MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Treatment of Tobacco Use Disorders

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Disclosures

My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:

Advisory Board: Alkermes Inc

Consultant: Karuna Inc, Ethismos, Charles River Analytics

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Public Health Burden of Tobacco Dependence

- Nearly 68 million smokers in the US
- 3 million tobacco-related deaths annually worldwide-- 440,000 in the US

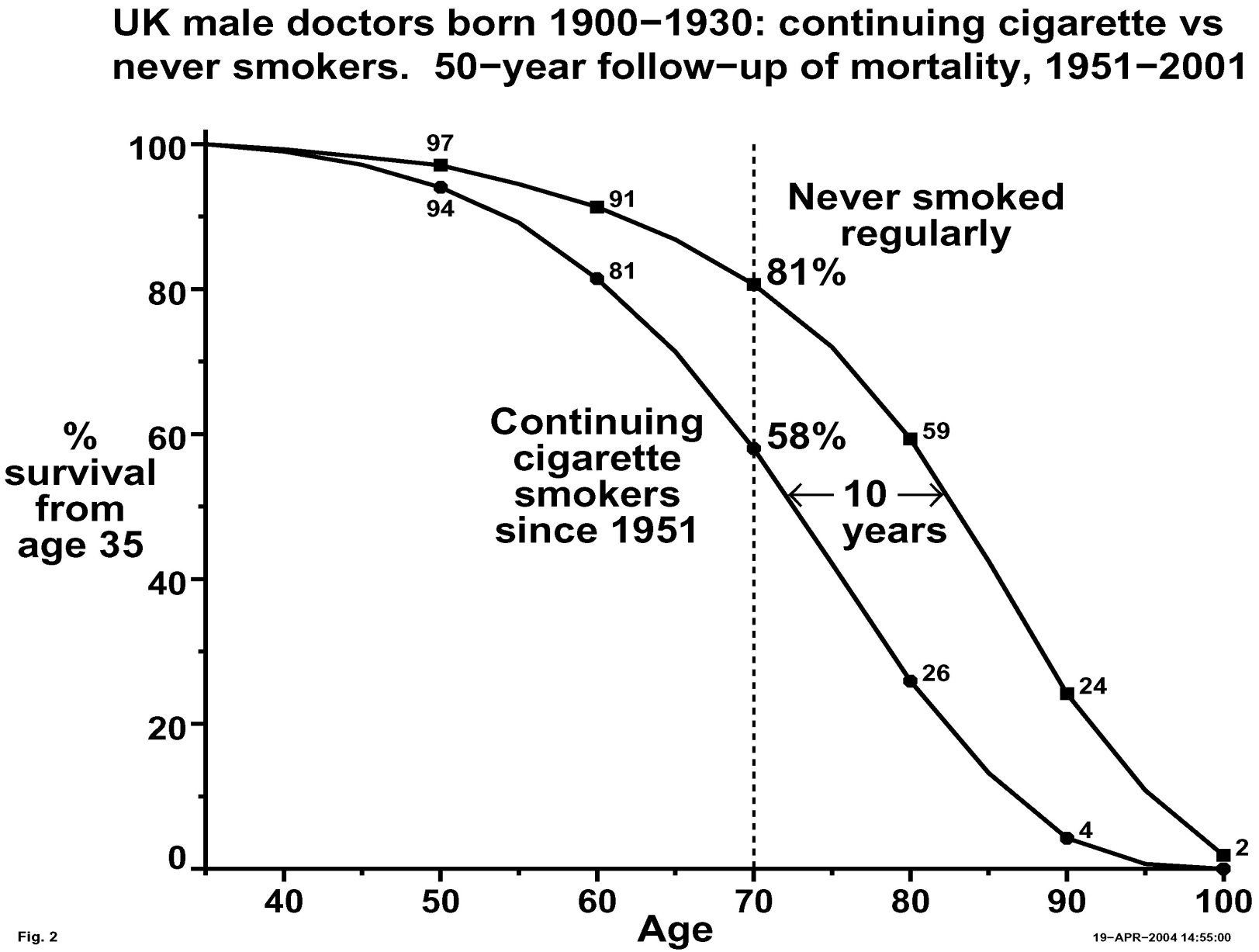
- 16% of Americans currently smoke
- 25% of Americans are former smokers
- 54% of those with SMI smoke

- Numbers of smokers are INCREASING
- 100 million people died in the last century from smoking related causes
- WHO anticipates 1 billion smokers worldwide will die from smoking related causes this century

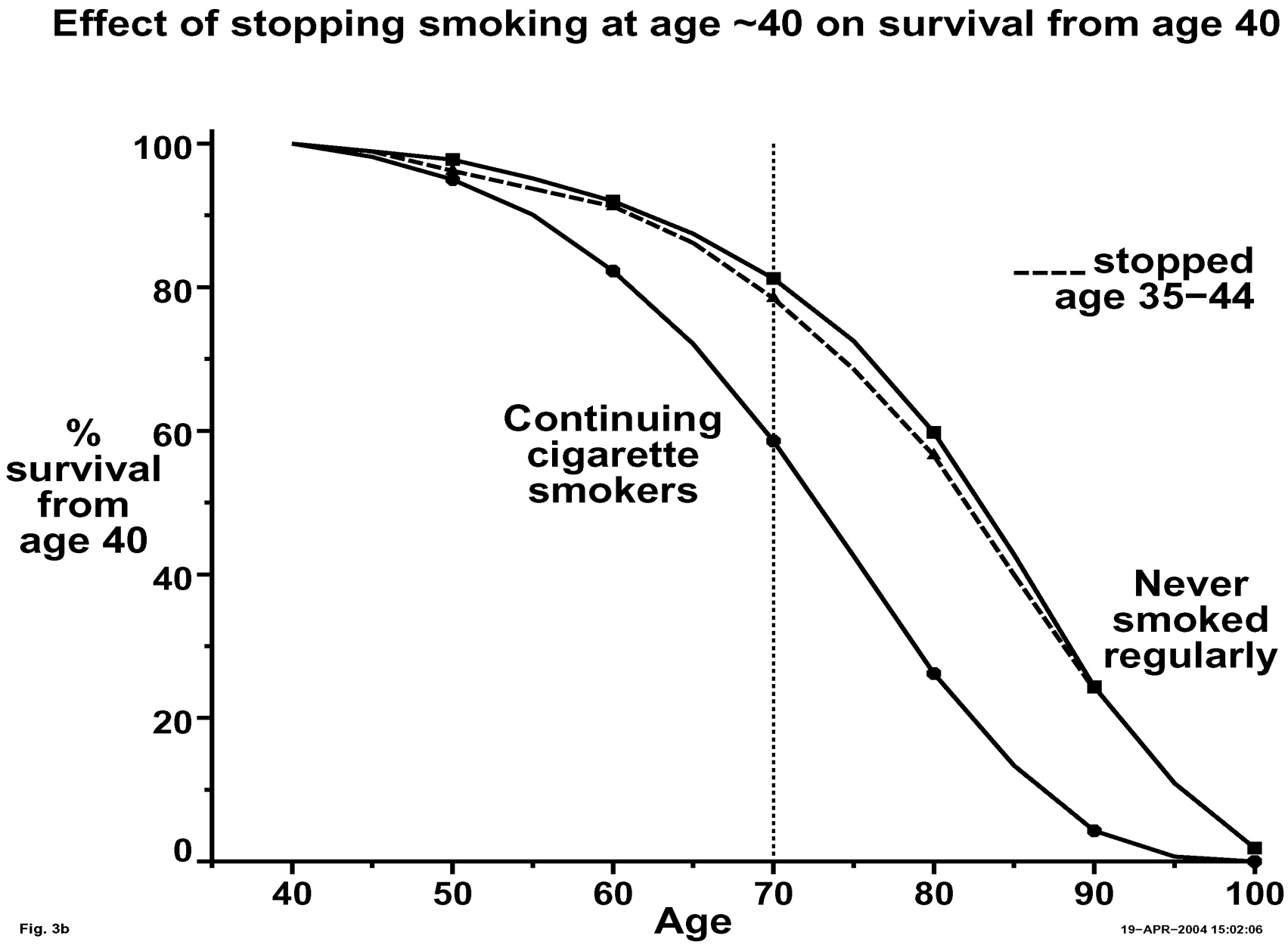
U.S. Drug Related Deaths

- **Opioid overdoses** killed more than 68,000 people in 2018, down from 72,000 in 2017.
- Over 88,000 **alcohol** related deaths per year and increasing.
- Over 430,000 **tobacco** related deaths per year and not decreasing.

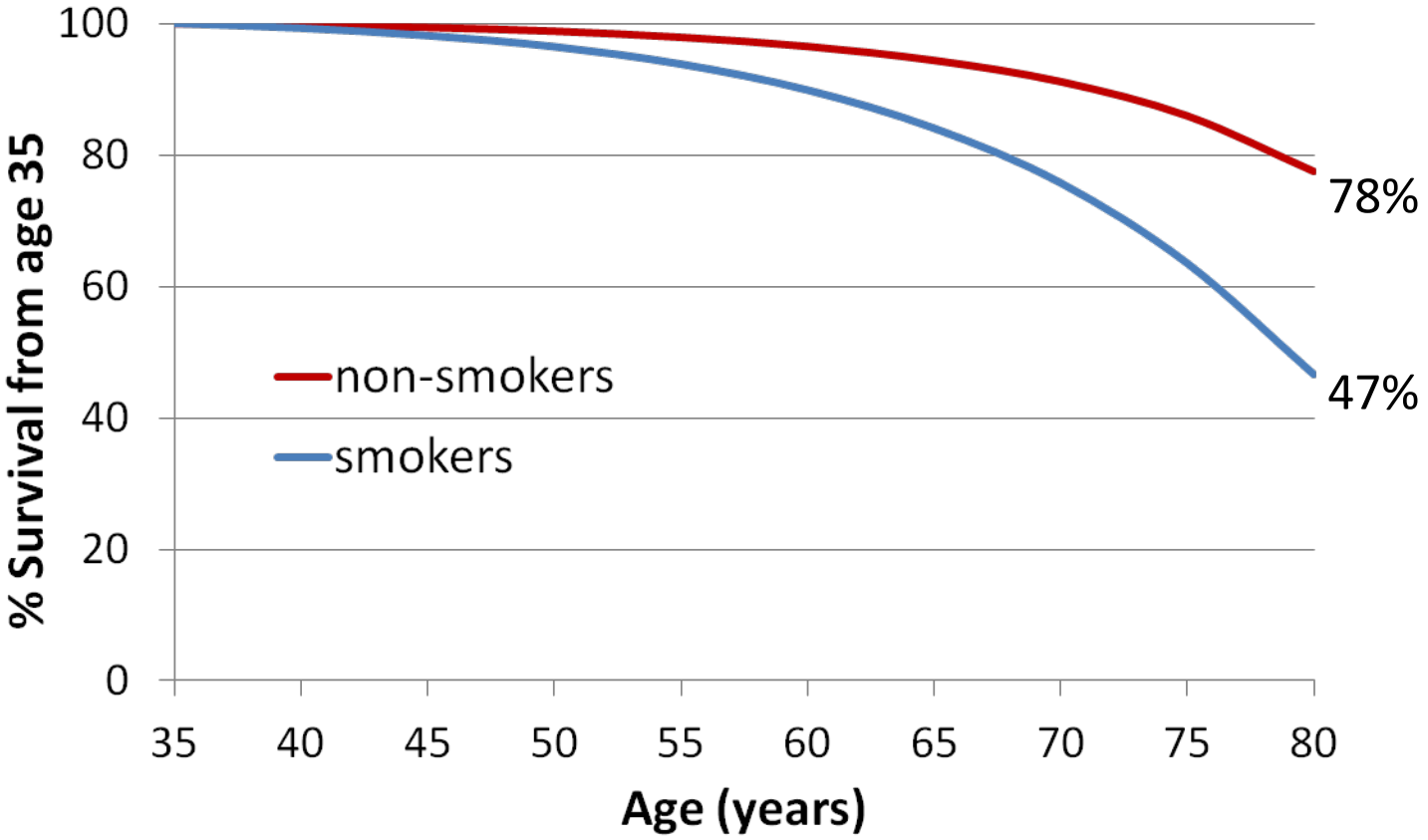
Smoking Kills



Quitting Helps



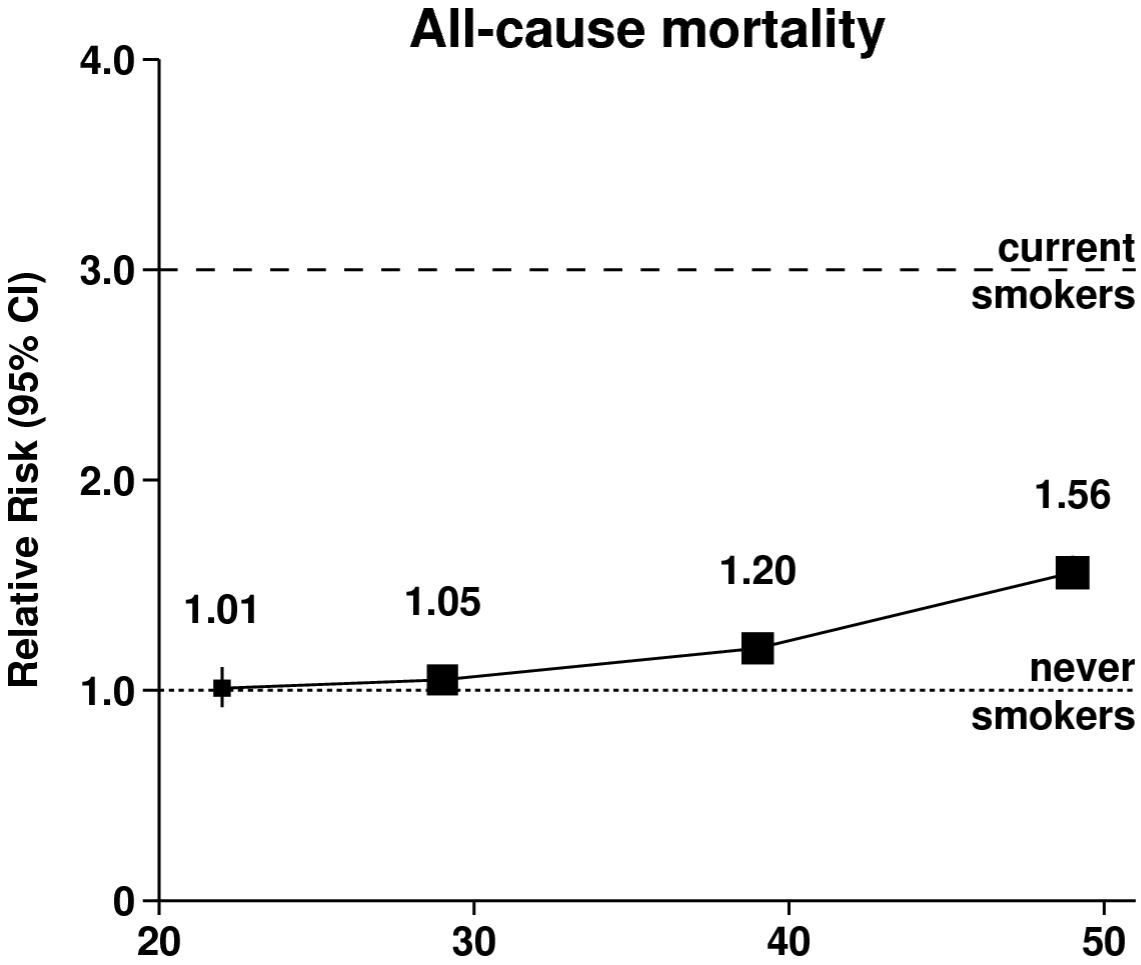
One Million Women Study: Effect of 3-fold difference in annual death rates on survival at ages 35-79



Adapted from the One Million Women Study
Pirie, Peto, et al., Lancet 2013

THE MILLION WOMEN STUDY

Quitting by age 50 halves mortality



Pirie, Lancet, 2013

jama.com

January 8, 2014

Volume 311, Number 2
Pages 105-214

JAMA®

Journal of the
American Medical Association

50 Years after the first Surgeon General's report of an association between smoking and cancer, adult smoking has declined 55% in the general US population.

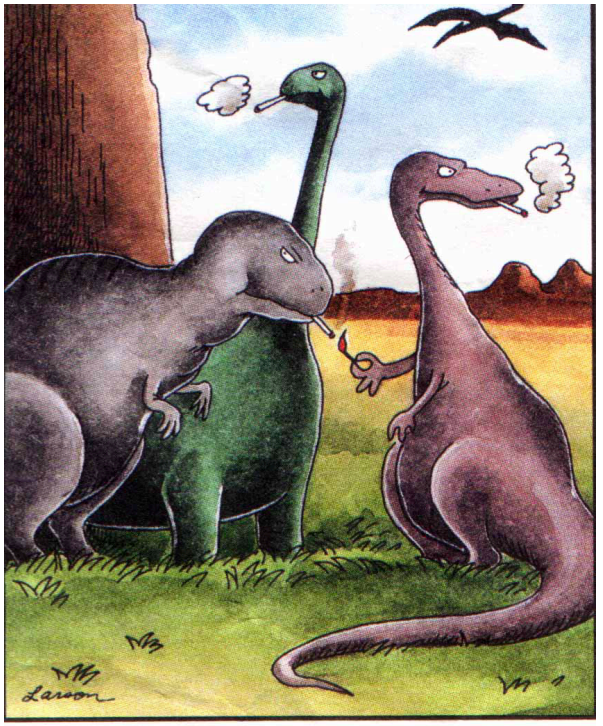
Smoking prevalence among adults with SMI in the US today is 53%.

This is higher than in the US general population in 1964.

Smoking-Related Mortality in Those with Psychiatric Disorders

- In those with one or more lifetime hospitalizations for schizophrenia, bipolar disorder, or MDD,

- HALF died from to 1 of 19 diseases identified by CDC as causally linked to tobacco use



The real reason dinosaurs became extinct

Callaghan, 2014

Quitting Reduces

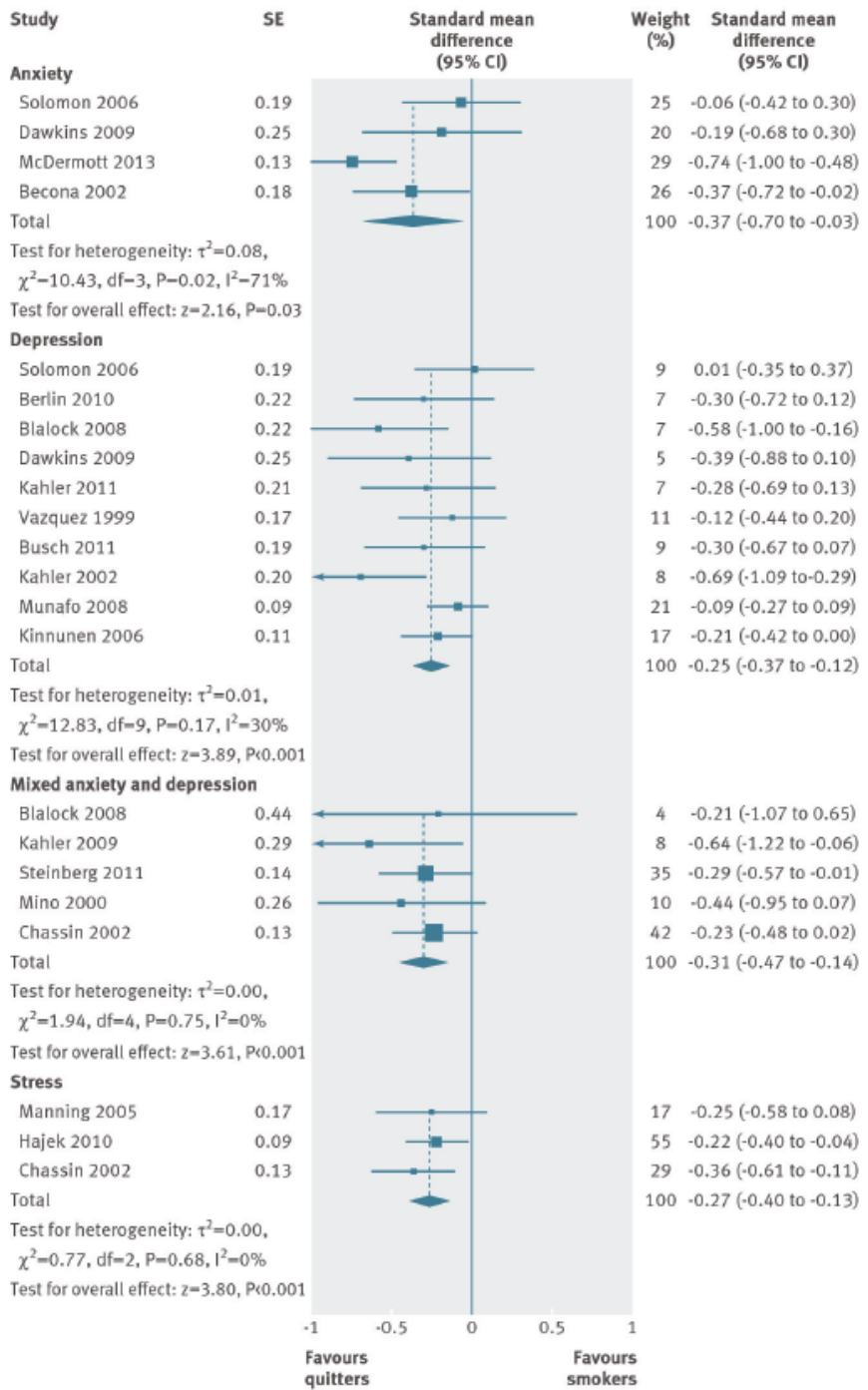
- Death
- MI
- Stroke
- Progression of atherosclerosis
- Bronchitis
- Morbidity from Diabetes
- Cancer Risk
- Progression of COPD

META-ANALYSIS CONFIRMS: SMOKING CESSATION IMPROVES PSYCHIATRIC SYMPTOMS, QUALITY OF LIFE

- 26 studies
- Change in psychiatric symptoms was compared between continuing smokers and successful quitters
- **Depression, anxiety, stress and quality of life** improved among those who quit smoking significantly compared to those who continued smoking.
- It did not matter whether one had a pre-existing psychiatric diagnosis or not!!!
- Effect sizes comparable to those observed for antidepressant medications!!!

Taylor et al. BMJ 2014

Smoking Cessation Is Associated with Improved Psychiatric Symptoms



Taylor et al., BMJ, 2014

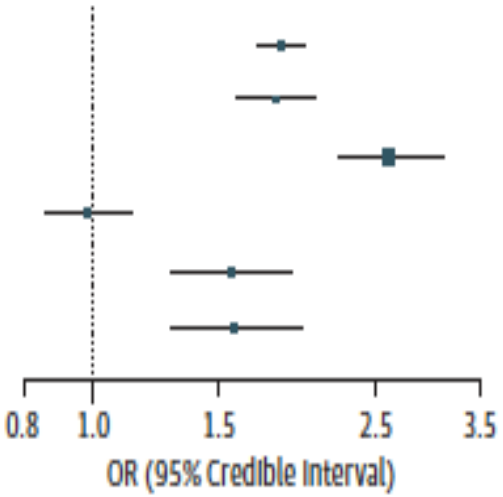
Addiction to Nicotine: Mechanism and Therapeutic Targets

- Acetylcholine stimulates nicotinic cholinergic receptors on dopaminergic and glutamatergic neurons in hippocampus prefrontal cortical areas as well as nucleus accumbens and other reward areas
- Nicotine stimulates a4b2, a7 and other nAChRs in brain
- Therapies target Nicotinic Receptors: NRT, Varenicline, Cytisine
- Or downstream targets such as dopaminergic targets: Bupropion, agents specific for subtypes of dopaminergic receptors under development
- **Exception:** Nicotine stimulation upregulates receptor expression, especially high-affinity a4b2 receptors

Cessation Works: Pharmacotherapy + Behavioral Therapy Doubles to Triples Abstinence Rates

Figure. Odds Ratios for Smoking Abstinence of 6 Months or More

Comparison (Intervention vs Control)	No. of Studies	Total No. of Individuals	Absolute Quit Rates: Intervention n/N (%)	Absolute Quit Rates: Control n/N (%)	Odds Ratio (95% Credible Interval)
NRT vs placebo	119	51225	4704/27258 (17.3)	2464/23967 (10.3)	1.84 (1.71-1.99)
Bupropion vs placebo	36	11440	1214/6409 (18.9)	535/5031 (10.6)	1.82 (1.60-2.06)
Varenicline vs placebo	15	6293	964/3496 (27.6)	332/2797 (11.9)	2.88 (2.40-3.47)
Bupropion vs NRT	8	2581	191/954 (20.0)	375/1627 (23.0)	0.99 (0.86-1.13)
Varenicline vs NRT	0	0	NA	NA	1.57 (1.29-1.91)
Varenicline vs bupropion	3	1622	174/823 (21.1)	111/799 (13.9)	1.59 (1.29-1.96)



Cahill et al., JAMA 2014

Cessation Works: Pharmacotherapy + Behavioral Therapy Doubles to Triples Abstinence Rates

First Line Tx: 1a. Varenicline, Dual NRT,
1b. Bupropion, Single NRT
1c. Varenicline + NRT (single study)
Cahill et al., *JAMA,* 2014
Anthenelli et al., Lancet 2016

Varenicline & Dual NRT *superior to* bupropion & single NRT
Cahill et al., *JAMA,* 2014

Varenicline + NRT more effective than placebo + varenicline
Koegelenberg et al., *JAMA,* 2014

Addiction Treatment Works: Expect and Treat Relapses

For tobacco dependence: average of 5 attempts at abstinence before long-term abstinence achieved

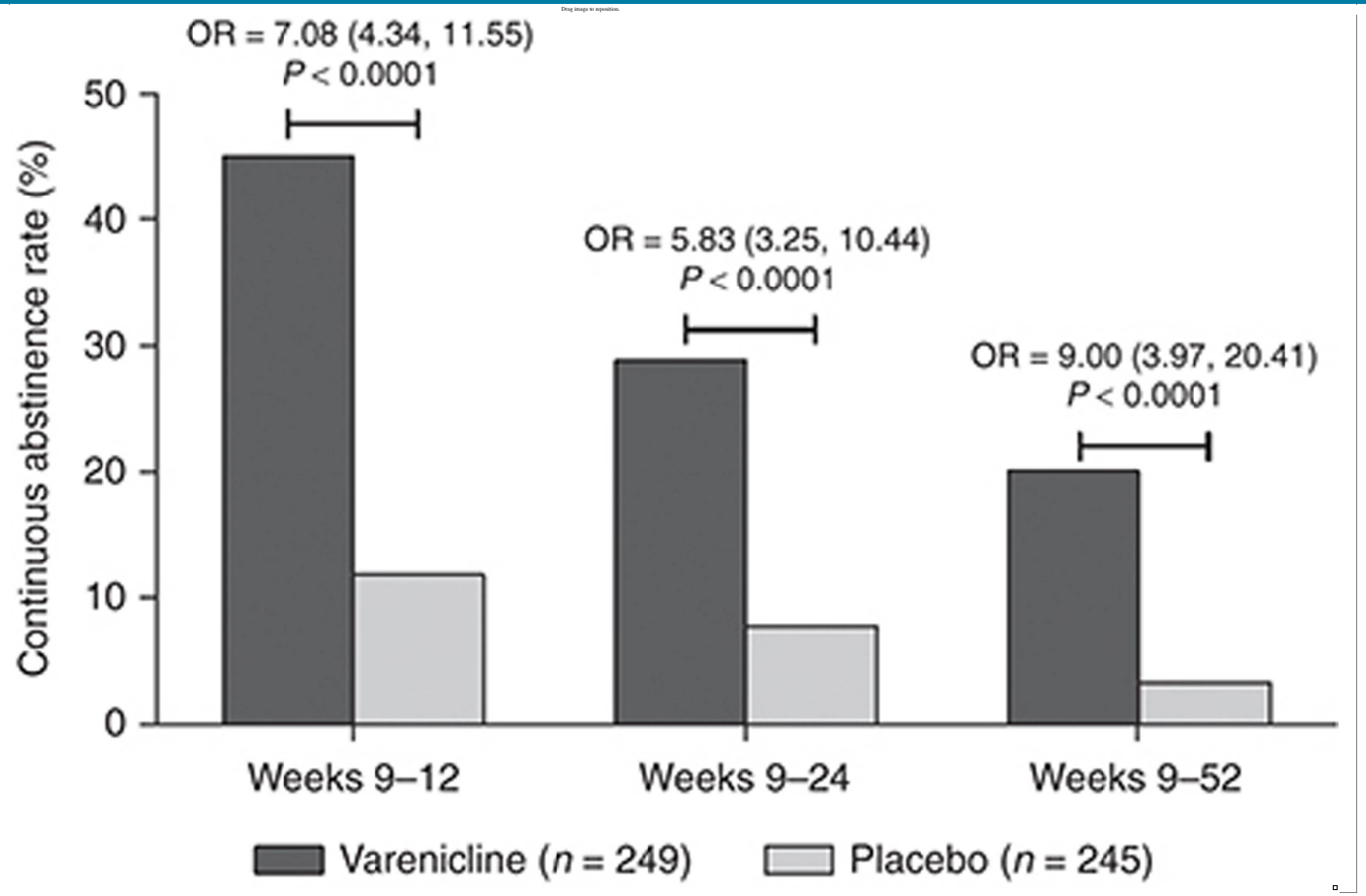
Treatments double to triple abstinence rates and are Underutilized!

New clinical practice guidelines: Treat all smokers

Offer pharmacotherapy and behavioral support to all smokers willing to accept such treatment, not just those who report being ‘ready to quit’

Barua, et al., Am Col Cardiology 2018

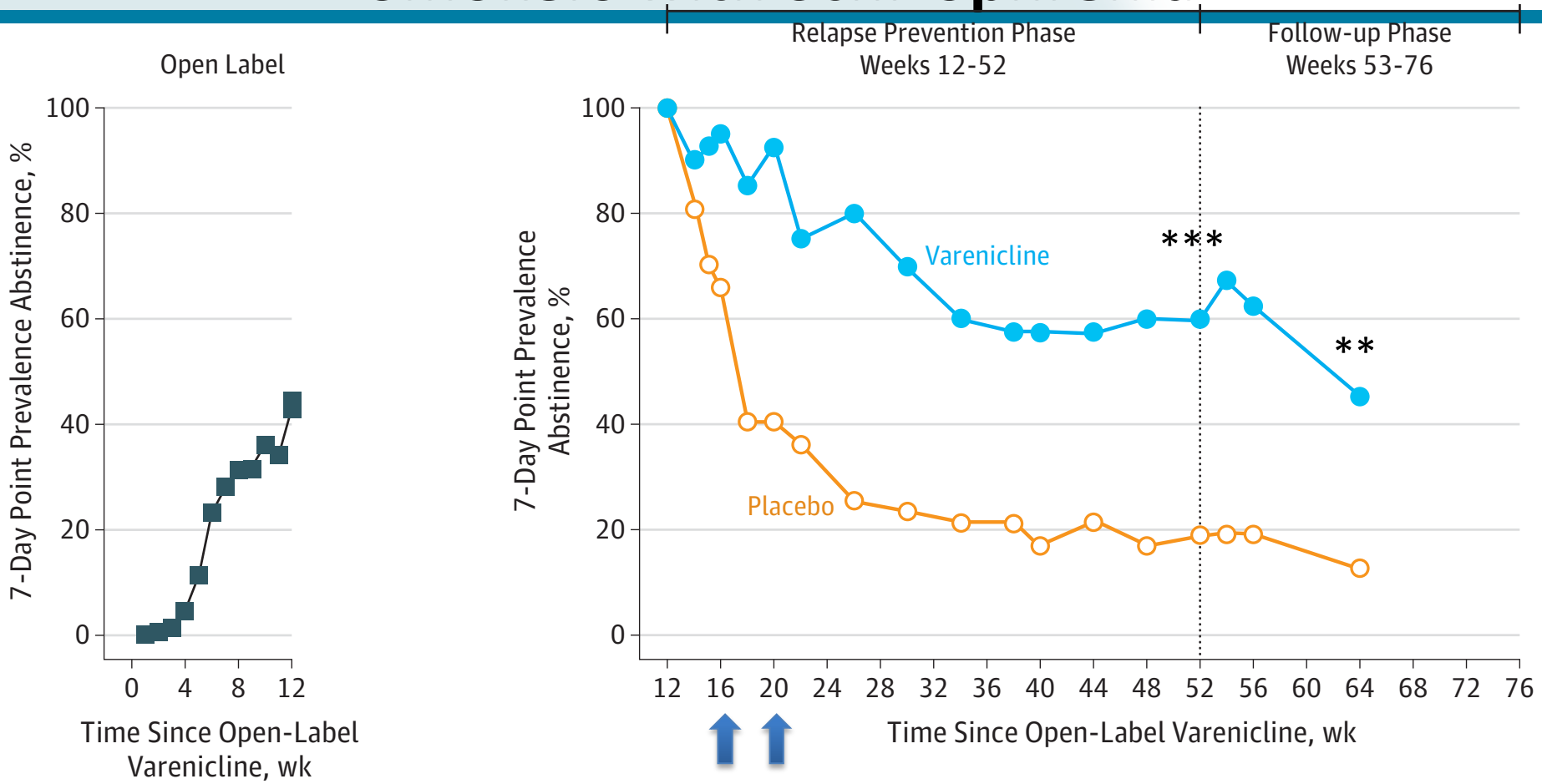
Repeat Cessation **Attempts** Are **Effective**



Varenicline, 12-week trial, was associated with significantly higher quit rates than placebo in those who had failed one or more prior varenicline trials.

Gonzales, *Clin Pharmacol Ther*, 2014

Varenicline Maintenance Treatment for One Year Triples Abstinence Rates at One Year in Smokers with Schizophrenia



43% attained abstinence with 12 weeks open label varenicline and were randomized to 40 weeks varenicline or placebo + Group CBT

Evins, Cather, et al., *JAMA*. 2014

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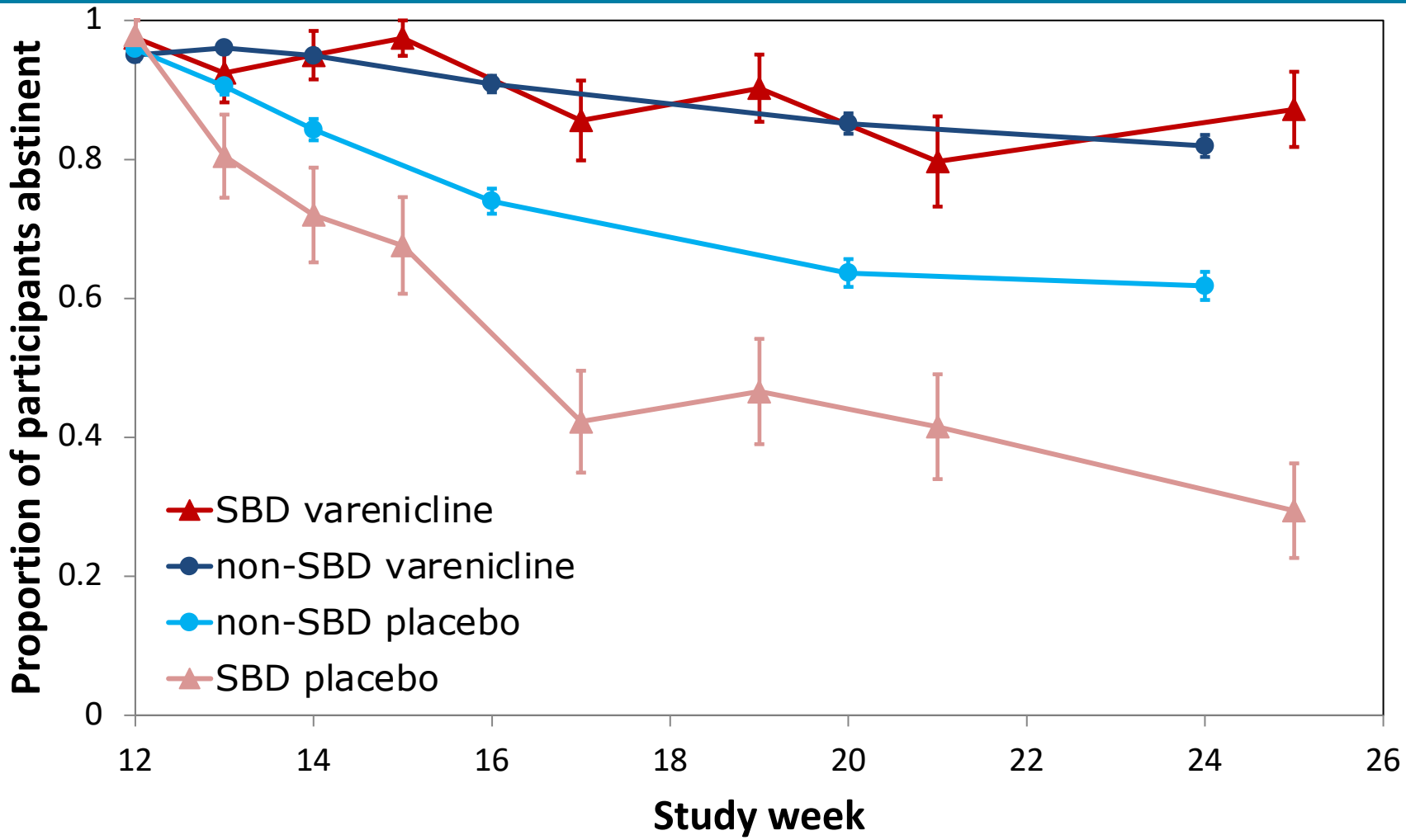
Maintenance Tx Normalizes the Relapse Curve for Smokers with Schizophrenia and Bipolar Disorder



Evins, Cather, et al., *Schiz Res*.. 2017

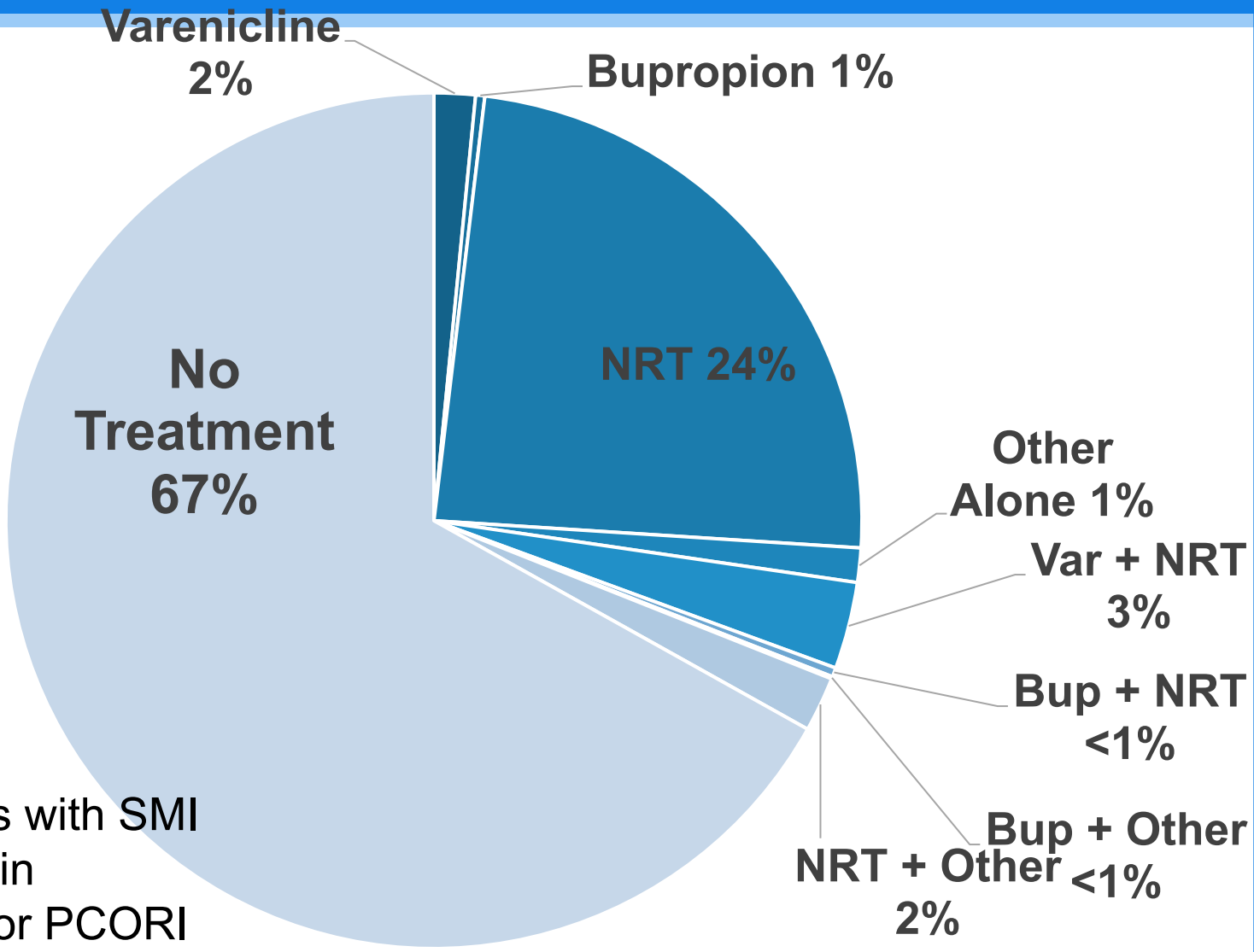
Smoking Cessation Tx Recommended but Underutilized, Particularly in Psychosis

- 2010 PORT guidelines for tx of schizophrenia recommend physician advice to quit and medication with bupropion with or without NRT for all smokers with schizophrenia.
- Smoking rates are not declining in those with psychosis
- Psychiatrists rarely offer counseling to quit smoking. In one study, only 12.4% of smoking patients were advised to quit.
- Smokers with SMI are even less likely to receive a medication to help them to quit.
- Varenicline especially underutilized in smokers with psychosis

Treatment is effective in the long run and is under-prescribed

Buchanan et al., 2010; Himloch and Daumit, 2003; Thorndike et al., 2001; Huang et al., 2014; Cook 2014

Percent of Smokers with SMI Offered Medication Cessation Treatment: Prior Year



From 1166 adults with SMI Enrolled in 2017 in Greater Boston for PCORI Large Pragmatic Trial

EAGLES Trial

- Compare risk of clinically significant neuropsychiatric AEs & efficacy of varenicline, bupropion, NRT patch, placebo
- >8000 Smokers aged 18 to 75 years; ≥10 cigs/day
- > 4000 smokers, no lifetime psychiatric diagnosis
- > 4000 smokers, 1+ clinically stable, lifetime diagnoses

Mood Disorders	**Major depressive disorder (MDD), bipolar I, bipolar II**
Anxiety Disorders	**Panic disorder with or without agoraphobia, post-traumatic stress disorder, obsessive-compulsive disorder, social phobia, generalized anxiety disorder**
Psychotic Disorders	**Schizophrenia, schizoaffective disorder**

Anthenelli RM, Benowitz NL, West R, St. Aubin L, McRae T, Lawrence D, Ascher J, Russ C, Krishen A, Evins AE. Effects of varenicline and bupropion in smokers with and without psychiatric disorders. *Lancet*. 2016 Apr 22.

Clinical Characteristics of the EAGLES Psychiatric Cohort

- Included:
  - Stable but symptomatic
  - Half on psychotropic medication at baseline (>95% with psychotic disorder)
  - Half with major depressive disorder had recurrent depression
  - One third had a second psychiatric diagnosis / comorbidity
  - One fourth had a prior substance use disorder
  - One eighth had made a prior suicide attempt

  - Excluded those with active self-injurious behaviors, imminent suicide risk, or active SUD

Primary Endpoint: Composite Neuropsychiatric Adverse Event

Primary Safety Endpoint: Percent of subjects reporting worsening or new onset of one or more of the following during treatment and up to 30 days after last dose:

≥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

AE, adverse event; NPS, neuropsychiatric

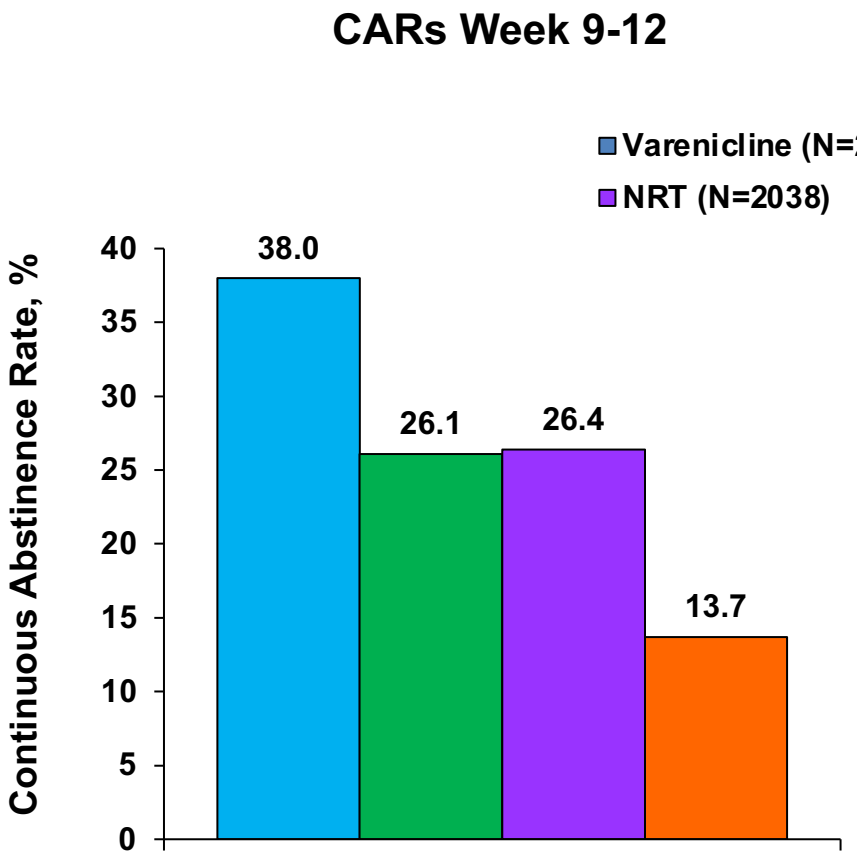
Designed in collaboration with FDA and EMA to be broad and capture an array of events

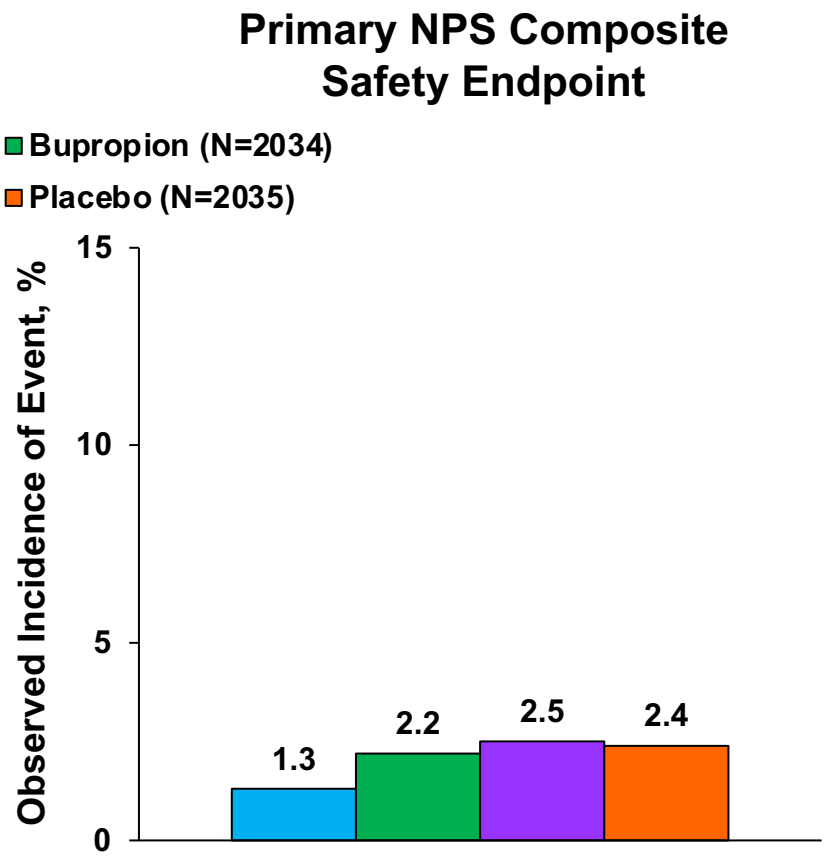
Severity assessment

Moderate = interferes to some extent with subject's usual function

Severe = interferes significantly with subject's usual function

EAGLES Allows Comparison of Neuropsychiatric Safety and Efficacy in Those without Psychiatric Illness





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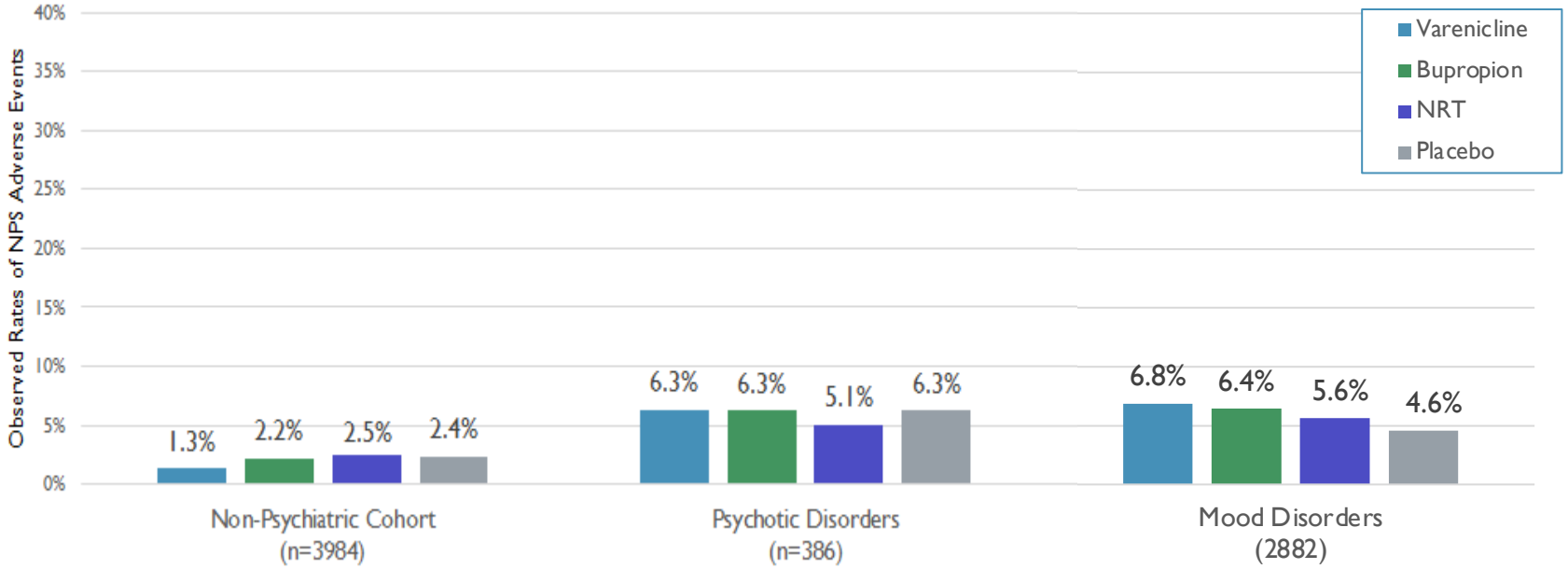
SAFETY

Varenicline, Bupropion Do NOT Increase NPSAEs

Continuous Abstinence During Weeks 9 Through 12 in Adult Smokers Without or With a History of Psychiatric Disorder



Non-psychiatric cohort (n=3984)				Psychotic disorders (n=386)				Mood disorders (n=2882)			
Varenicline (n=990)	Bupropion (n=989)	Nicotine patch (n=1006)	Placebo (n=999)	Varenicline (n=95)	Bupropion (n=96)	Nicotine patch (n=99)	Placebo (n=96)	Varenicline (n=731)	Bupropion (n=716)	Nicotine patch (n=713)	Placebo (n=722)

Evins et al., J Clin Psychopharm 2019; Anthenellii et al., Lancet 2016

Neuropsychiatric (NPS) safety data based on EAGLES (Evaluating Adverse Events in a Global Smoking Cessation Study)[1,2], an FDA required trial to evaluate NPS safety in over 8000 smokers with and without a psychotic, anxiety or mood disorder†

SAFETY

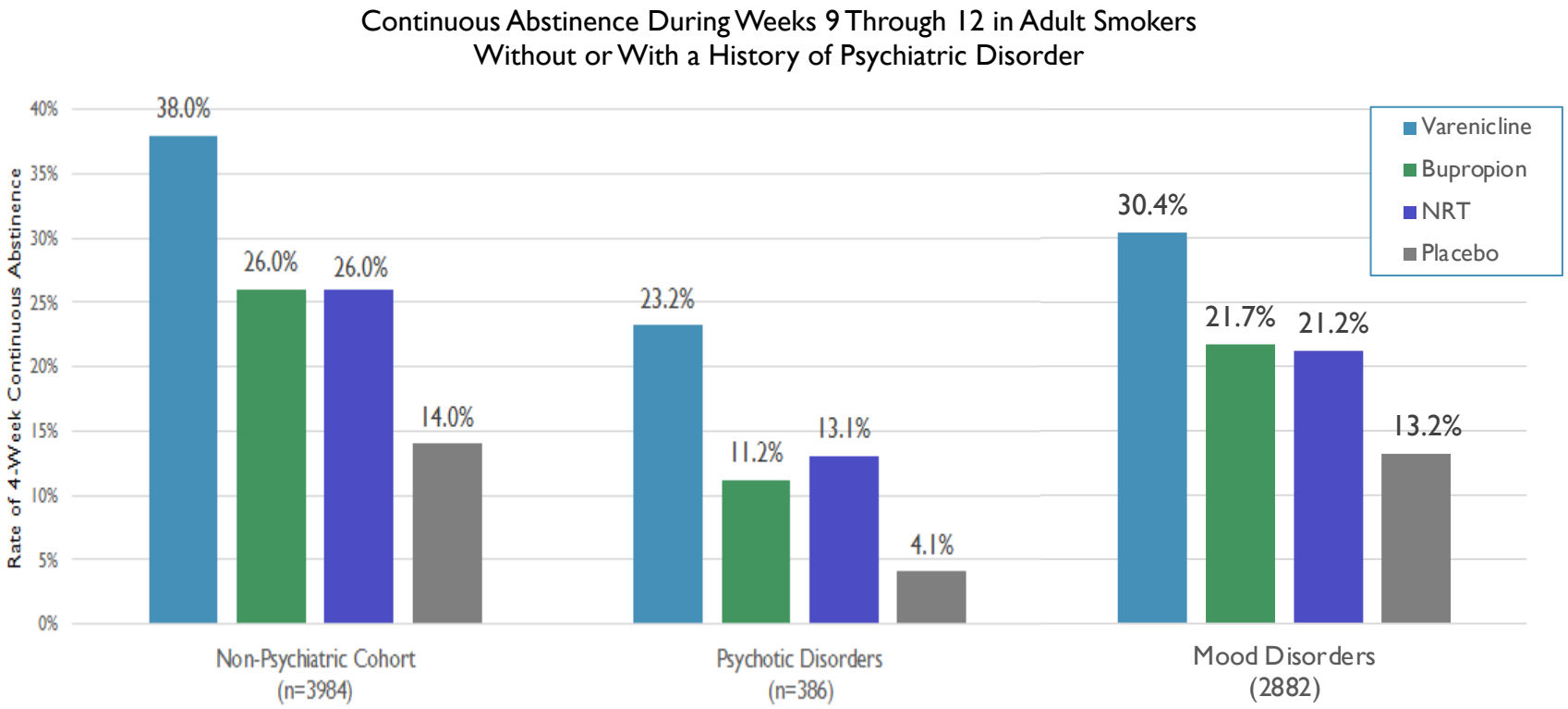
Neuropsychiatric (NPS) safety data based on EAGLES (Evaluating Adverse Events in a Global Smoking Cessation Study)[1,2], an FDA required trial to evaluate NPS safety in over 8000 smokers with and without a psychotic, anxiety or mood disorder†

EAGLES provides data that can be used to counsel smokers on the likelihood of experiencing a moderate to severe NPS adverse events during a smoking cessation attempt.

- Risk of NPS AEs is independent of treatment
  - ~2% NPS AE rate in smokers without mental illness
  - ~5-7% NPS AE rate in smokers with mental illness
- NPS AE rates during a cessation attempt are not different across active treatments or placebo
- No pattern of NPS AEs in the most worrisome NPS AEs
- No psychiatric subgroup appears to be at particularly increased risk

EFFICACY Comparative efficacy data based on EAGLES[2]

Varenicline was superior to bupropion, NRT and placebo, while bupropion and NRT were superior to placebo for biochemically-confirmed tobacco abstinence.‡



‡ "N" and analyses based on all-randomized populations in the EAGLES trial published in Antheneli et al., *The Lancet* (2016) and Evins et al., J Clin Psychopharm 2019

Figure 2a.

Relative Efficacy Consistent Across Psych and Non-Psych Cohorts

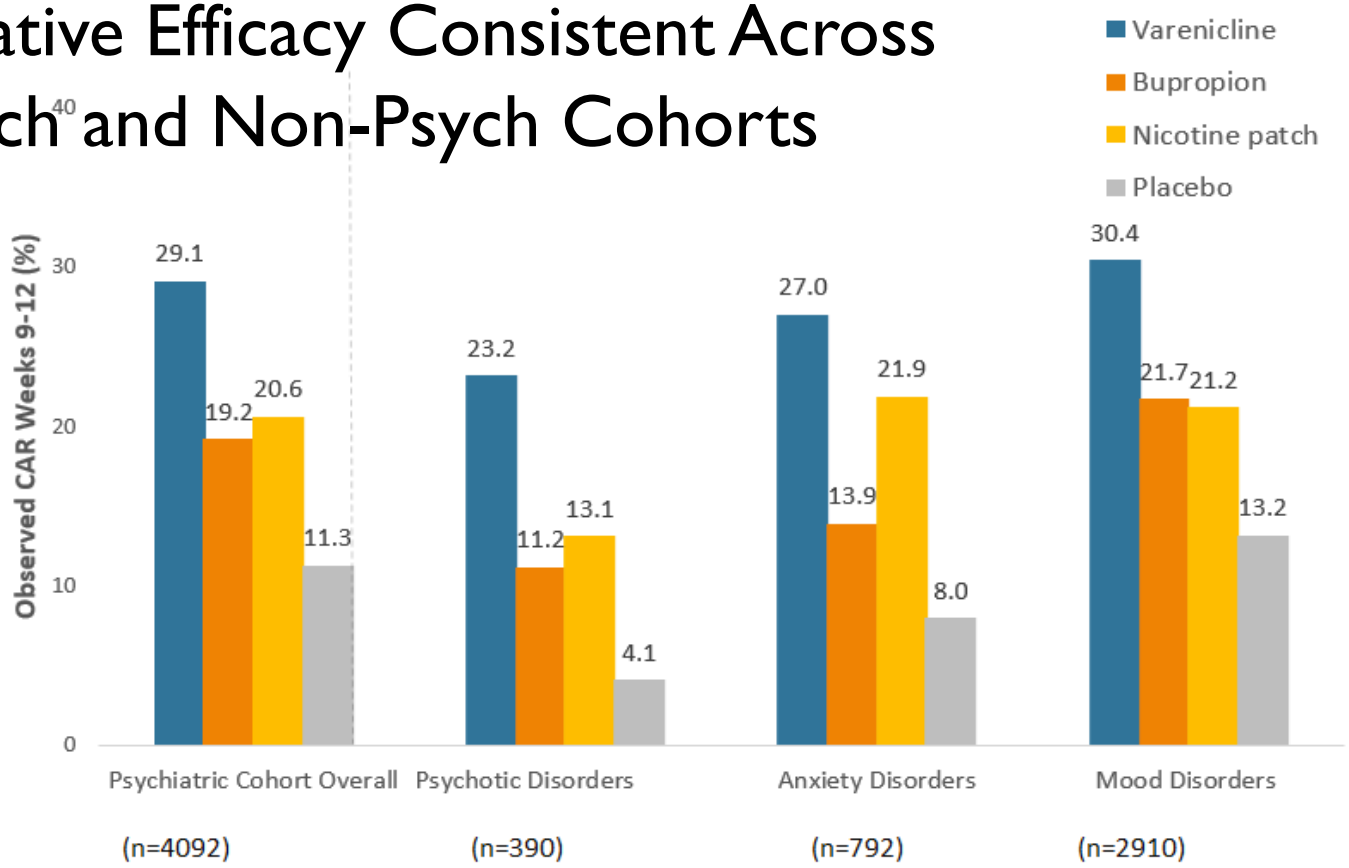


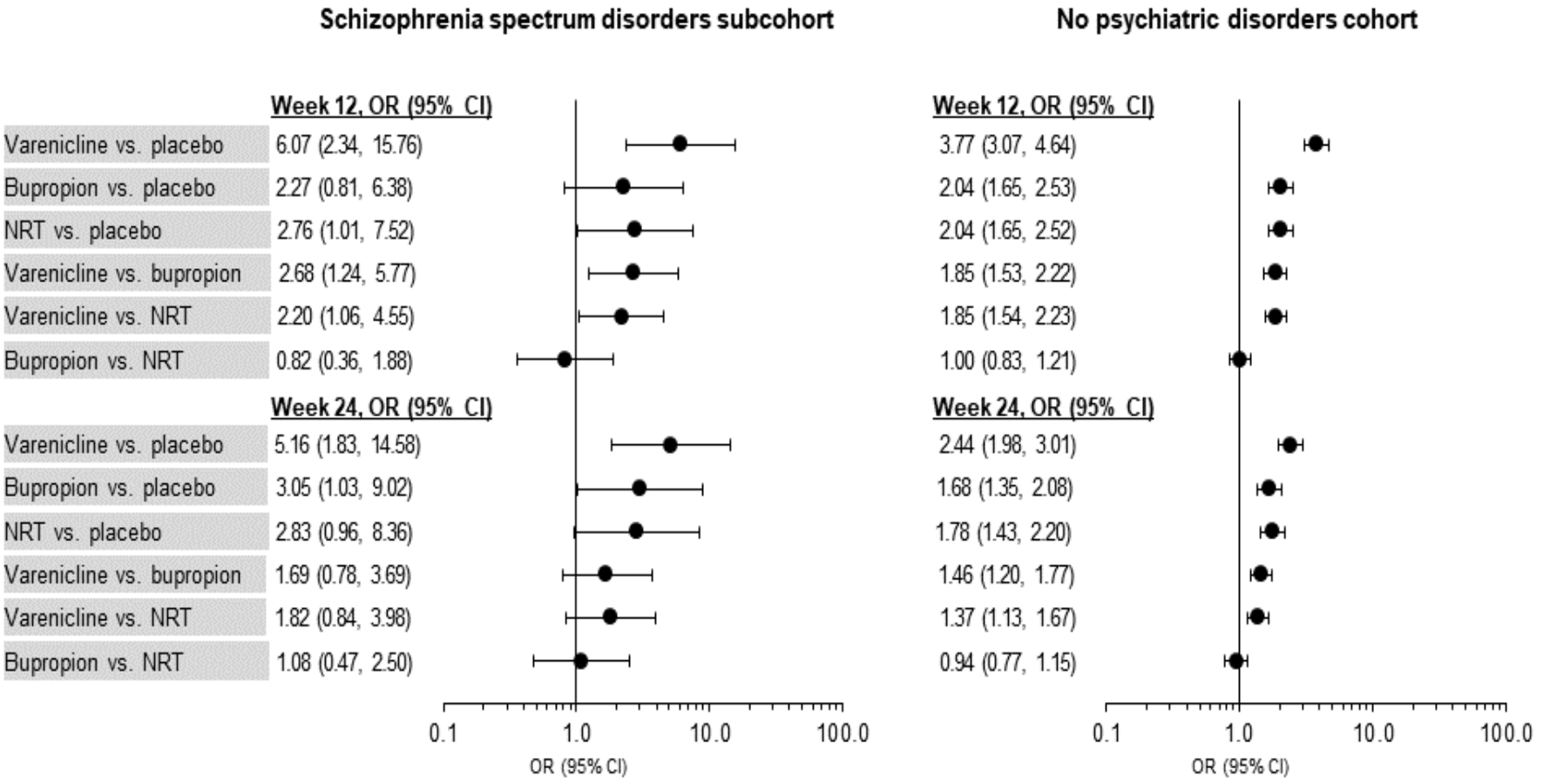
Figure 2b.

Treatment comparison	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Varenicline vs placebo	4.57 (2.59 to 8.06)	6.93 (1.61 to 29.84)	4.55 (2.05 to 10.11)	3.03 (2.13 to 4.32)
Bupropion vs placebo	2.22 (1.21 to 4.06)	2.99 (0.63 to 14.14)	1.91 (0.81 to 4.51)	1.91 (1.32 to 2.76)
Secondary comparisons				
Nicotine patch vs placebo	2.76 (1.53 to 4.97)	3.40 (0.74 to 15.61)	3.43 (1.52 to 7.74)	1.80 (1.24 to 2.61)
Varenicline vs nicotine patch	1.66 (1.11 to 2.49)	2.04 (0.75 to 5.55)	1.33 (0.72 to 2.46)	1.68 (1.23 to 2.32)
Bupropion vs nicotine patch	0.80 (0.51 to 1.27)	0.88 (0.28 to 2.73)	0.56 (0.28 to 1.12)	1.06 (0.76 to 1.48)
Varenicline vs bupropion	2.06 (1.35 to 3.17)	2.32 (0.82 to 6.58)	2.38 (1.21 to 4.69)	1.59 (1.16 to 2.18)

CAR, continuous abstinence rate; CI, confidence interval; OR, odds ratio

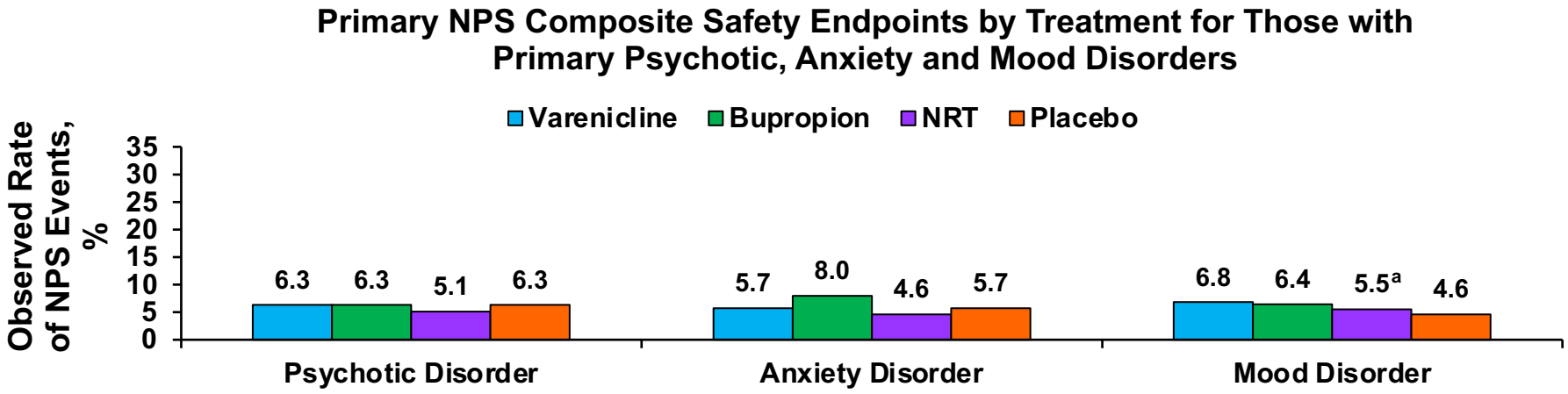
Evins et al., J Clin Psychopharm 2019

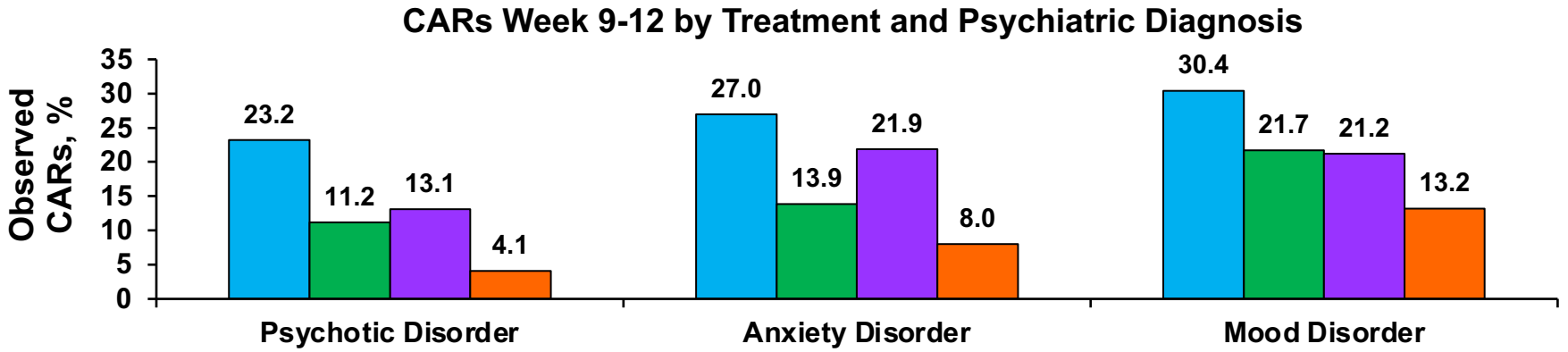
EFFICACY Comparative efficacy data based on EAGLES[2]



Evins et al., Psych Services 2020

Risk / Benefit:
EAGLES Allows Comparison of Neuropsychiatric Safety and Efficacy in Those with Psychiatric Illness





Adapted from Evins, et al., J Clin Psychopharm 2019

a. One additional participant (NRT group/mood subcohort) who reported suicide ideation was identified after clinical database lock and was not included in the analysis

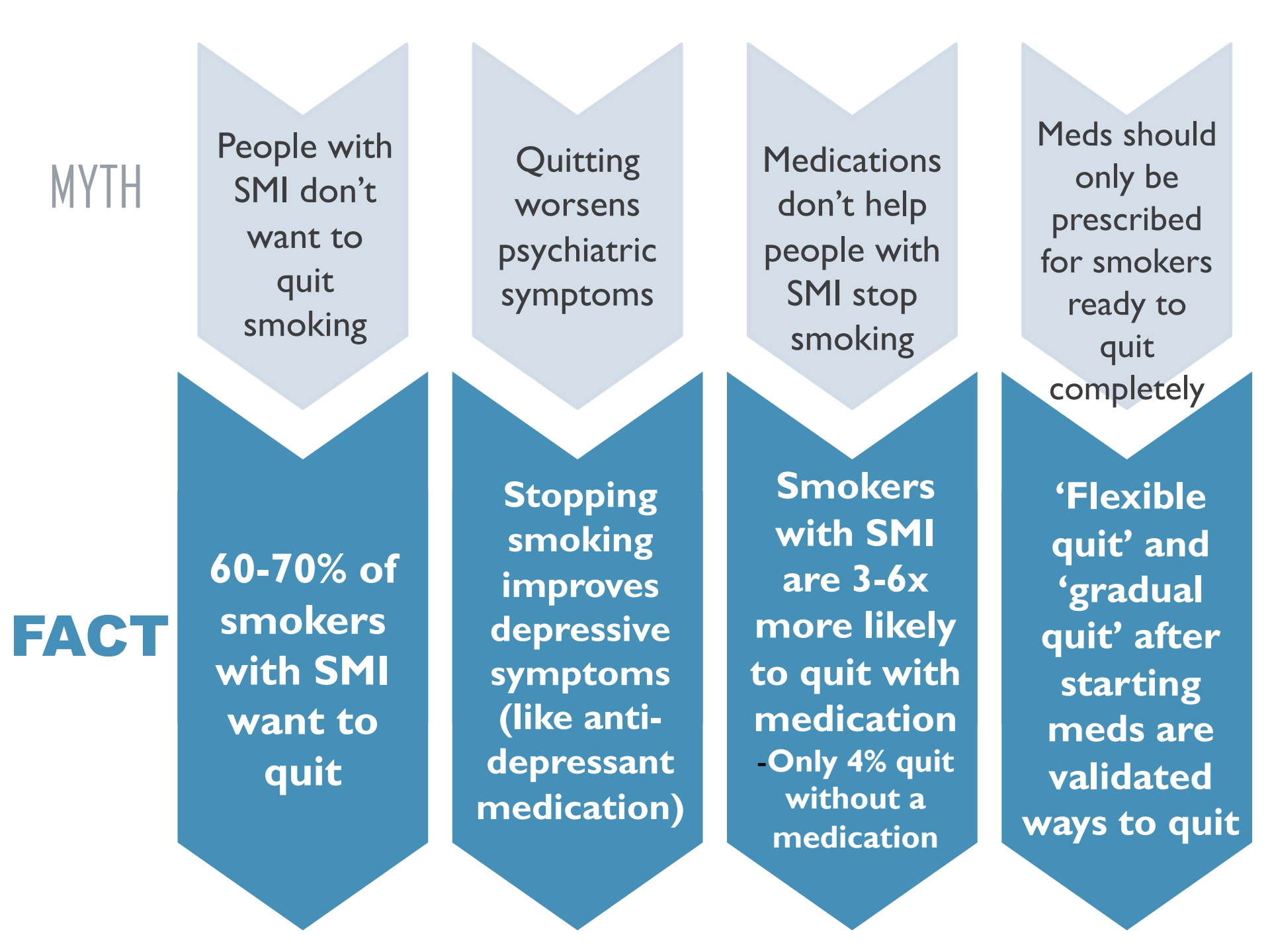
EFFICACY Comparative efficacy data based on EAGLES[2]

Varenicline was superior to bupropion, NRT and placebo, while bupropion and NRT were superior to placebo for biochemically-confirmed tobacco abstinence.‡

"FDA removes warnings on smoking cessation medication"

Pharmacy Times, December 16, 2016

FDA and EMA removed boxed warnings for varenicline and bupropion in 2016 based on results of EAGLES, a required, randomized, double-blind, triple dummy, active-and placebo-controlled clinical trial conducted by Pfizer in collaboration with GlaxoSmithKline, designed in consultation with the FDA and the European Medicines Agency (EMA). It is the largest smoking cessation clinical trial ever conducted and the largest samples of smokers with psychotic, anxiety, and mood disorders ever conducted.

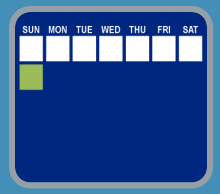

MYTH
People with SMI don't want to quit smoking
Quitting worsens psychiatric symptoms
Medications don't help people with SMI stop smoking
Meds should only be prescribed for smokers ready to quit completely
FACT
60-70% of smokers with SMI want to quit
Stopping smoking improves depressive symptoms (like anti-depressant medication)
Smokers with SMI are 3-6x more likely to quit with medication
-Only 4% quit without a medication
'Flexible quit' and 'gradual quit' after starting meds are validated ways to quit

2018 American College of Cardiology Expert Consensus Decision Pathway on Tobacco Cessation Treatment

- Recommend/Prescribe Pharmacotherapeutic Cessation Aid to ALL Smokers, not just those who state they are ready to quit.
- Prescribe to all smokers willing to start a pharmacotherapy
- Follow up in 2-4 weeks for tolerability
- For those who decline, continuous engagement to quit at each clinic visit

Barua et al., JACC 2018

Three Ways to Quit Smoking: All Start with Smoking Cessation Medication



Fixed Quit

For people who want to quit smoking in a week

- Set a target quit date 1 week after starting smoking cessation med
- Can keep smoking for the first week while they prepare to quit
- Take smoking cessation medication for 12-24 weeks

Flexible Quit

Recommended

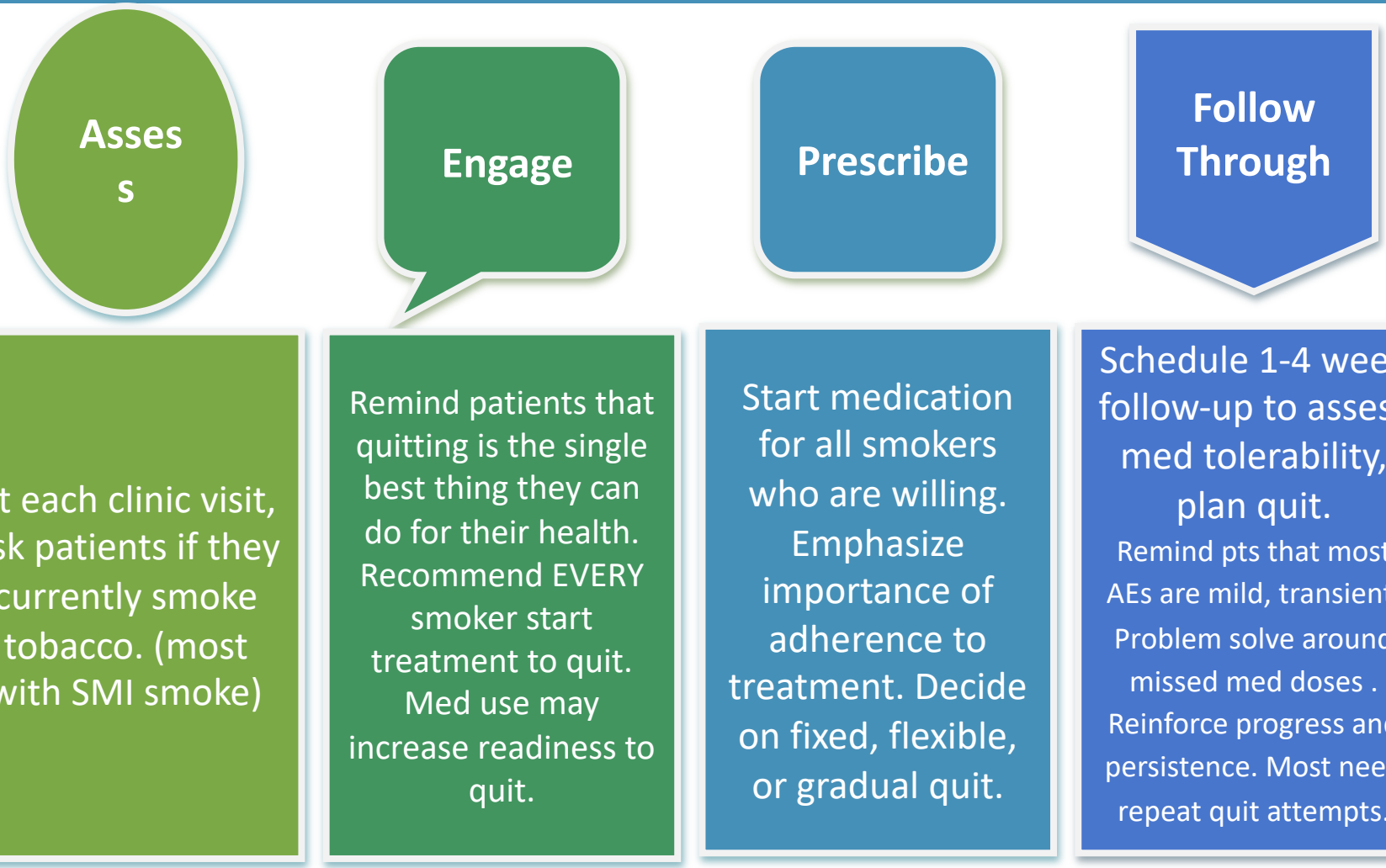
- Start taking smoking cessation medication and pick a quit date 8 to 35 days after starting treatment
- *Can keep smoking for up to a month on smoking cessation medication while preparing to quit*
- Take smoking cessation meds for 12-24 weeks

Gradual Quit

For people not able/willing to quit abruptly

- Start taking smoking cessation med and reduce smoking by 50% over 4 wks, by another 50% in the next 4 wks, etc. Goal of quitting by 12 weeks.
- Continue smoking cessation med for an additional 12 weeks, for a total of 24 weeks

Steps to Address Smoking



How To:

Varenicline

Available as 0.5 and 1.0 mg tabs

- 0.5 mg/d at hs x 3 d
- 0.5 mg bid x 4 d
- 1.0 mg bid x 11 weeks
- Additional 3-9 months Tx recommended in those who achieve abstinence
- 12-month safety data published: well tolerated

Renal excretion, used in chronic renal disease with dose reduction

No significant drug-drug interactions or effect on cytochrome enzymes

Nausea, headache, insomnia, and vivid dreams are common

How To:

Dual Nicotine Replacement Therapy

Nicotine patch +

Dosing: 21 mg/d x 4-6 weeks then
- 14 mg/d x 4 weeks then
- 7 mg/d x 3-4 weeks

Apply one new patch every 24 hours (preferable am) to dry, clean skin

Move site with each new patch to avoid skin irritation

Remove patch at night if bothered by insomnia or vivid dreams

Nicotine gum, lozenge

Dosing: up to 20 mg/d x 4-5 weeks then
- Up to 14 mg/d x 4 weeks then
- Up to 10 mg/d x 3-4 weeks

Do not chew, break, crush, or swallow whole

Gum: Chew a few times then 'park it' between cheek and gum

Move around mouth until it melts (lozenge) or loses flavor (gum)

Do not eat or drink for 15 minutes before or during use

How To:

Bupropion SR or XL

Dosing:
150mg QD x 3 days, then
150mg BD

Insomnia common

Meta-analysis of 182 studies with 70,000 smokers:[9]
Varenicline **triples** chances of quitting vs. placebo
and increases odds of quitting by **50%** over NRT and bupropion

NRT and bupropion nearly **double** odds of quitting vs. placebo (80% increase)

EAGLES is a Confirmatory Trial for Efficacy

- Efficacy conclusions replicate and extend findings from smaller trials and meta-analyses in those with and without mental illness
- The efficacy data are clear

  Varenicline > bupropion and nicotine patch > placebo

- Agreement with overall, growing body of evidence, raising confidence in the findings

Neuropsychiatric Adverse Events During Smoking Cessation Are Independent of Treatment

- NPS AEs are seen in trials regardless of treatment
- Clinicians who prescribe a treatment and observe a NPS AE likely attribute this AE to the treatment.
- This happened in our large maintenance treatment trial of varenicline, in trials of bupropion, and in clinical practice.

Evins, et al., JAMA 2014; Evins, et al., J Clin Psychopharm 2007

Why Might There be Significant NPS AEs Among Smokers, Independent of Treatment (and Abstinence)?

- Smoking is an addiction; like all drug addictions, there are:
  - Well documented brain changes
  - Increased neuropsychiatric events, e.g. suicide
  - Suicide risk reduced in smokers who quit
- People with psychiatric illness are more likely to smoke
- Attempts to quit smoking are not risk free, with or without pharmacologic support and independent of abstinence
  - Well replicated in smokers with history of depression

Volkow et al., Am. J. Psych, 1999; Fehr et al., Am J Psych 2008; Li, et al., J Psych Res 2012; Berlin et al., NTR 2011; Brown 1996; Tsoh, et al., Am J Psych 2000; Torres, et al., Psychol Med 2010; Evins, et al., JAMA 2014, Evins et al.. Psychol Med 2017

EAGLES is a Landmark Study of Clinical and Public Health Importance

- The EAGLES trial is the first:
  - To compare safety and efficacy of all 3 FDA approved smoking cessation therapies in large samples of patients with and without a history of psychiatric disorder
  - To allow for comparison of safety and efficacy of smoking cessation aids in smokers with different mental illnesses

Varenicline Safety in 17 RCTs and 5 Large Observational Studies

Pooled Analysis of ALL Psychiatric Adverse Effects in 17 RCT's of Varenicline

Varenicline increased incidence of nausea but not psychiatric adverse events

Varenicline increased abstinence rates by 124% vs. placebo and 22% vs. bupropion

Having a psychiatric illness increased the risk for psychiatric adverse events in smokers trying to quit equally in those assigned to varenicline and placebo

In a large observational study in 35,800 outpatients trying to quit smoking, there were fewer psychiatric adverse events in those prescribed varenicline than those prescribed NRT

Results replicated now in multiple studies in different practice populations: DoD, VA, UK NHS

Gibbons and Mann 2013; Tonstad et al., 2010; Kotz et al., 2015

Implication of EAGLES: Offer Treatment to ALL Smokers, Especially Those with SMI

- Confirms NPS safety and efficacy of smoking cessation treatments for smokers with mental illness, a group that is:
  - More likely to smoke, to smoke heavily, and be dependent
  - Less likely to quit without a cessation aid
  - More likely to relapse after discontinuation of cessation aids
  - More likely to benefit from maintenance treatment
- Smokers with mental illness are less likely to receive a pharmacotherapeutic cessation aid from a medical provider
  - This contributes to the 25 year mortality gap in those with mental illness from diseases causally related to smoking
  - 28 year mortality gap for those with schizophrenia

Risk/Benefit Considerations

- Clinicians **overestimate** the risk of NPS AEs with varenicline and bupropion, particularly in those with psychotic illnesses
- And **underestimate** the benefit of varenicline and bupropion on improving quit rates
- It is imperative we find ways to increase use of the most effective smoking cessation treatment for our patients who try time and again to quit smoking

Huang et al., BMC Public Health 2014

Varenicline (Chantix)

- Selective, partial a4 b2 and full a7 NAChR agonist
- FDA approved 2006 as an aid for smoking cessation
- Reduces nicotine withdrawal symptoms
  - Stimulates NAChRs
- Reduces nicotine-induced dopamine release and reward
  - Blocks binding of nicotine at NAChRs
- Superior efficacy vs placebo (and bupropion and NRT)
- Well tolerated from a psychiatric standpoint in all controlled studies to date as well as all large epidemiologic studies.

Varenicline and Bupropion Improved Health Related Quality of Life

- Treatment with Varenicline (n=696) and Bupropion (n=671) Significantly Improved Self Rated Quality of Life Over Placebo (n=685) at 12, 24, and 52 Weeks
- Significant positive association between smoking cessation and self rating of vitality, self-control, anxiety, and overall mental health profile
- Replication of several studies demonstrating reduced self report of anxiety after smoking cessation…

Hays et al., 2010

Combination Pharmacotherapy for Nicotine Dependence

May improve abstinence rates

For smokers who have relapsed after treatment with single agent, consider maintenance treatment or combination treatment:

- **NRT: long acting (patch) + short acting (gum, inhaler or nasal spray) + CBT**
- **Bupropion 150 mg bid + NRT + CBT**
- **Varenicline + NRT**

Behavioral Interventions

- Current guidelines recommend behavioral tx + pharmacotherapy
  - Motivational enhancement
  - Relapse prevention
  - Partner support
- Guidelines are based on several large meta-analyses of controlled trials
- Telephone counseling provides a modest benefit in quit rates vs minimal intervention, patient follow through can be low
  - **www.trytostop.org or 1-800-TRY-TO-STOP**
- Physical exercise can decrease cravings and attenuate weight gain

USPHS, 2000; Stead et al., 2003; Barua et al., 2019

Nicotine Withdrawal Syndrome

- Peaks in 4 days
- Lasts for several weeks
- Can be severe, not life threatening
  - Anxiety
  - Awakening during sleep
  - Depression
  - Difficulty concentrating
  - Impatience
  - Irritability/anger
  - Restlessness
  - Decreased heart rate
  - Weight gain

Tobacco Abstinence: Effects on Metabolism

- Smoking speeds hepatic metabolism of many medications
- Serum concentrations of medications that are stable in smokers may rise following abstinence, allowing lower doses
- CYP 1A1, 1A2, and 2E1
  - Abstinence associated with 30-42% reduction in 1A2 activity over the first 1-3 days of abstinence
  - Therapeutic drug monitoring and 10% dose reduction has been recommended
- Take care when prescribing bupropion to those on clozapine because of additive seizure risk

Seppala NH, et al.,1999; Desai HD, et al., 2001; Faber & Fuhr, 2004.

Summary – Nicotine Dependence

- Give physician advice to quit smoking to all smokers at every visit
- Prescribe/Offer Pharmacotherapeutic Cessation Aid to All Smokers
  - (as for Other Chronic Illnesses with Behavioral Component eg. Type 2 Diabetes, Hypertension)
- Choose a Quit Plan: Fixed, Flexible, or Gradual.
- Develop a “quit day” plan, refer or review coping skills, build in self-rewards, and provide written cues to reinforce abstinence
- Long-term pharmacotherapy may be warranted, both to sustain abstinence and to improve symptoms

Evins AE and MGH Center for Addiction Medicine; Barua et al., 2018 ACC Expert Consensus Pathway

Cannabis Use Disorder

- Growing clinical problem
- Fueled by commercialization of legal cannabis and misinformation regarding addictive potential of THC
- Followed by flourishing black market
- Targeting adolescents
- Lacing/diluents/contaminants appear to be common
- Pulmonary public health crisis unfolding currently involves lipid pneumonia, possible toxicity to THC itself

Cannabis Use Disorder

- Most common chief complaint of adolescents admitted for inpatient drug treatment
- Characterized by craving and cannabis withdrawal syndrome
  - Irritability/angry outbursts,
  - sleep disturbance
  - Nightmares/strange dreams
  - Physical tension/restlessness
  - Anxiety/nervousness
  - Depressed mood
  - Reduced appetite/nausea

Public Health Crisis Linked to Vaping

- Pulmonary illness associated primarily with vaping of THC, but in some cases only nicotine was vaped according to the history.
- Shortness of breath, some requiring intubation, bypass
- Over 900 reported ill, 12 deaths in 2019 and growing
- Vitamin E acetate used as diluent associated with lipid pneumonia in some cases
- Possible toxicity of THC itself

Cocaine Use Disorder

- Major epidemic since 1980
- Availability of cheap, high-potency drug
- Includes freebase/crack
- 30 million in US have used cocaine
- < 20% become regular users
- 17% risk of dependence
- Lacing common
  - Levamisole in up to 80% of samples in some locations
  - 3-13% risk of agranulocytosis with sustained exposure

Pharmacology of Cocaine Use Disorder

- Dopamine stimulation of neurons in nucleus accumbens normally limited by dopamine reuptake
- Cocaine blocks dopamine reuptake
- Assoc. with excessive dopamine stimulation in reward system of brain - “HIGH”
- Also assoc. with depletion of dopamine in nerve terminals of dopaminergic neurons - “LOW”
- Compensatory down-regulation of post-synaptic dopamine receptors
  - Protracted syndrome of refractoriness to reward

Cocaine Use Patterns

- Binge symptoms:
  - Intense euphoria
  - Paranoia, anxiety, dysphoria, tremor, hyperactivity
  - Panic attacks, depression, mania
- Withdrawal:
  - Onset: <24 hrs, peak: 2-4 days
  - Duration: 7-10 days
  - Protracted depression: 1-3 months
  - Intense cravings: 1-3 months

Treating Acute Cocaine Intoxication

- Acute cocaine intoxication:
  - Onset: seconds
  - Duration: 30-60 min
  - Dysphoria: within hours
  - Recovery: < 48 hrs
  - OD requires life support, airway
- Cocaine delusional disorder
  - Diazepam for agitation
  - Antipsychotics for delusions
- Hospitalize if suicidal or delusional

Treating Cocaine Withdrawal

- Pharmacotherapy not required in mild withdrawal states
- For severe cocaine withdrawal:
  - Amantadine – indirect dopamine agonist, increases dopamine levels
  - Propranolol – B-adrenergic blocker reduces anxiety / severe adrenergic symptoms - 1 mg IV q min, up to 8 min
- Seizures: IV diazepam

Treating Cocaine Use Disorder

Relapse prevention: Pharmacotherapy

- Disulfiram effective in 3 trials
  - Inhibits DA-beta hydroxylase
  - Reduced craving & relapse
- Baclofen – GABA-B agonist: 20 mg tid
- Topiramate increases GABA & inhibits glutamate:
  25 mg po qd, slowly increase to 200 mg qd (Kampman, 2004)
- Modafinil enhances glutamate levels: 200-400 mg po qd

- However, Overall:
  - Disulfiram: evidence not supportive
  - Topiramate, other anticonvulsants: evidence not supportive
  - Anticonvulsants: evidence not supportive
  - Antipsychotics: evidence not supportive

Treating Cocaine Use Disorder

Relapse prevention: Psychotherapy

- Contingency Management
- Manual-guided CBT
- 12-step facilitation
- Individual plus group therapy
- Behavioral reinforcement:
  - Urine testing with contingencies
  - Restrict access to money & friends
- High-intensity support to disrupt binge cycles

Treating Cocaine Use Disorder

As with any substance use disorder, treat anxiety and depressive symptoms in those suspected of having an independent mood or anxiety disorder, especially if these symptoms appear to be interfering with attainment of abstinence

Co-morbid depression:

- SSRIs – effective if depressed
- "May" also reduce cocaine use
- Avoid TCAs, may be associated with cardiac arrhythmia when combined with cocaine

Co-morbid bipolar disorder: No adequate med trials

- Consider combination therapy if rapid cycling