

The Top 10 Clinical Implications From the EAGLES and CATS Trials

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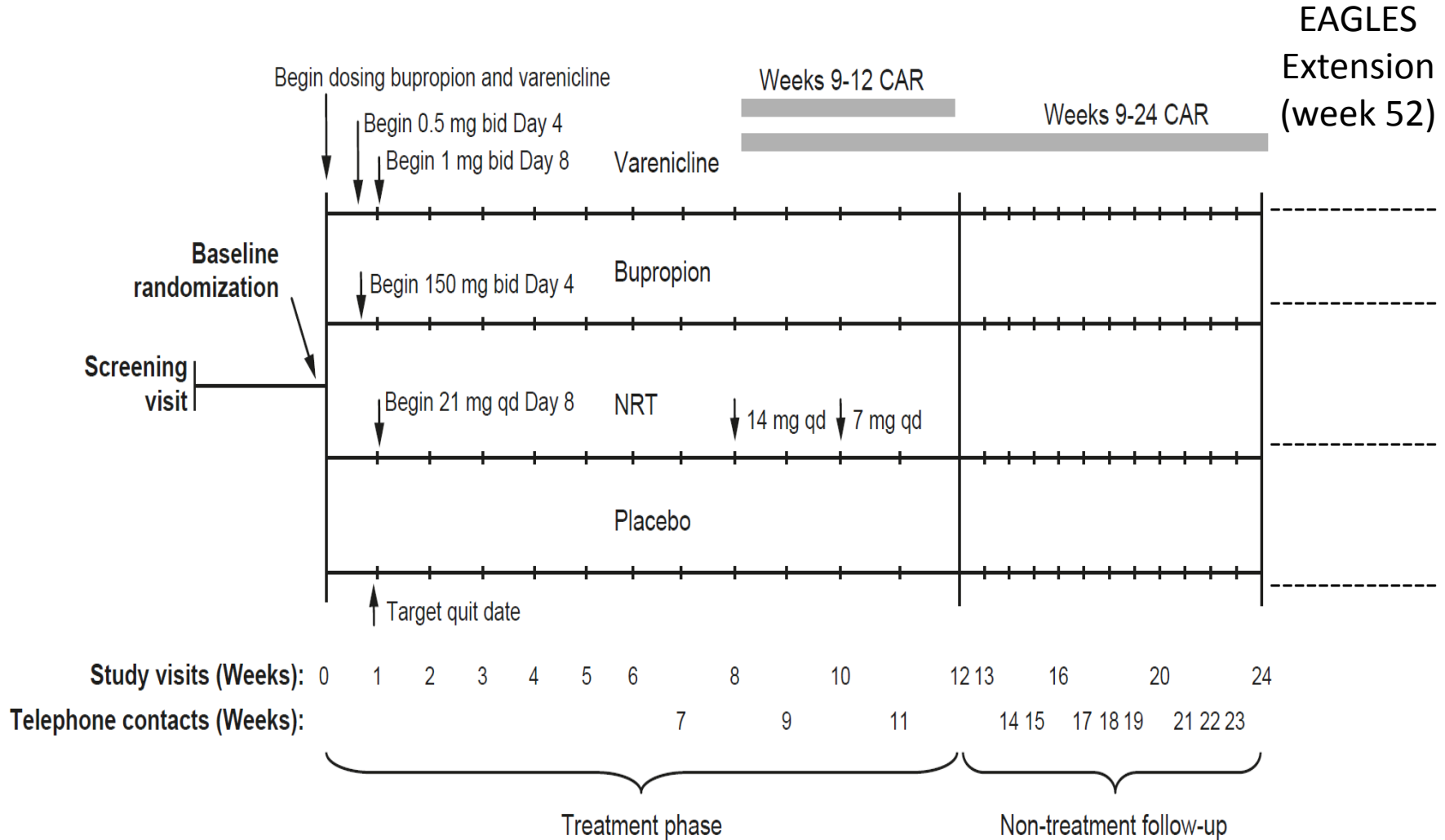
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Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES)

- Anthenelli RM et al. *Lancet* 2016;387:2507–2520
 - Multicenter, double-blind, randomized, controlled trial
 - 140 centers; 16 countries
 - Psychiatric and Non-Psychiatric Cohorts
 - Varenicline vs. bupropion vs. NRT (patch) vs. placebo
 - triple dummy design
 - 1000 subjects per treatment arm and cohort (total $N = >8000$)
 - Balanced by diagnostic group within Psychiatric Cohort
 - Brief smoking cessation counseling at all visits/contacts

EAGLES Study Design



Anthenelli et al., Lancet 2016

CAR, continuous abstinence rate; NRT, nicotine replacement therapy (transdermal nicotine patch)

EAGLES Continues to Produce New Findings

1. Anthenelli et al. *Lancet* 2016
2. West et al. *Addiction* 2018
3. Benowitz et al. *JAMA Internal Medicine* 2018
4. Evins et al. *Journal of Clinical Psychopharmacology* 2019
5. Anthenelli et al. *Journal of General Internal Medicine* 2019
6. Heffner et al. *Journal of Affective Disorders* 2019
7. Ayers et al. – Anxiety Disorders
8. Evins et al. – Psychotic Disorders
9. Cinciripini et al. – Major Depressive Disorder
10. Gaznick et al. – Lifetime History of Suicidality
11. Correa et al. – Comorbidity/Multimorbidity
12. West et al. – Bayesian Analysis

#1: Incidence of clinically significant NPSAEs is low in smokers w/o MHCs

- About 1 in 50 (2%) smokers without a mental health condition (MHC) experience a moderate-to-severe neuropsychiatric adverse event (NPSAE) when making a medication-assisted quit attempt.
- These rare events occur regardless of which medication (NRT, bupropion, varenicline, placebo) is used and they seldom manifest as serious adverse events.

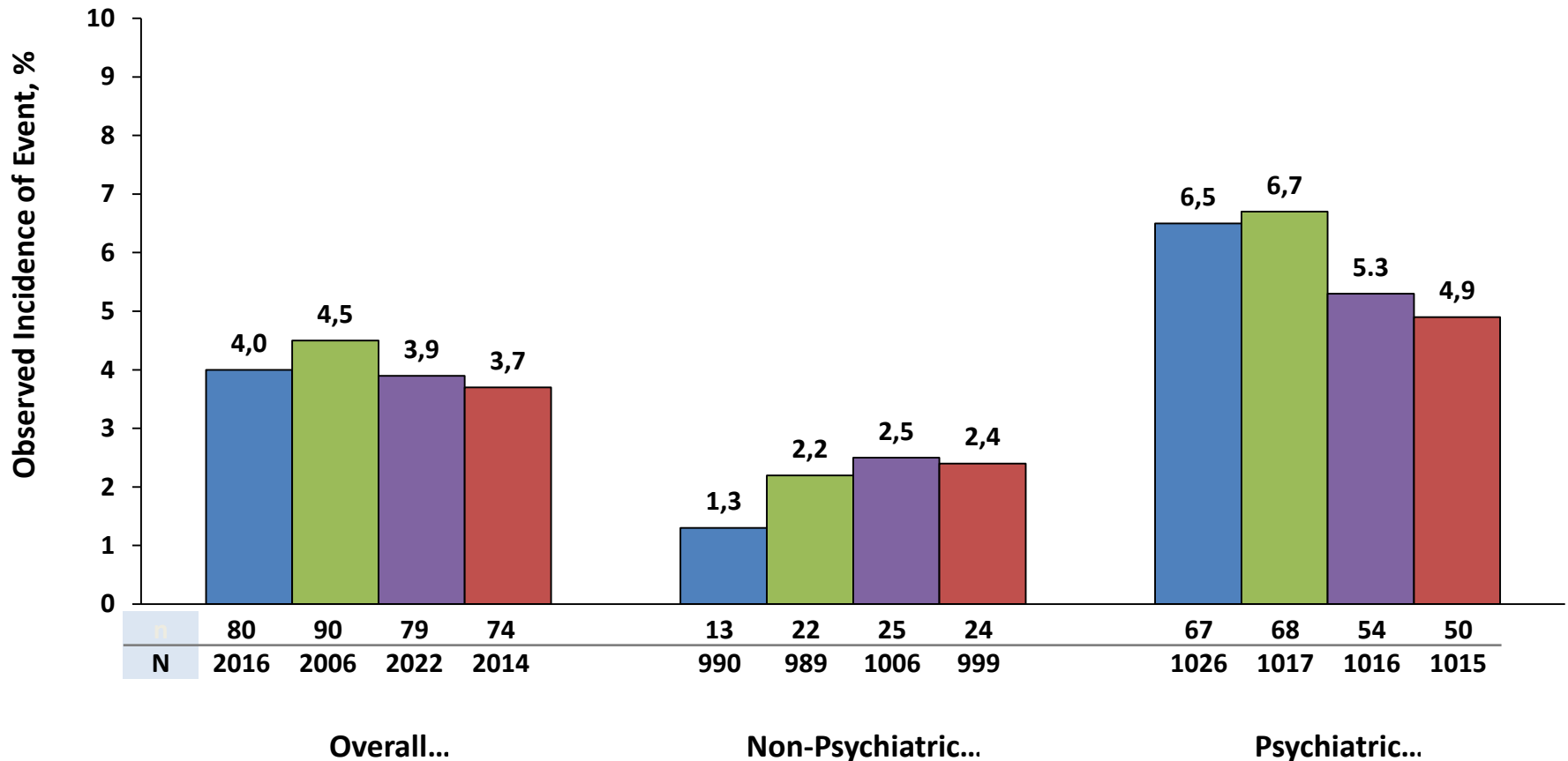
#2: Incidence of clinically significant NPSAEs is higher in smokers with MHCs

- While still relatively infrequent (~6% overall), the incidence of moderate-to-severe NPSAEs in smokers with MHCs is ~3-times higher regardless of the medication/placebo used
- The incidence of moderate-to-severe NPSAEs appears highest in individuals with serious mental illness such as bipolar disorder and schizophrenia

Primary Neuropsychiatric AE Composite Endpoint

Observed Incidence

■ Varenicline ■ Bupropion ■ NRT ■ Placebo



#2: Smokers with MHCs more likely to experience moderate to severe NPSAEs when trying to quit; however, vast majority do not, and risk does not appear related to any particular treatment

Bipolar Disorder: Risk Difference (RD)* = 7.7; 95% CI = 4.2-11.3

Schizophrenia Spectrum Disorders: RD* = 4.0; 95% CI = 1.6 – 6.3

Panic Disorder: RD* = 4.0; 95% CI = 0.3 – 7.6

PTSD: RD* = 3.8; 95% CI = -1.0 – 8.5

GAD: RD* = 3.3; 95% CI = -0.5 – 7.2

(Risk Difference [RD]* across all treatments compared with same in the non-psychiatric cohort)

- Reassure
- Know the risk factors
- Monitor for moderate-to-severe NPSAEs and adjust treatment accordingly

#3: FDA revises description of mental health side effects of the stop-smoking medicines Chantix (varenicline) and Zyban (bupropion) to reflect clinical trial findings

- **[12-16-2016]** Based on a U.S. Food and Drug Administration (FDA) review of a large clinical trial that we required the drug companies to conduct,¹ we have determined the risk of serious side effects on mood, behavior, or thinking with the stop-smoking medicines Chantix (varenicline) and Zyban (bupropion)* is lower than previously suspected....The results of the trial confirm that the benefits of stopping smoking outweigh the risks of these medicines.
- As a result of our review of the large clinical trial, **we are removing the *Boxed Warning***, FDA's most prominent warning, for serious mental health side effects **from the Chantix drug label**. The language describing the serious mental health side effects seen in patients quitting smoking will **also be removed from the *Boxed Warning* in the Zyban label**.[†]
- Similar regulatory actions taken by European Medicines Agency, Health Canada, and in Israel and France

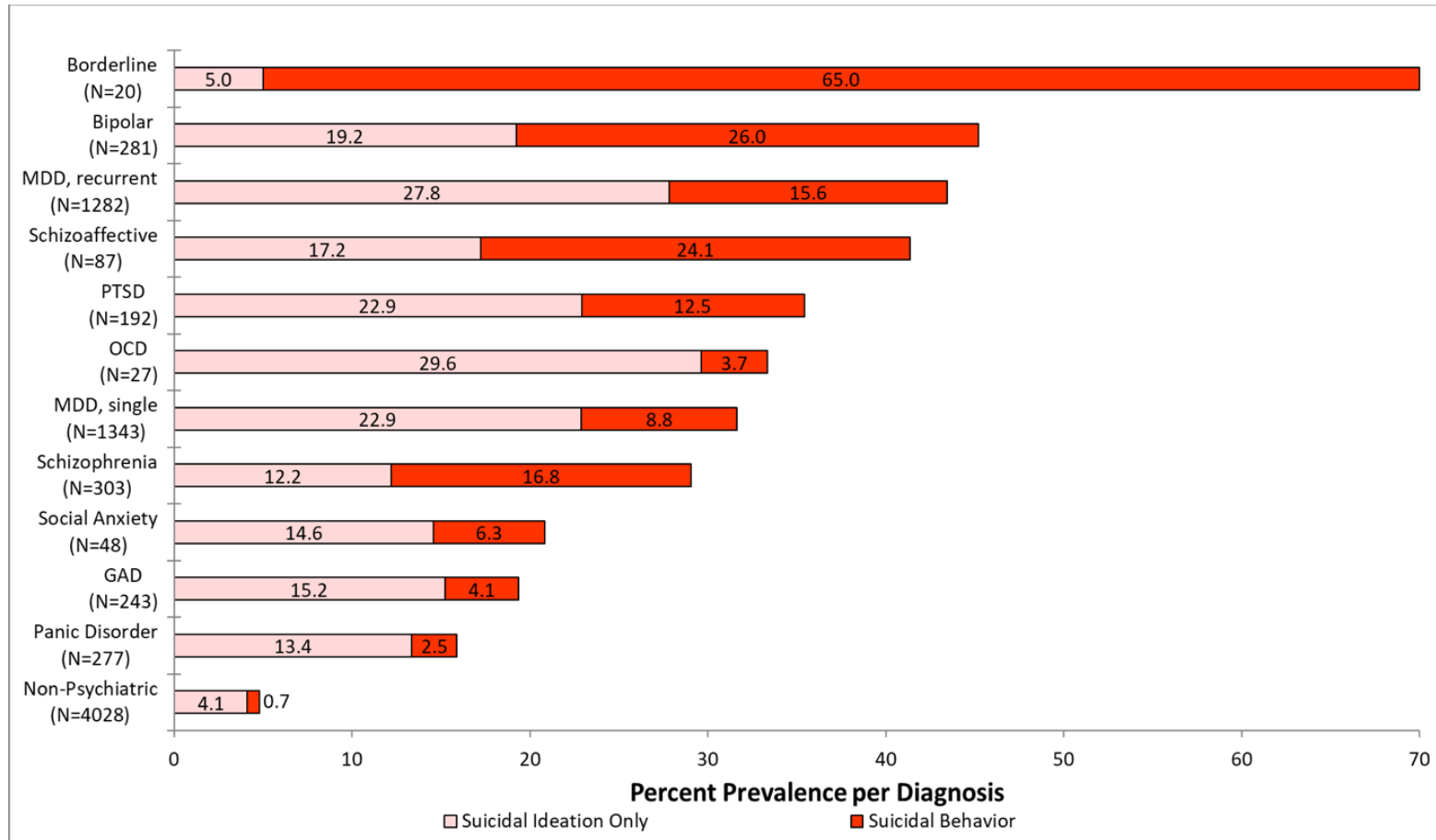
#4: Several Characteristics Predict Risk of Experiencing Moderate-to-Severe NPSAEs Regardless of Treatment

- In both smokers with and without mental health conditions
 - Current symptoms of anxiety
 - Past history of suicidal ideation or behavior
 - Being of White race
- In smokers with histories of mental health conditions
 - Being younger and of female sex
 - Having a history of comorbid psychiatric and substance use disorders
 - Greater smoking duration
 - Higher severity of nicotine dependence

#5: Since SI/SB predicts risk, screen for this, especially among smokers with MHCs

- Having a past history of SI/SB is common among smokers with MHCs especially among individuals with MHCs marked by mood lability (e.g., borderline personality, bipolar disorder, recurrent MDD) and pathological rumination (PTSD, OCD)
- Since past h/o SI/SB predicts moderate-to-severe NPSAEs, inquire about such history and monitor these smokers more carefully

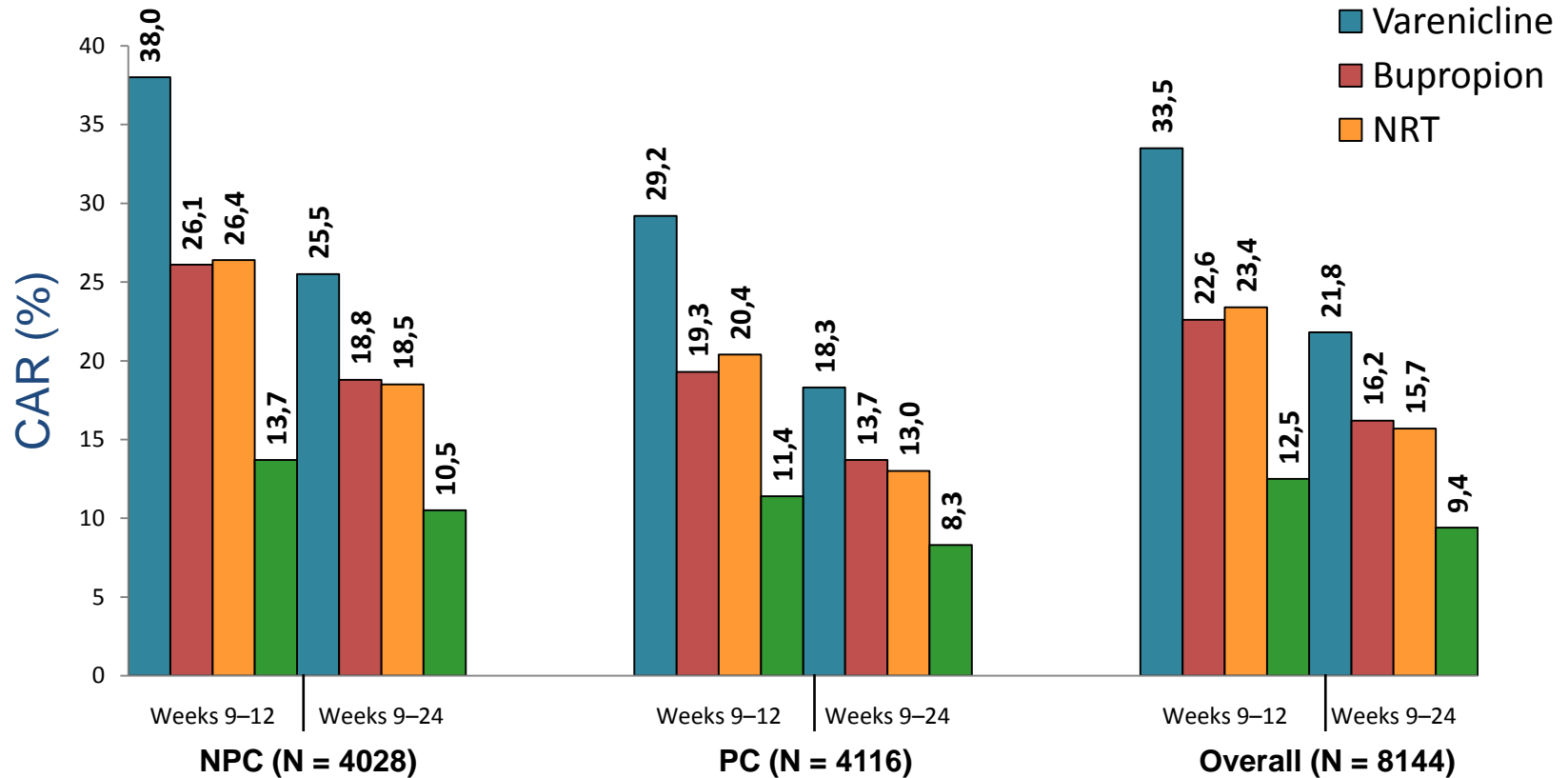
Lifetime Prevalence of Suicidal Ideation/ Behavior in Smokers with and without Mental Health Conditions



#6: In general, regarding relative effectiveness--
Varenicline > bupropion = mono NRT > placebo

- Varenicline is the most effective smoking cessation monotherapy in smokers with and without MHCs
- In most instances, except for PTSD and Panic Disorder, where NRT's effects were similar to varenicline's, varenicline was superior to both bupropion and NRT
- In almost all instances, except for bipolar disorder, all 3 medications were more effective than placebo

Relative Efficacy of 1st–Line Smoking Cessation Aids



<u>OR (95% CI)</u>	NPC (N = 4028)		PC (N = 4116)		Overall (N = 8144)	
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)

Summary of EAGLES Efficacy Odds Ratios (ORs) Compared With Placebo in Smokers with Various MHCs

	VAR	BUP	NRT
PTSD	3.2	1.2	3.1
GAD	4.5	2.4	2.4
PD	8.5	3.3	7.4
MDD (single)	2.5	1.8	1.7
MDD (recurrent)	3.7	2.1	2.1
SSD	7.4	3.2	3.7
BD	2.6	1.3	0.7

Bolded ORs reflect 95% CIs > 1.

ORs and 95% CIs are for Continuous Abstinence Rates (CAR) during weeks 9-12.

Caveat: Non-significant values may reflect limited power in these EAGLES subcohorts.

#7: Smokers with MHCs have lower odds of quitting compared with smokers w/o MHCs

- This varies by type of primary diagnosis:
 - Schizophrenia Spectrum Disorder ↓ 54%
 - Panic Disorder ↓ 47%
 - PTSD ↓ 42%
 - Bipolar Disorder ↓ 35%
 - Generalized Anxiety Disorder ↓ 28%
 - Major Depression ↓ 20%

Partly relates to greater nicotine dependence severity, but other factors at play

#8: Although effective, medications are underused, especially among smokers with MHCs

Prior Treatment With Smoking Cessation Meds

	BD	<u>SSD</u>	PTSD	GAD	PD	MDD single	MDD recurrent	NPC
NRT	25%	<u>15%</u>	25%	28%	25%	29%	32%	25%
BUP	12%	<u>4%</u>	11%	11%	9%	12%	14%	9%
VAR	14%	<u>8%</u>	14%	16%	17%	20%	17%	14%

9: Younger age, higher levels of cigarette dependence, and having a MHC independently predict failure to achieve smoking abstinence

Odds of Successful Quitting

+ Associations

Older age

Higher BMI

Older age started smoking

- Associations

U.S. enrollment site

Black (versus White) race

Mood disorder

Anxiety disorder

Psychotic disorder

Taking psychotropic meds

FTCD score

Prior use of NRT

- No treatment x covariate interactions
- Pharmacotherapy efficacy not affected by prior use of that treatment

#10: CATS found no evidence that any of the smoking cessation medications were associated with increased risk of serious cardiovascular events

- EAGLES Extension Study (CATS) found no evidence that any of the smoking cessation medications were associated ↑ risk of cardiovascular events

Summary and Conclusions

- Varenicline, bupropion and nicotine patch are well tolerated and effective in adult smokers with and without mood, anxiety, and psychotic disorders
- Their relative effectiveness (varenicline > bup = patch > placebo) did not vary across psychiatric diagnoses
 - Bipolar Disorder: Bupropion and NRT effect sizes descriptively lower
 - PTSD & Panic Disorder: Varenicline and NRT had similar effect sizes
- Smokers with MHCs have higher risk of NPSAEs and are less likely to quit overall than smokers without MHCs
- Smoking cessation medications do not increase the risk of serious cardiovascular events in the general population of smokers
- Study results apply to those with stable psychiatric disorders and no current active substance use disorders