



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

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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

UK male doctors born 1900–1930: continuing cigarette vs never smokers. 50-year follow-up of mortality, 1951–2001

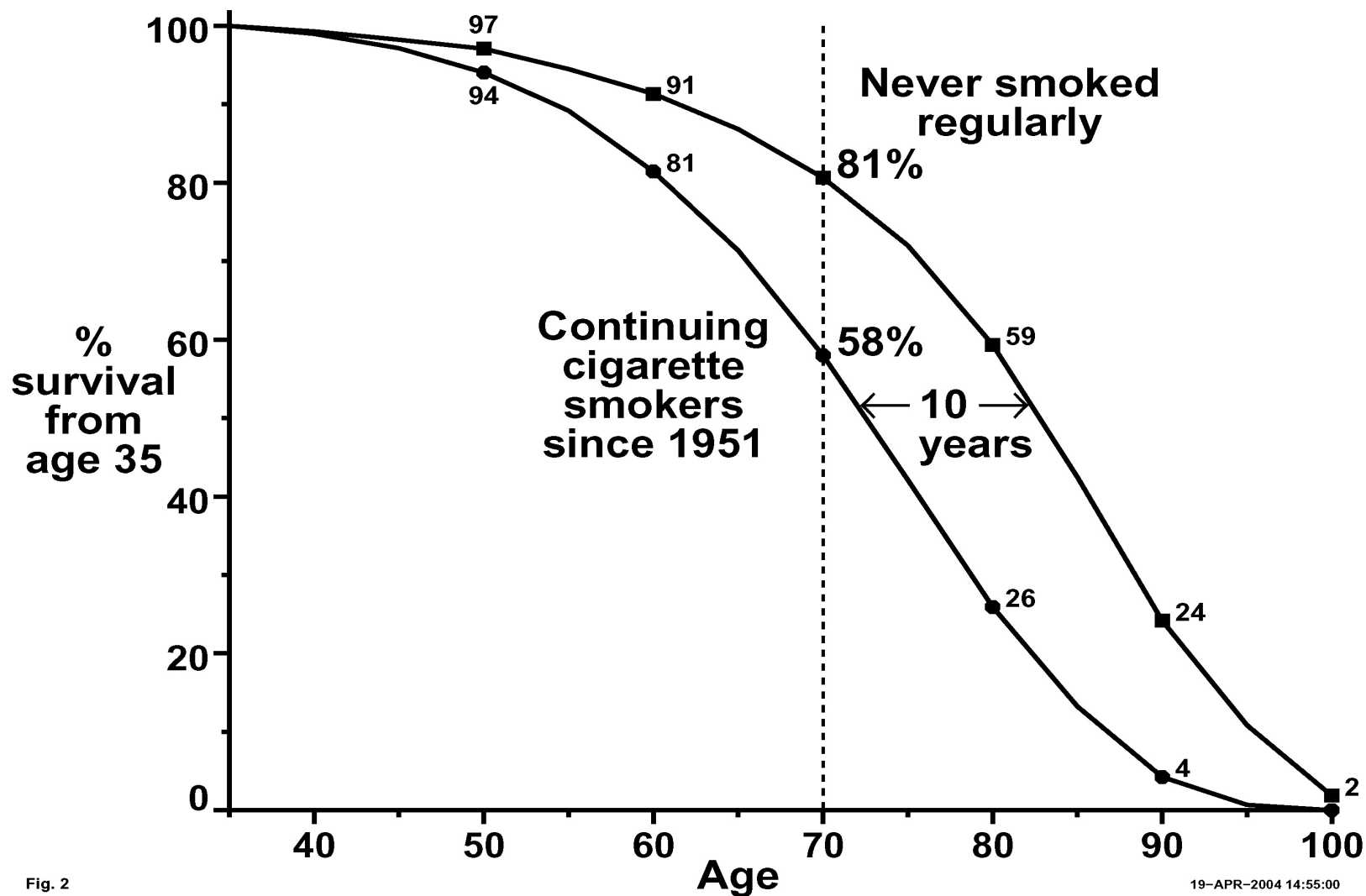


Fig. 2

Quitting Helps

Effect of stopping smoking at age ~40 on survival from age 40

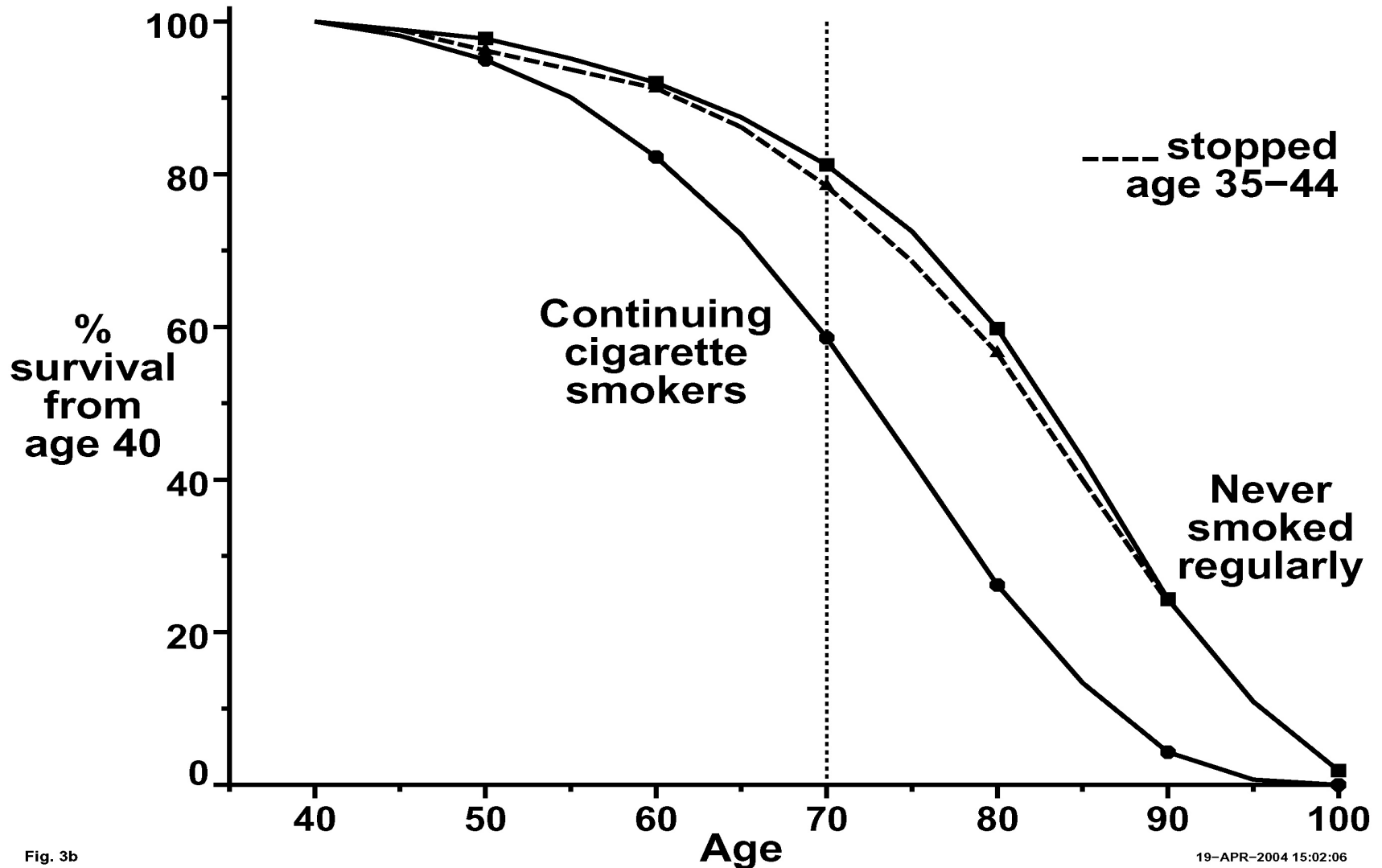
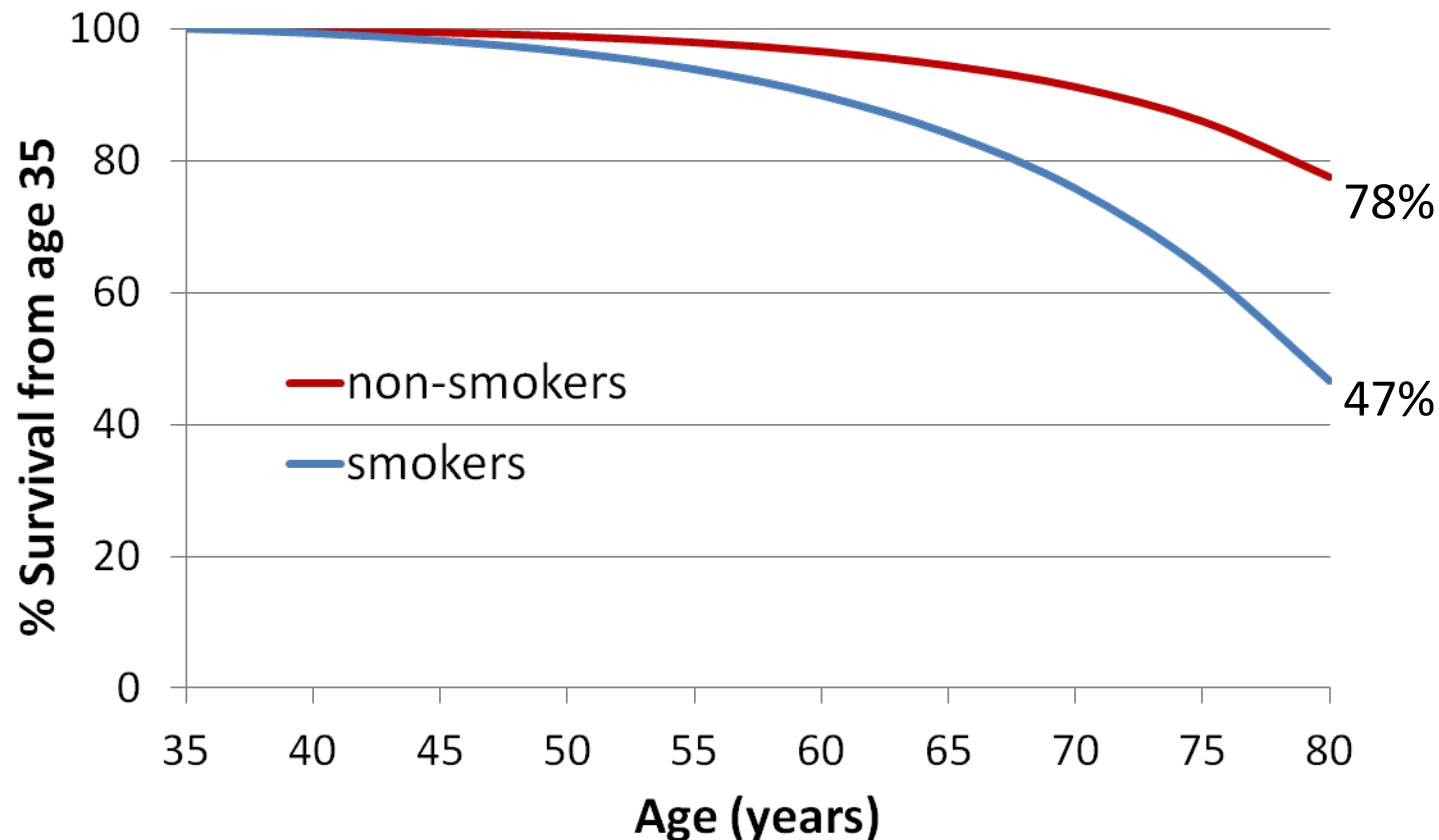


Fig. 3b

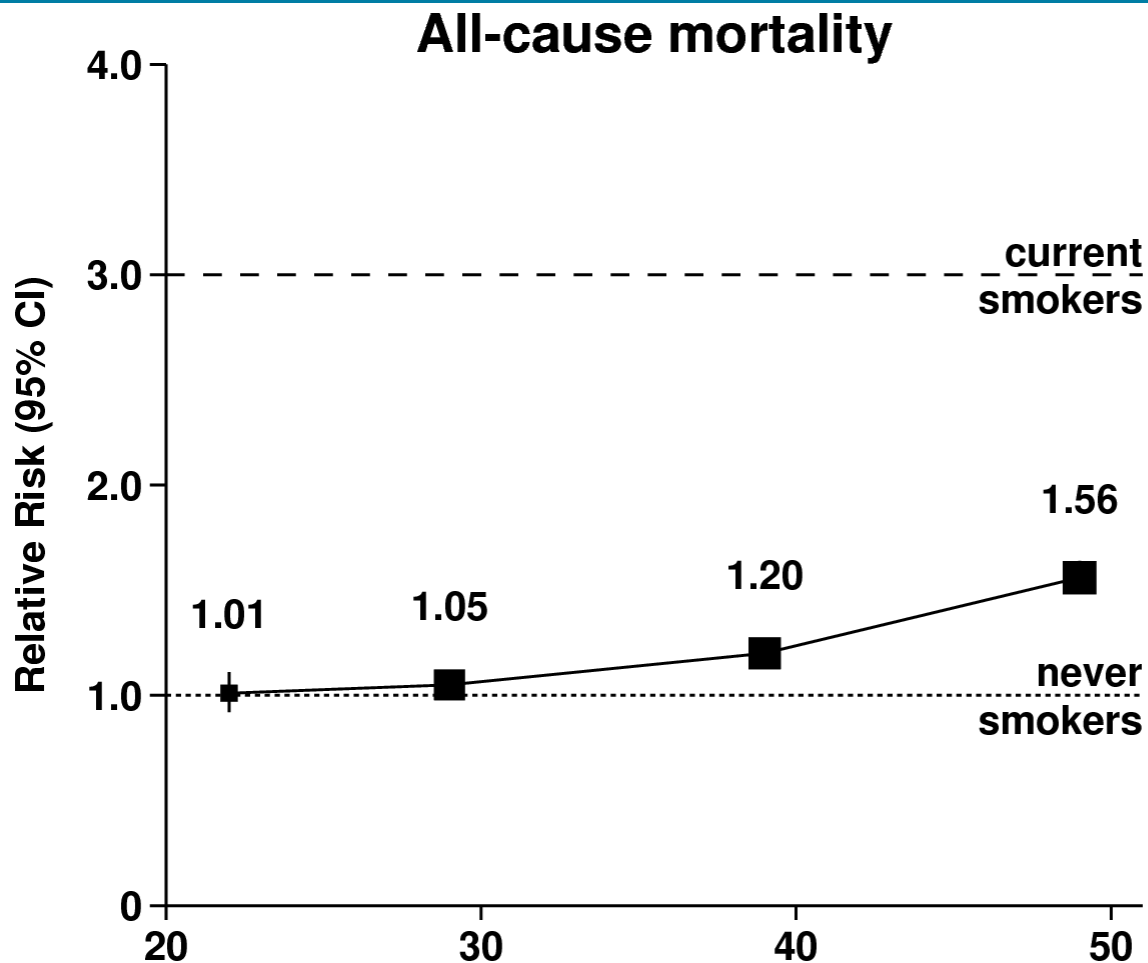
One Million Women Study: Effect of 3-fold difference in annual death rates on survival at ages 35-79



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

THE MILLION WOMEN STUDY

Quitting by age 50 halves mortality



— Ex-smokers, by age at stopping

— Pirie, Lancet, 2013

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.

1930

20,679^{*} Physicians say "LUCKIES are less irritating"

1943

1941

The Journal of the American Medical Association
Published Under the Auspices of the Board of Trustees
Vol. 143, No. 4 CHICAGO, ILLINOIS MAY 27, 1950
CONTENTS: 388 In Asthma: Mucous Membranes

TOBACCO SMOKING AS A POSSIBLE ETIOLOGIC FACTOR IN BRONCHIOGENIC CARCINOMA
A Study of Six Hundred and Eighty-Four Proved Cases
ERNEST L. WYNDER
EVARTS A. GRAHAM, M.D., St. Louis

BRITISH MEDICAL JOURNAL
LONDON SATURDAY SEPTEMBER 30, 1959
SMOKING AND CARCINOMA OF THE LUNG
PRELIMINARY REPORT
RICHARD DOLL, M.D., M.R.C.P.
Member of the Statistical Research Unit of the Medical Research Council
A. BRADFORD HILL, PH.D., D.Sc.
Medical Statistics, London School of Hygiene and Tropical Medicine; Honorary Research Unit of the Medical Research Council

1964

SMOKING and HEALTH
REPORT OF THE ADVISORY COMMITTEE TO THE SURGEON GENERAL OF THE PUBLIC HEALTH SERVICE
U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service

1966

Caution: Cigarette Smoking May Be Hazardous to Your Health

1969

Come to where the flavor is. Come to Marlboro Country.

1985

VIRGINIA SLIMS

You've come a long way, baby.

SURGEON GENERAL'S WARNING: Smoking By Pregnant Women May Result in Fetal Deaths, Premature Birth, and Low Birth Weight.

1994

2013

"I NEVER THOUGHT SMOKING WOULD DO THIS."

Terrie, age 52
Diagnosed at 40 with throat cancer
North Carolina

You can quit. Talk with your doctor for help.

2013

AMERICA'S MOST WANTED TOBACCO VILLAINS

THE USUAL SUSPECTS
TOP CIGARETTE & SMOKELESS TOBACCO BRANDS USED BY SMIS

1. Camel
2. Marlboro
3. Grizzly
4. Camel Lights
5. Camel Lights
6. Camel Lights

2010

DON'T LET MINORS BUY TOBACCO. IT'S THE LAW.

Break the chain of tobacco addiction. Keep tobacco out of the hands of America's youth. It's the right thing to do.
For tools and tips: www.fda.gov/BreakTheChain

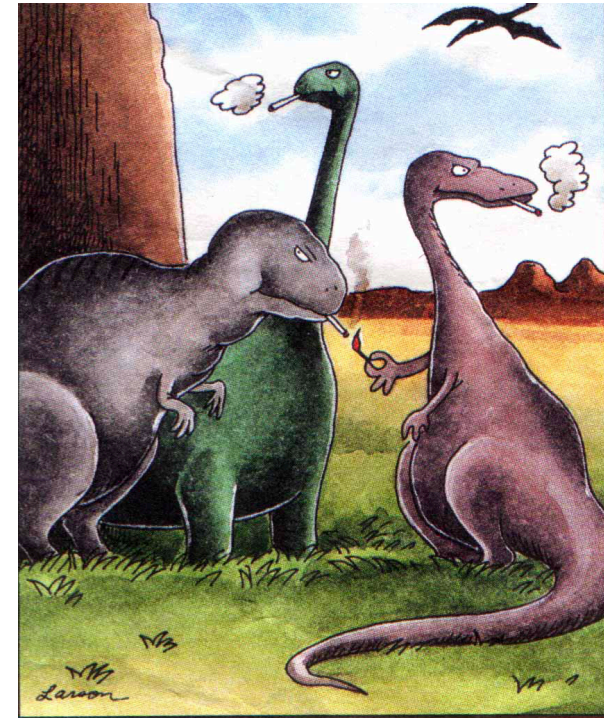
2013

Smoke-free Laws for Bars, Worksites, and Restaurants

50 YEARS OF TOBACCO CONTROL

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

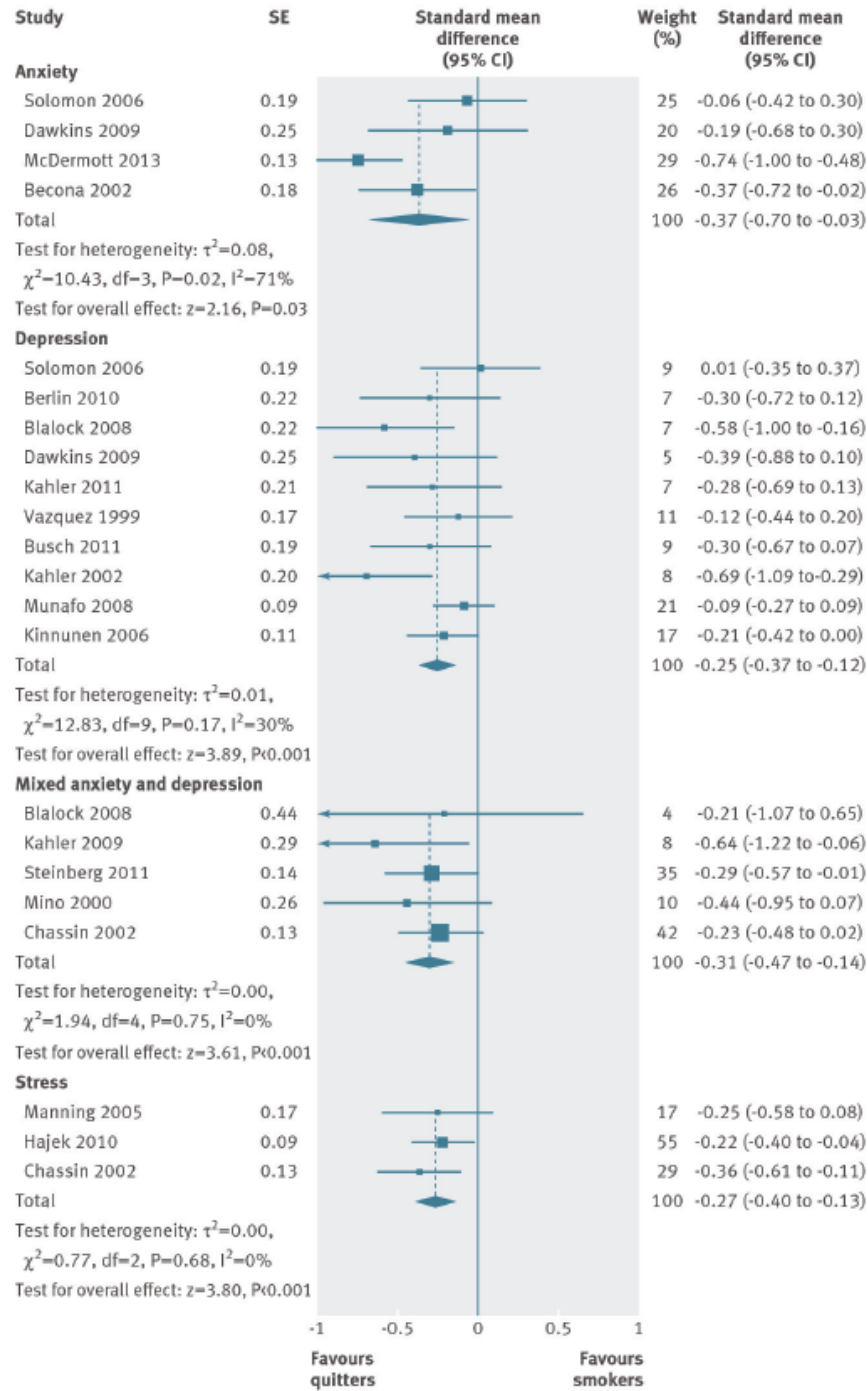
- Death
- MI
- Stroke
- Progression of atherosclerosis
- Bronchitis
- Morbidity from Diabetes
- Cancer Risk
- Progression of COPD

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!!!

Smoking Cessation Is Associated with Improved Psychiatric Symptoms



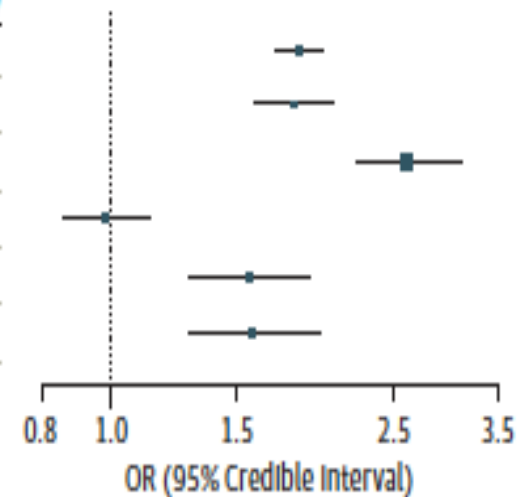
Addiction to Nicotine: Mechanism and Therapeutic Targets

- 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 $\alpha 4\beta 2$, $\alpha 7$ 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 $\alpha 4\beta 2$ 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		Odds Ratio (95% Credible Interval)
			Intervention n/N (%)	Control n/N (%)	
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

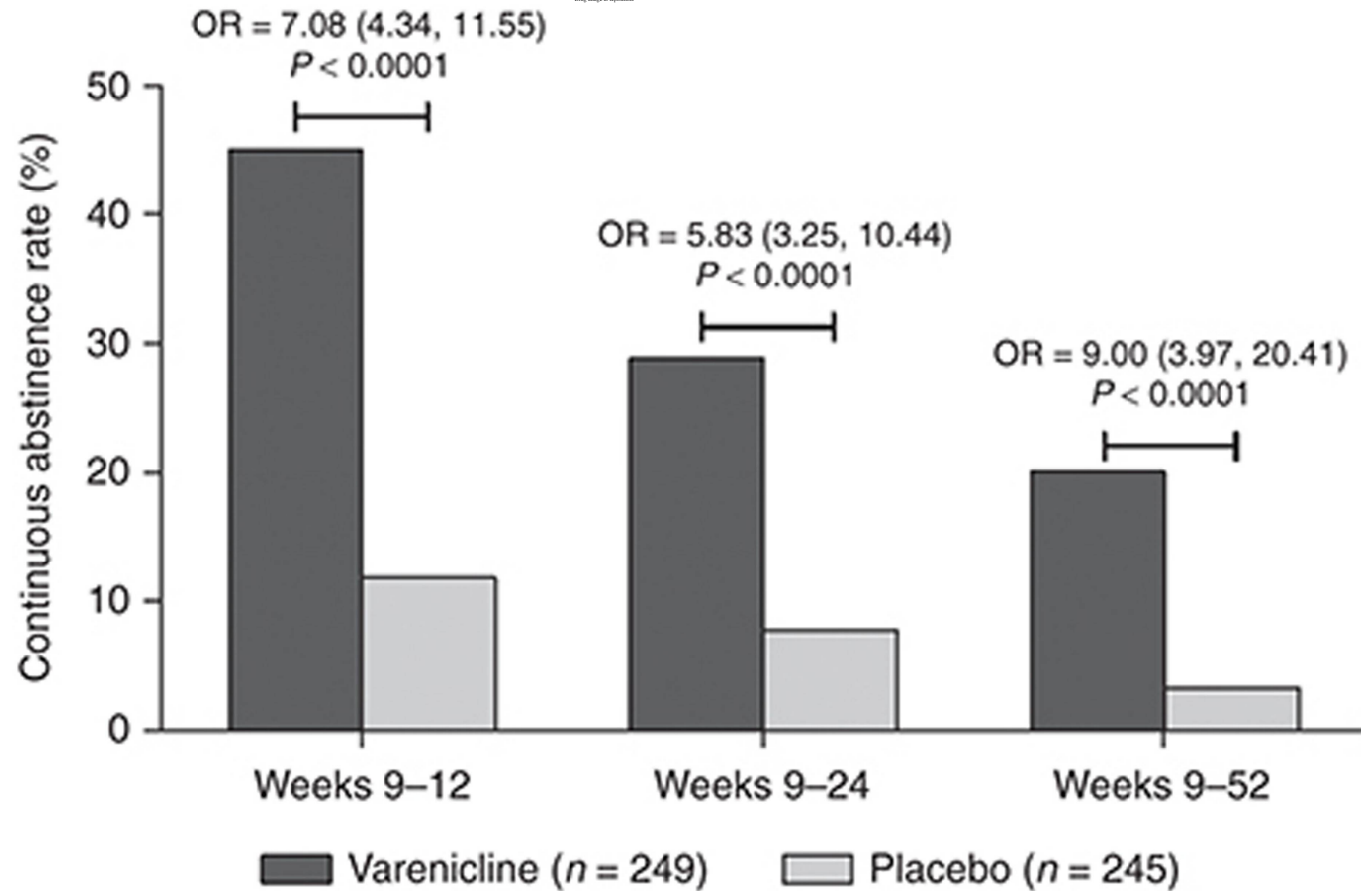
For tobacco dependence: average of 5 attempts at abstinence before long-term abstinence achieved

Treatments double to triple abstinence rates and are Underutilized!

New clinical practice guidelines: Treat all smokers

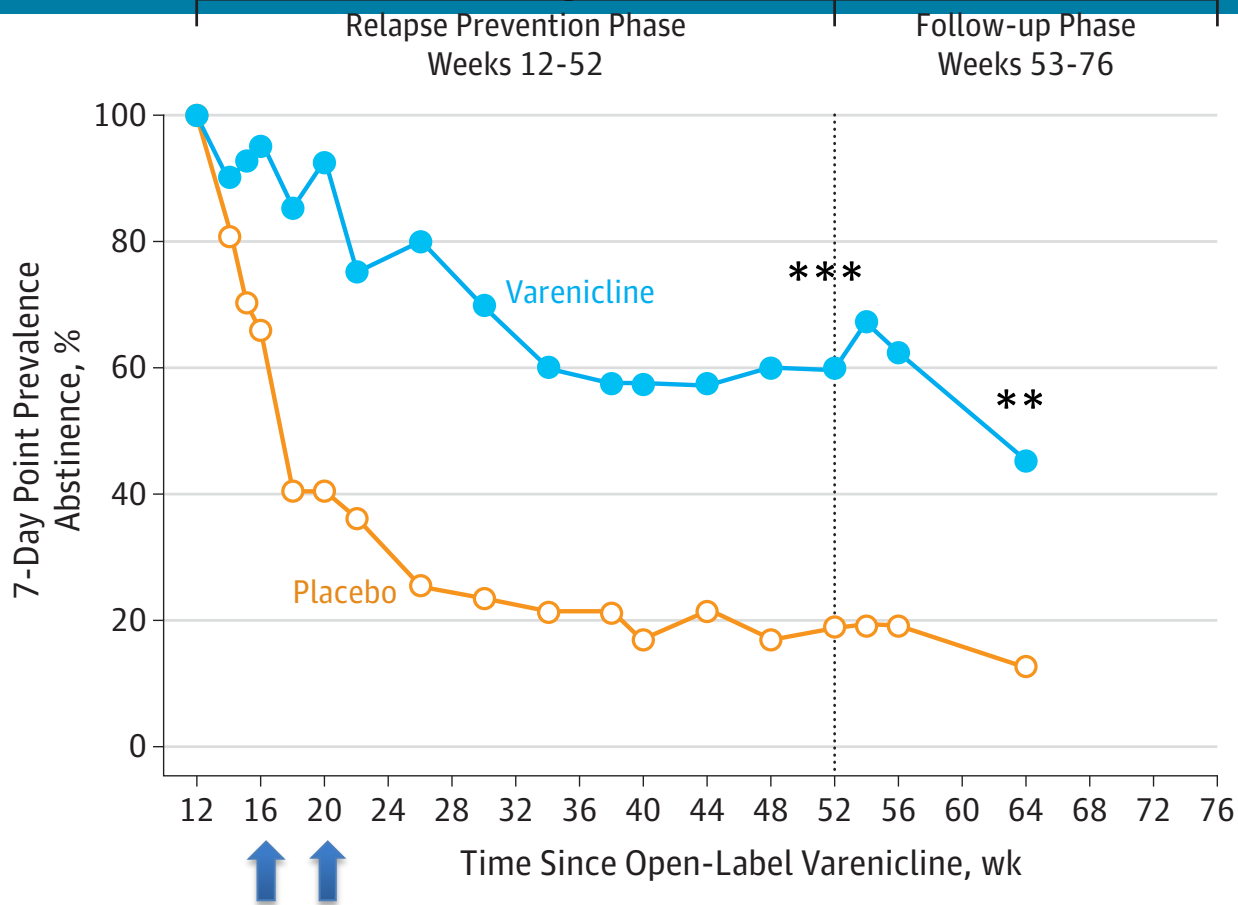
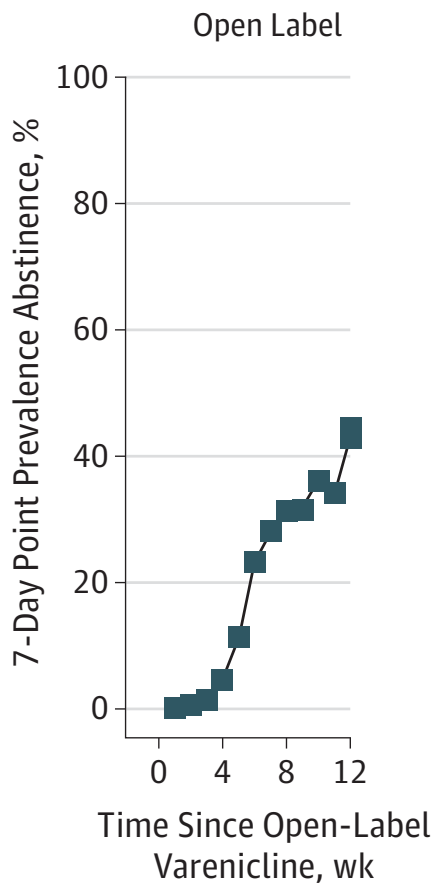
Offer pharmacotherapy and behavioral support to all smokers willing to accept such treatment, not just those who report being 'ready to quit'

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.

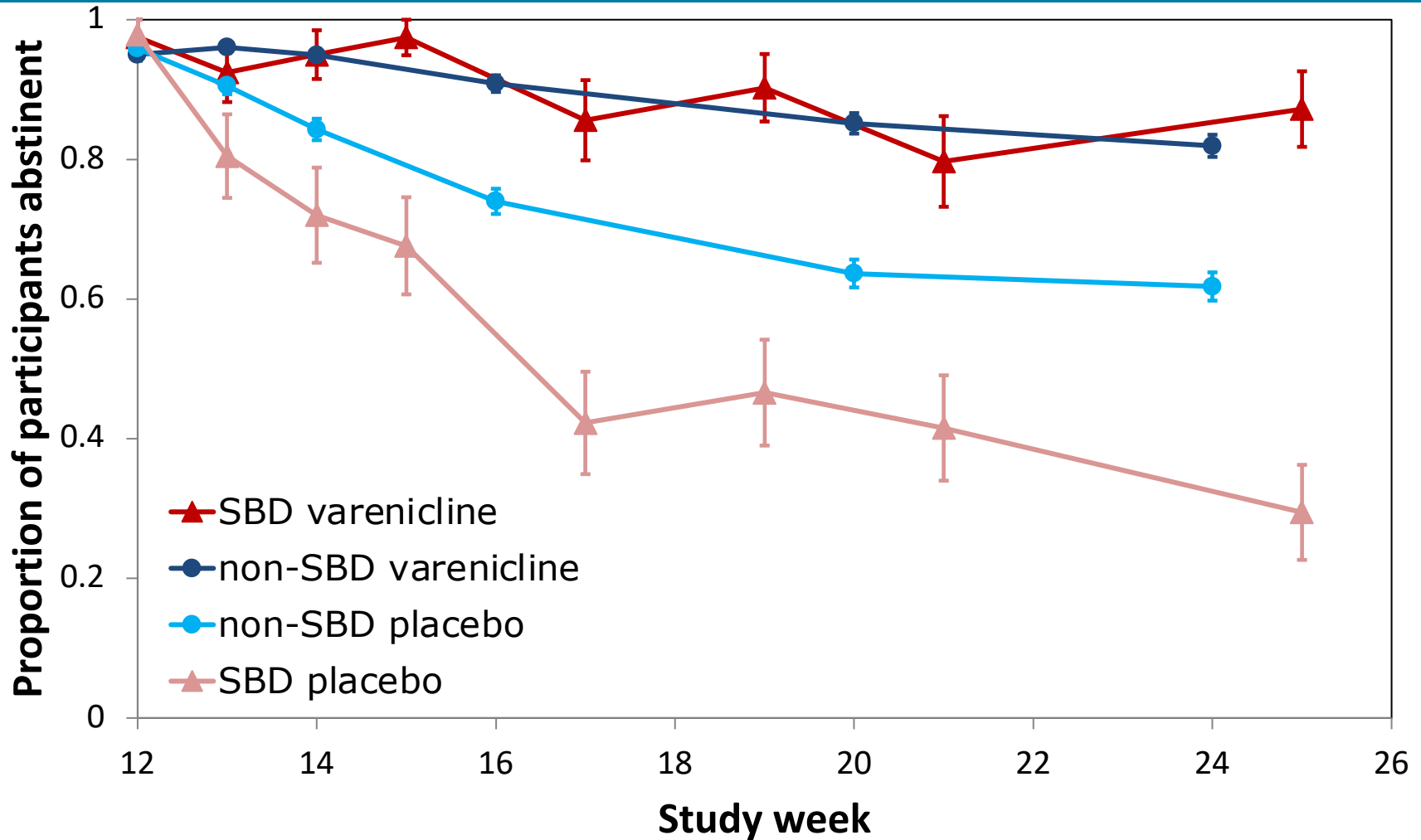
Varenicline Maintenance Treatment for One Year Triples Abstinence Rates at One Year in Smokers with Schizophrenia



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 www.mghcme.org

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

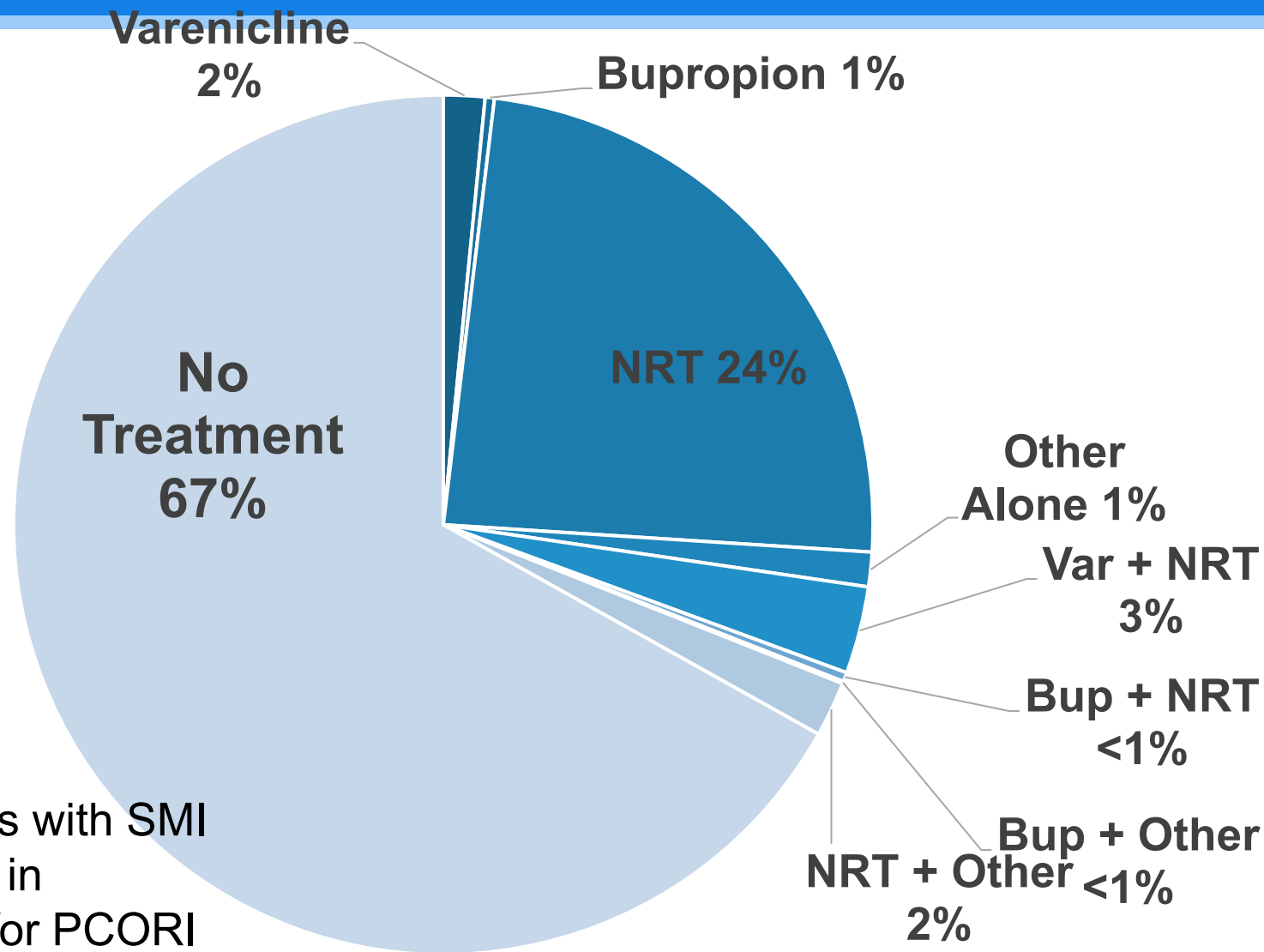


Smoking Cessation Tx Recommended but Underutilized, Particularly in Psychosis

- 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

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

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

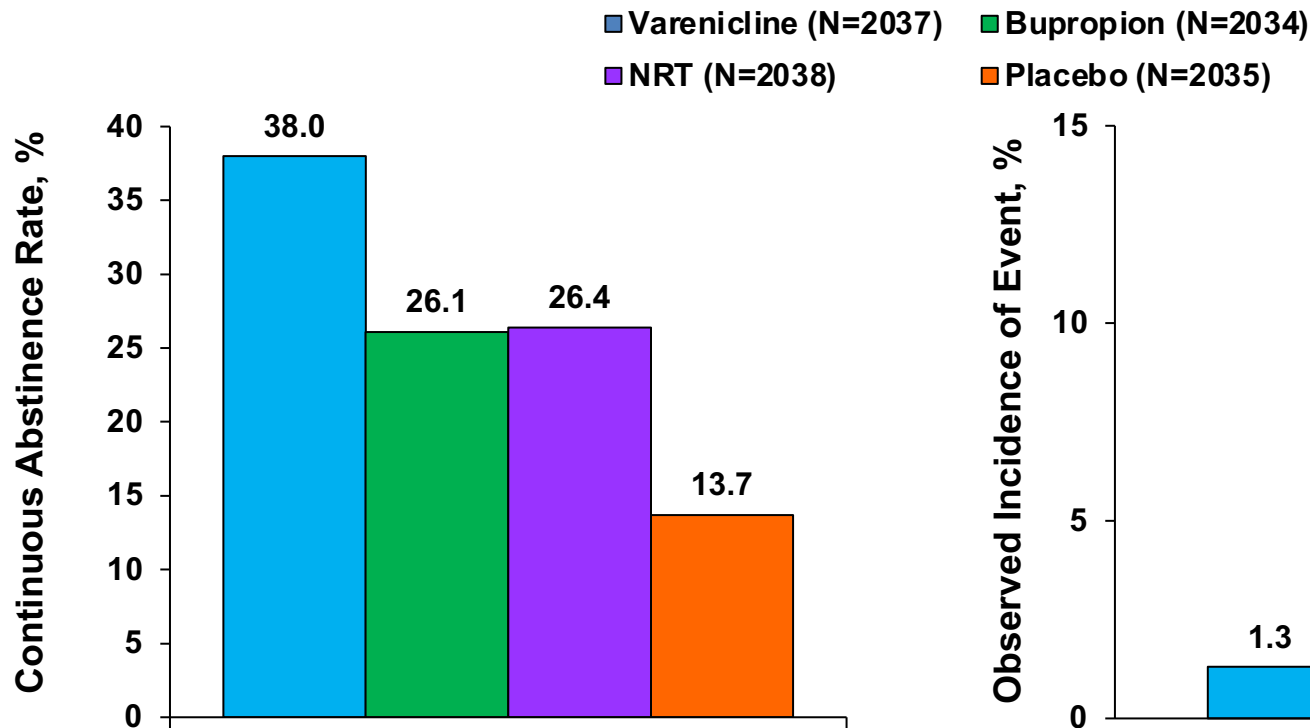
Severity assessment

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

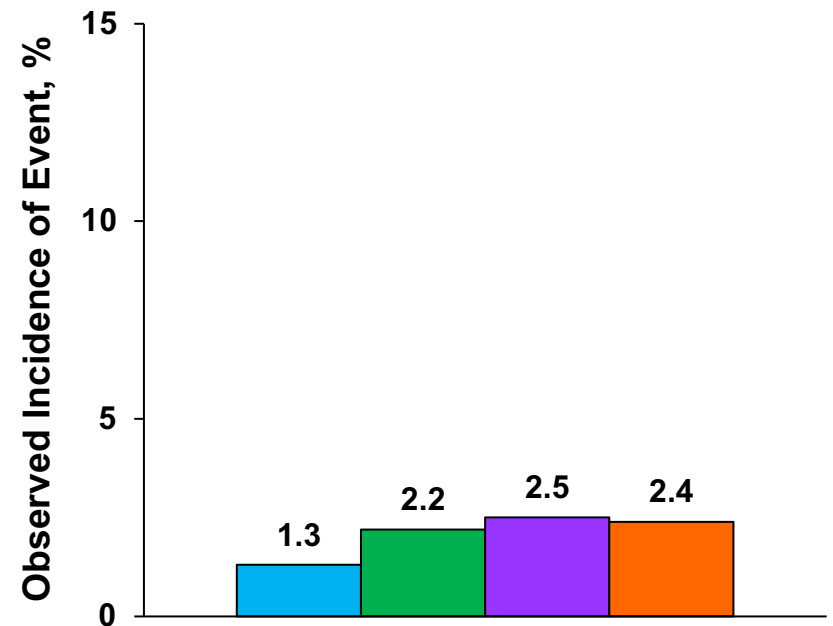
Severe = interferes significantly with subject's usual function

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

CARs Week 9-12



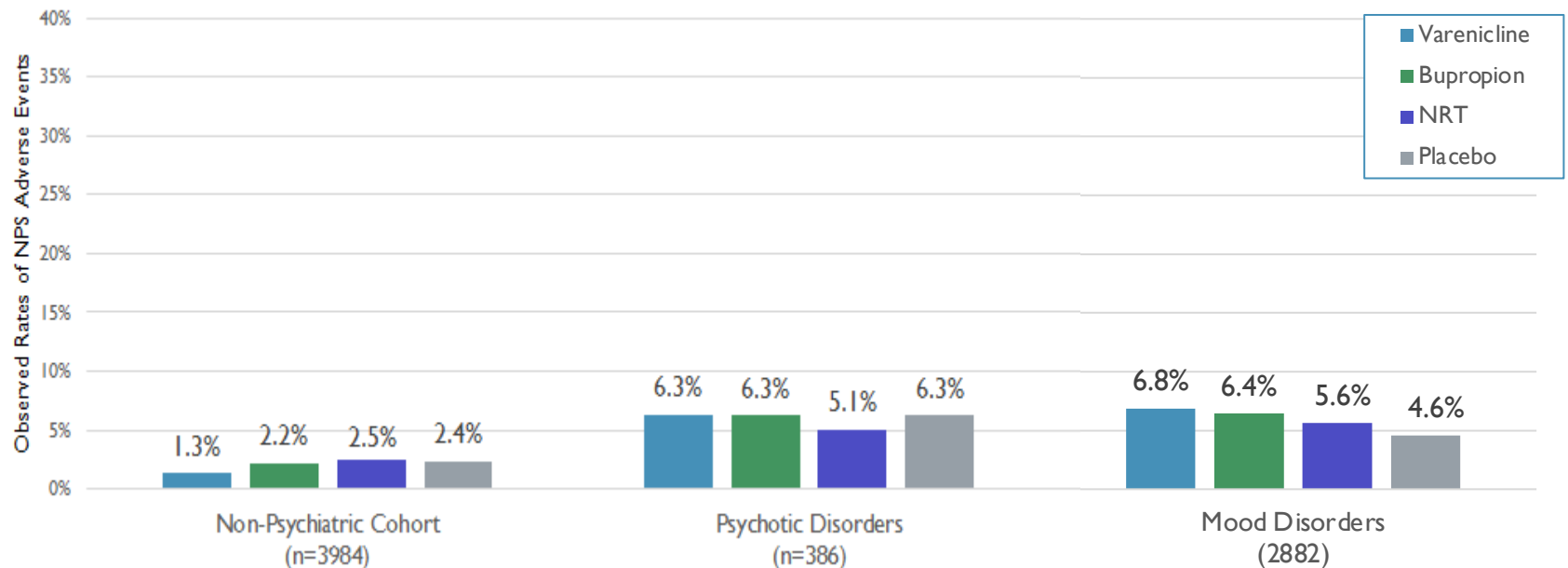
Primary NPS Composite Safety Endpoint



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)
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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.

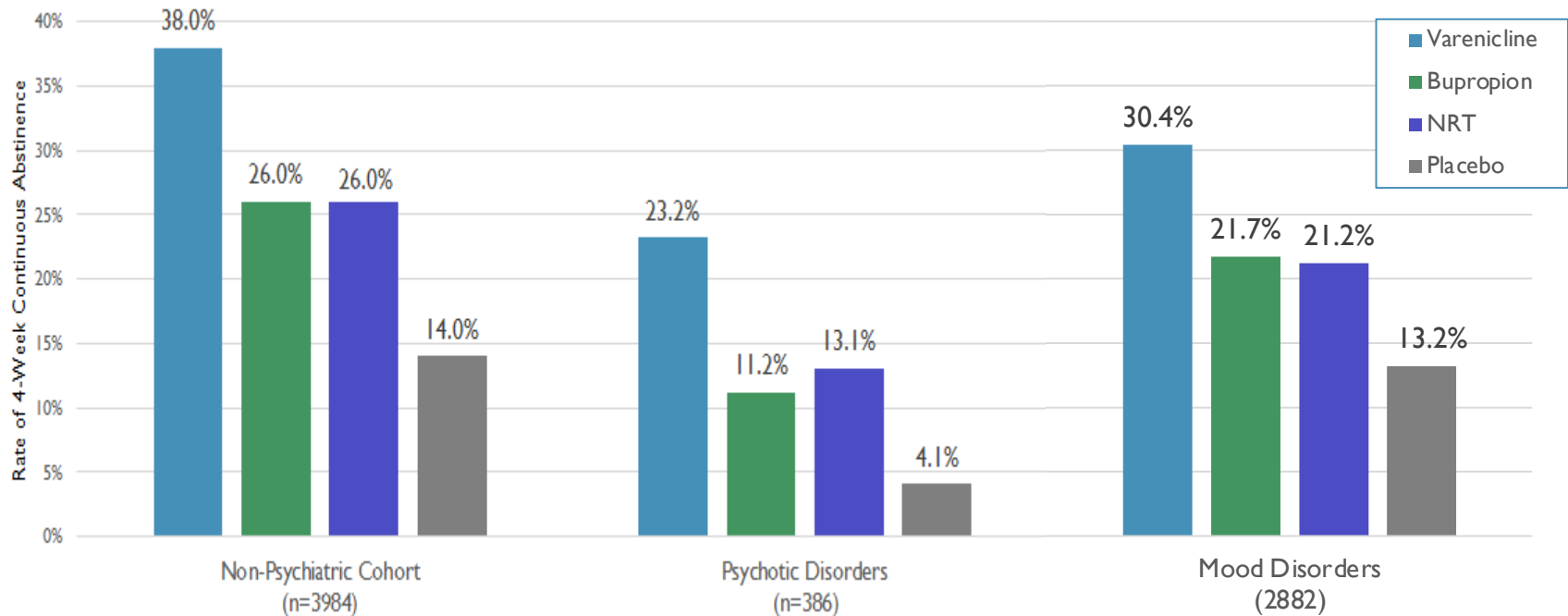
- Risk of NPS AEs is independent of treatment
 - ~2% NPS AE rate in smokers without mental illness
 - ~5-7% NPS AE rate in smokers with mental illness
- NPS AE rates during a cessation attempt are not different across active treatments or placebo
- No pattern of NPS AEs in the most worrisome NPS AEs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

EFFICACY

Comparative efficacy data based on EAGLES²

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

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



[†] | [‡] "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 Psych⁴⁰ and Non-Psych Cohorts

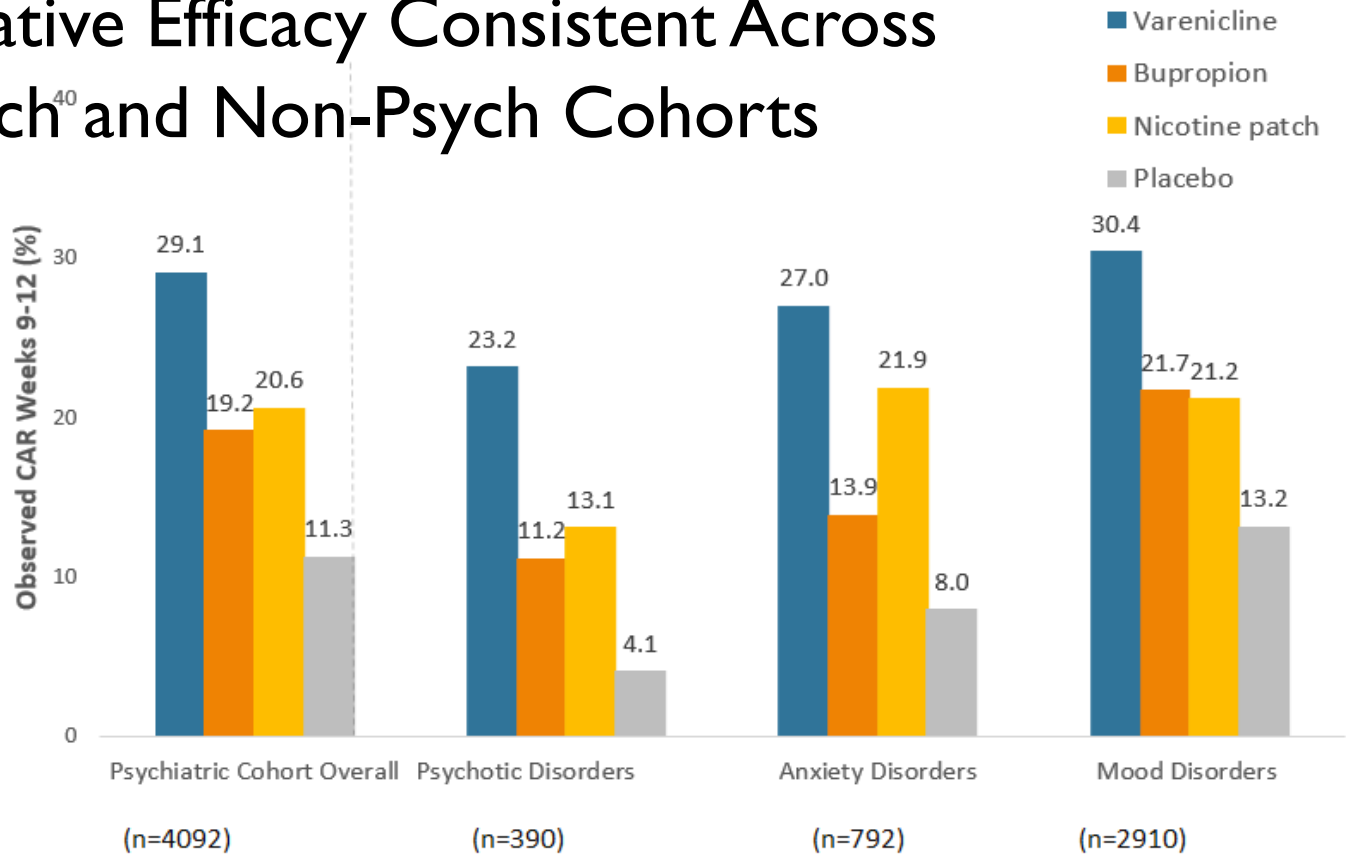


Figure 2b.

Treatment comparison

Varenicline vs placebo

Bupropion vs placebo

Secondary comparisons

Nicotine patch vs placebo

Varenicline vs nicotine patch

Bupropion vs nicotine patch

Varenicline vs bupropion

OR (95% CI)

4.57 (2.59 to 8.06)

2.22 (1.21 to 4.06)

2.76 (1.53 to 4.97)

1.66 (1.11 to 2.49)

0.80 (0.51 to 1.27)

2.06 (1.35 to 3.17)

OR (95% CI)

6.93 (1.61 to 29.84)

2.99 (0.63 to 14.14)

3.40 (0.74 to 15.61)

2.04 (0.75 to 5.55)

0.88 (0.28 to 2.73)

2.32 (0.82 to 6.58)

OR (95% CI)

4.55 (2.05 to 10.11)

1.91 (0.81 to 4.51)

3.43 (1.52 to 7.74)

1.33 (0.72 to 2.46)

0.56 (0.28 to 1.12)

2.38 (1.21 to 4.69)

OR (95% CI)

3.03 (2.13 to 4.32)

1.91 (1.32 to 2.76)

1.80 (1.24 to 2.61)

1.68 (1.23 to 2.32)

1.06 (0.76 to 1.48)

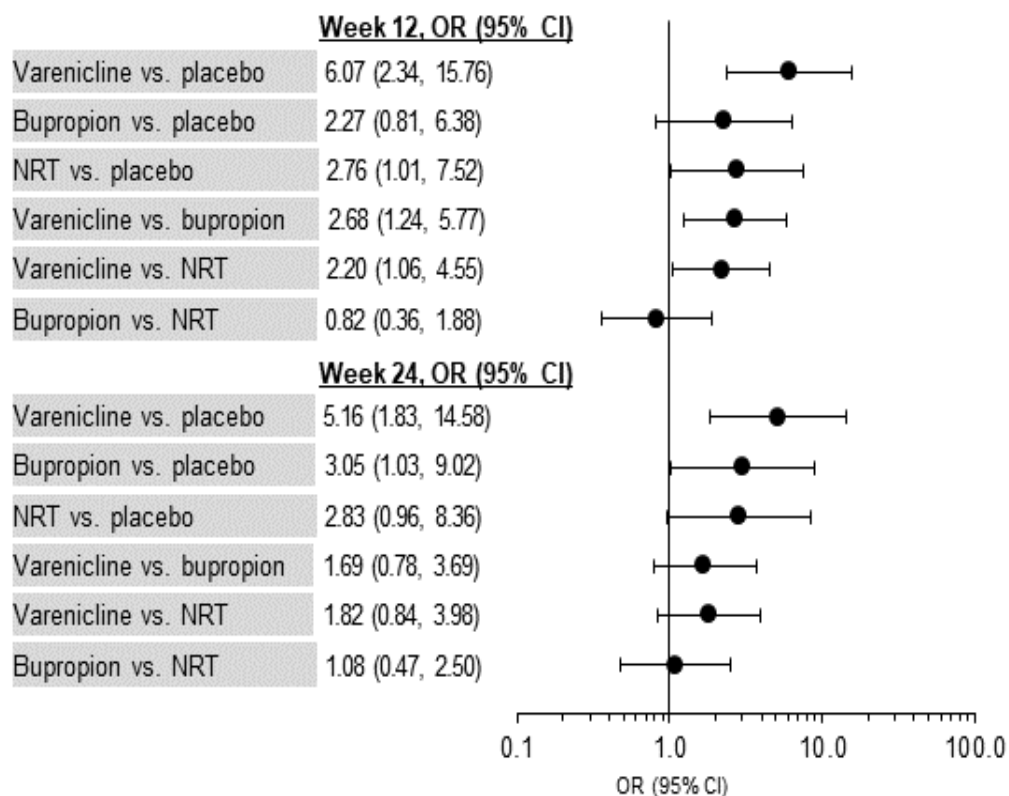
1.59 (1.16 to 2.18)

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

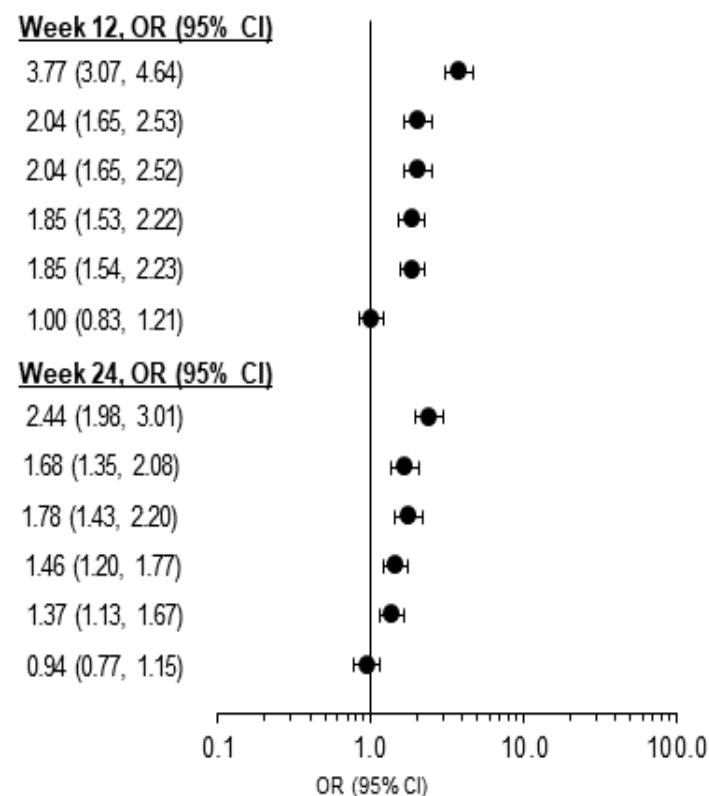
EFFICACY

Comparative efficacy data based on EAGLES²

Schizophrenia spectrum disorders subcohort

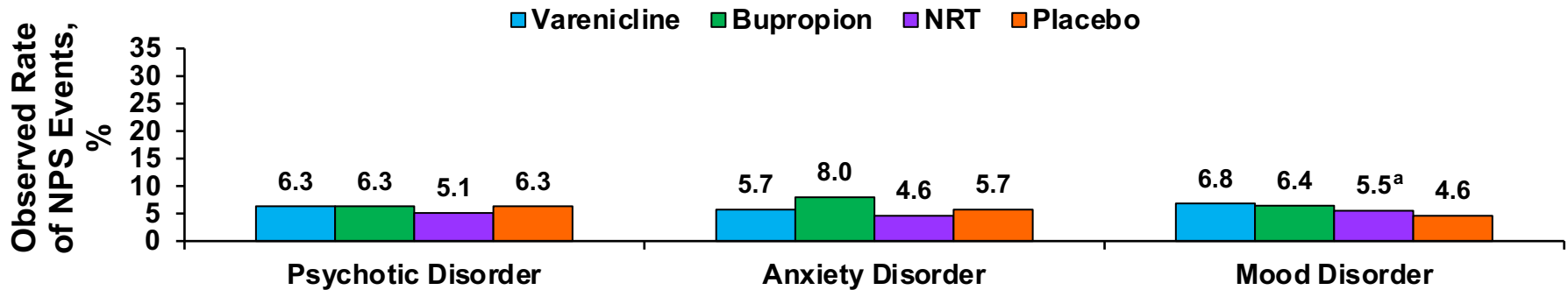


No psychiatric disorders cohort

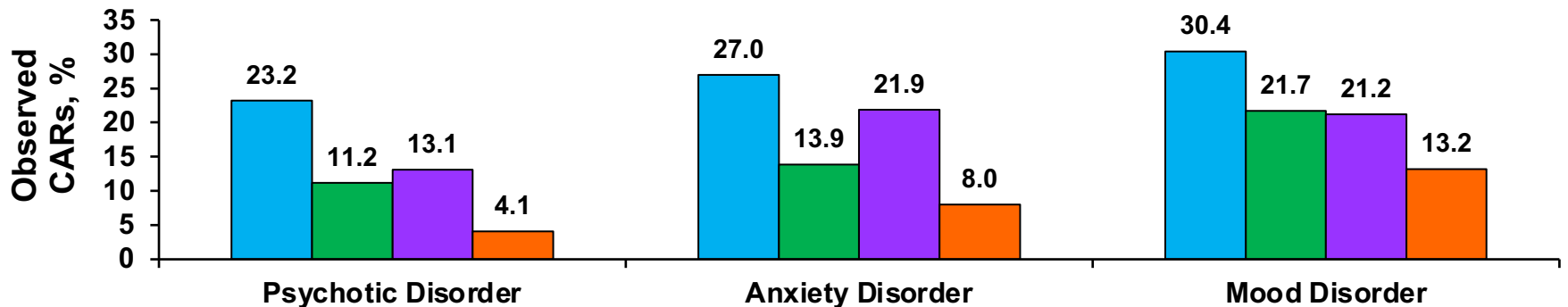


Risk / Benefit: EAGLES Allows Comparison of Neuropsychiatric Safety and Efficacy in Those with Psychiatric Illness

Primary NPS Composite Safety Endpoints by Treatment for Those with Primary Psychotic, Anxiety and Mood Disorders



CARs Week 9-12 by Treatment and Psychiatric Diagnosis



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 EAGLES²

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

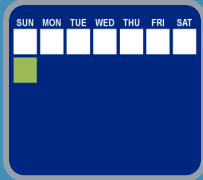
'Flexible quit' and 'gradual quit' after starting meds are validated ways to quit

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

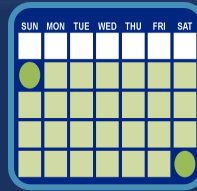
THREE WAYS TO QUIT SMOKING: All Start with Smoking Cessation Medication



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

Asses
s

At each clinic visit, ask patients if they currently smoke tobacco. (most with SMI smoke)

Engage

Remind patients that quitting is the single best thing they can do for their health. Recommend EVERY smoker start treatment to quit. Med use may increase readiness to quit.

Prescribe

Start medication for all smokers who are willing. Emphasize importance of adherence to treatment. Decide on fixed, flexible, or gradual quit.

Follow
Through

Schedule 1-4 week follow-up to assess med tolerability, plan quit. Remind pts that most AEs are mild, transient. Problem solve around missed med doses. Reinforce progress and persistence. Most need repeat quit attempts.

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.

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

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

Varenicline (Chantix)

- Selective, partial $\alpha_4 \beta_2$ and full α_7 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...

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

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