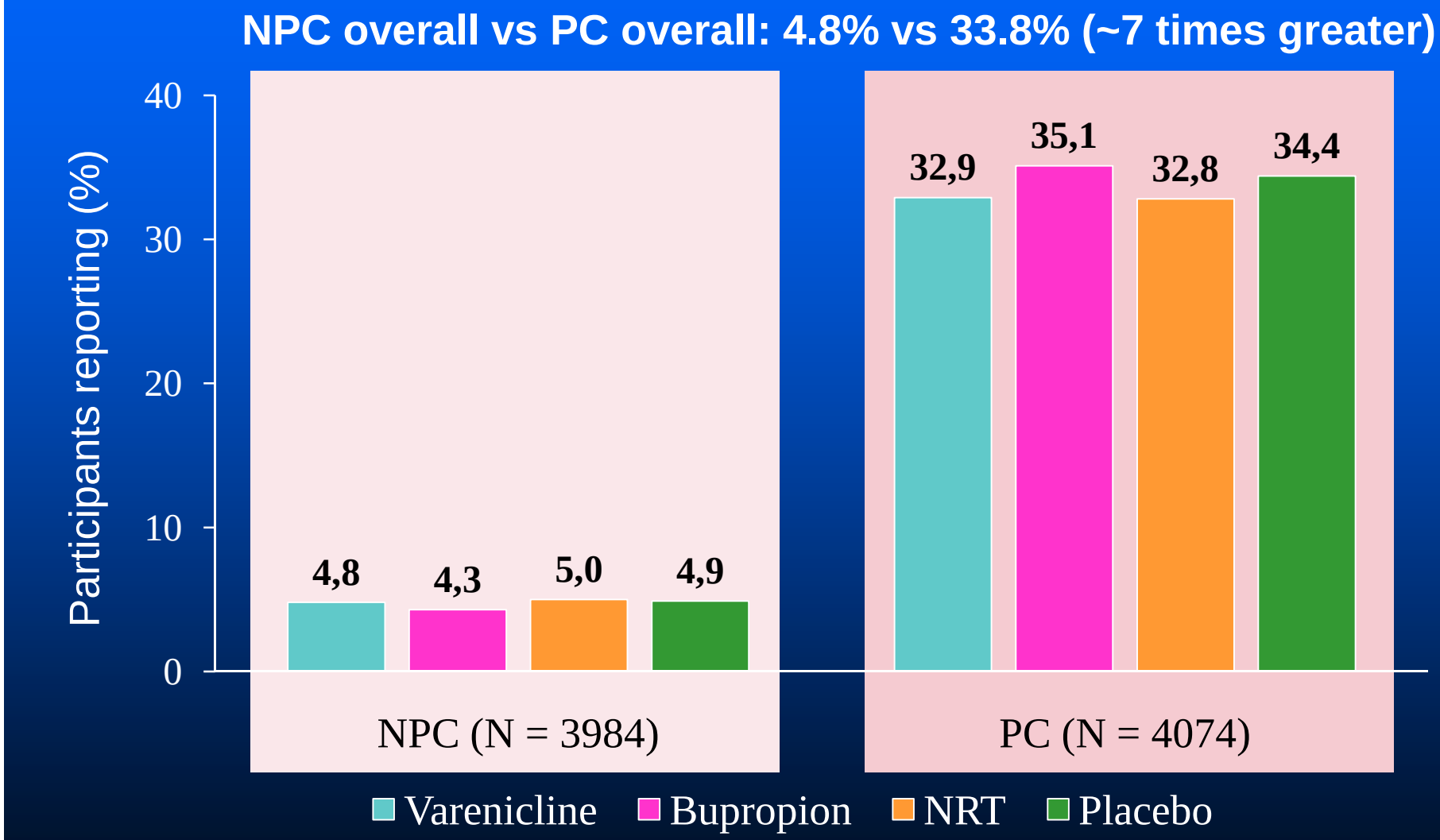

| OR (95% CI) | | | | | | |
|---|---|---|---|---|---|---|
| **Primary comparisons** | | | | | | |
| Varenicline vs. placebo | 4.00 (3.20, 5.00) | 2.99 (2.33, 3.83) | 3.24 (2.56, 4.11) | 2.50 (1.90, 3.29) | 3.61 (3.07, 4.24) | 2.74 (2.28, 3.30) |
| Bupropion vs. placebo | 2.26 (1.80, 2.85) | 2.00 (1.54, 2.59) | 1.87 (1.46, 2.39) | 1.77 (1.33, 2.36) | 2.07 (1.75, 2.45) | 1.89 (1.56, 2.29) |
| **Secondary comparisons** | | | | | | |
| NRT vs. placebo | 2.30 (1.83, 2.90) | 1.96 (1.51, 2.54) | 2.00 (1.56, 2.55) | 1.65 (1.24, 2.20) | 2.15 (1.82, 2.54) | 1.81 (1.49, 2.19) |
| Varenicline vs. NRT | 1.74 (1.43, 2.10) | 1.52 (1.23, 1.89) | 1.62 (1.32, 1.99) | 1.51 (1.19, 1.93) | 1.68 (1.46, 1.93) | 1.52 (1.29, 1.78) |
| Bupropion vs. NRT | 0.98 (0.80, 1.20) | 1.02 (0.81, 1.28) | 0.94 (0.75, 1.16) | 1.07 (0.83, 1.39) | 0.96 (0.83, 1.11) | 1.04 (0.88, 1.24) |
| Varenicline vs. bupropion | 1.77 (1.46, 2.14) | 1.49 (1.20, 1.85) | 1.74 (1.41, 2.14) | 1.41 (1.11, 1.79) | 1.75 (1.52, 2.01) | 1.45 (1.24, 1.70) |

# *EAGLES* Secondary Safety Endpoints: Suicidality Assessments

- Columbia - Suicide Severity Rating Scale (C-SSRS)[1]
  - Measures 4 constructs
    - » Severity of ideation
    - » Intensity of ideation
    - » Behavior subscale
    - » Lethality subscale
  - Administered at screening, baseline, Weeks 1–6, 8, 12, 13, 16, 20, and 24

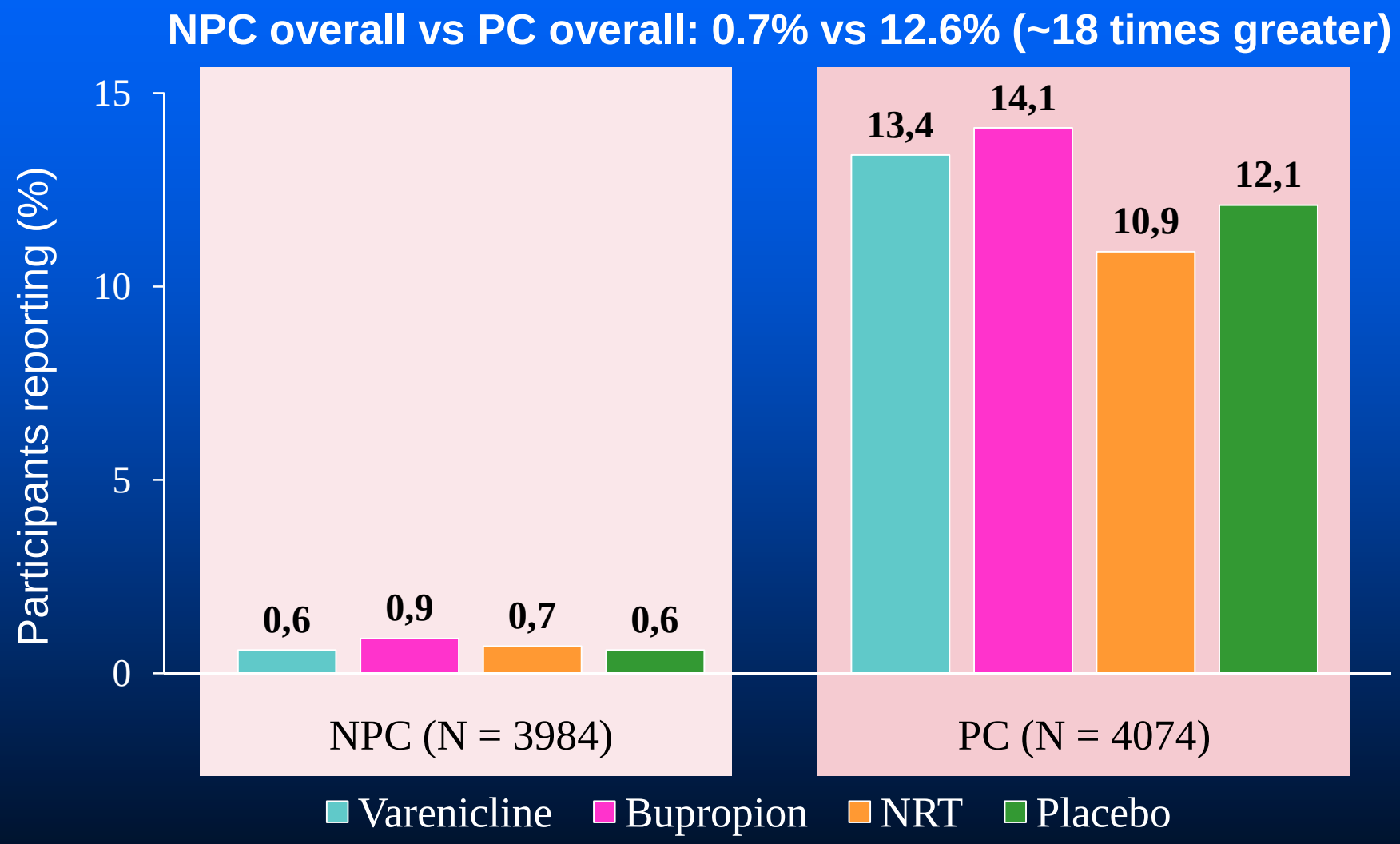
[1]Posner K et al. *Am J Psychiatry* 2011.

# Lifetime Rates of SI at Baseline – C-SSRS




C-SSRS, Columbia Suicide Severity Rating Scale; SI, suicide ideation.

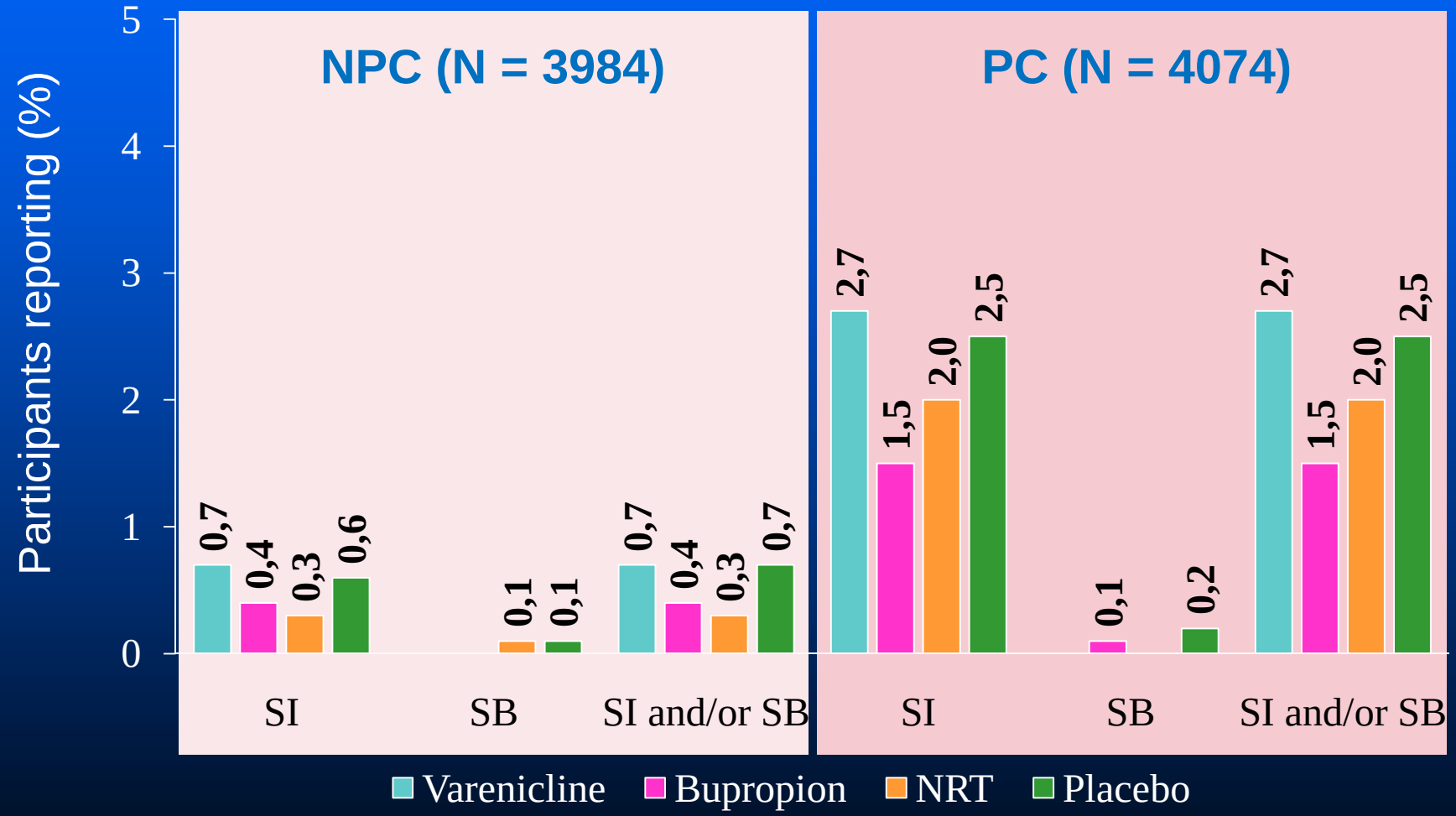
# Lifetime Rates of SB at Baseline – C-SSRS




C-SSRS, Columbia Suicide Severity Rating Scale; SB, suicide behavior.

# Rates of SI and/or SB During Treatment – C-SSRS

**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

# Observational Studies of Varenicline & Serious Neuropsychiatric (NPS) – Adverse Events (AEs)

| Study | Sample | Outcome | Adj. HR* |
|---|---|---|---|
| Meyer 2013 *Addiction* | 35,800 US MHS 2006-2007 | NPS hospital. (prim diag) 30 days | 1.14 (0.56, 2.34) |
| | | NPS hospital. (any diag) 30 days | 0.79 (0.50, 1.24) |
| | | NPS outpt visits | 0.71 (0.60, 0.84) |
| Thomas 2013 *BMJ* | 112,805 UK NHS 2006-2011 | Fatal/nonfatal self-harm 90 days | 0.88 (0.52, 1.49) |
| | | Initiated antidepressant 90 days | 0.75 (0.65, 0.87) |
| Kotz 2015 *Lancet Resp Med* | 158,209 UK NHS 2007-2012 | Depression | 0.65 (0.61, 0.68) |
| | | Fatal/nonfatal self-harm 6 mo | 0.60 (0.48, 0.76) |
| Cunningham 2016 *Addiction* | 15,255 US VA 2006-2007 | NPS hospital. (prim diag) 30 days | 0.15 – 2.00 all NS<br>Signif for Schiz only |
| | | NPS outpt visit in 30 days | 1.27 (1.07, 1.51)<br>+5 visits per 100 yrs tx |
| Molero 2015 *BMJ* | 69,757 Sweden (self-controlled) 2006-2009 | Hospital or outpt specialist psychoses, mood, or anxiety | 1.18 (1.05, 1.31)<br>(Specific to mood or anxiety tx in Psych-HX) |
| | | Fatal/nonfatal self-harm | 1.00 (0.72, 1.37) |
| Pasternak 2013 *Addiction* | 77,726 Denmark 2007-2010 | NPS ER visit or hosp. in 30 days (vs. bupropion) | 0.85 (0.55, 1.30) |

*All analyses used statistical adjustment to control for confounds, effect is a hazard ratio

From Prochaska JJ. Evidence from Observational Studies. Joint Meeting of the FDA Advisory Committees: *Serious Neuropsychiatric Adverse Events with Drugs for Smoking Cessation*, September 14, 2016.

# Large-Scale Observational Studies Evaluating Fatal/Non-Fatal Self-Harm in Smokers

| Endpoint | Author | Varenicline # Events/ Sample Size | Comparator # Events/ Sample Size | Hazard Ratio | 95% CI | |
|---|---|---|---|---|---|---|
| | | | | | Lower Limit | Upper Limit |
| Suicide attempt | Cunningham | 0 / 11,774 | 0 / 23,548 | NA | NA | NA |
| Suicide | Thomas | 2 / 30,352 | 6 / 78,407 | NA | NA | NA |
| Fatal Or Non Fatal Self Harm | Thomas | 19 / 30,352 | 69 / 78,407 | 0.88 | 0.52 | 1.49 |
| | Kotz | 119 / 51,450 | 540 / 106,759 | 0.56 | 0.46 | 0.68 |
| | Molero | 657 / 69,757 | NA | 1.00 | 0.72 | 1.37 |

From Prochaska JJ. Evidence from Observational Studies. Joint Meeting of the FDA Advisory Committees: *Serious Neuropsychiatric Adverse Events with Drugs for Smoking Cessation*, September 14, 2016.

# Summary of *EAGLES* Findings

- Higher rates of NPS AEs seen in smokers with psychiatric disease
- 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 and non-psychiatric cohorts

# Clinical Implications of the *EAGLES* and Observational Cohort Studies

- All 3 1st-line smoking cessation medications can be used safely and effectively in smokers with stable psychiatric disorders
- Serious neuropsychiatric adverse events occur more frequently in smokers with stable psychiatric disorders regardless of treatment, *so monitoring is important*
- Challenging to disentangle NPS AEs without placebo control
  - Tobacco withdrawal symptoms and signs
  - Potential drug-related adverse event
  - Emergence or recurrence of psychiatric symptoms
  - Another medication's side effect
  - Stress of quitting smoking
- EAGLES results shed light on this diagnostic dilemma

# Unintended Consequences of the Boxed Warning in Light of Totality of Evidence

- Contributes to misattribution of symptoms and "a rush to judgment"
- Overestimation of risk and underestimation of benefit
- Smokers and clinicians not taking advantage of effective medications

  2009-2013: overall sales of Rx & OTC products in the US decreased 36%[1]
- Another hurdle for those already facing many barriers

FDA Briefing Document; *Chantix and Serious Neuropsychiatric Adverse Events*, October 16, 2014 (accessed September 9, 2015).