Varenicline for Tobacco Dependence Treatment: Balancing benefits and risks

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Disclosures

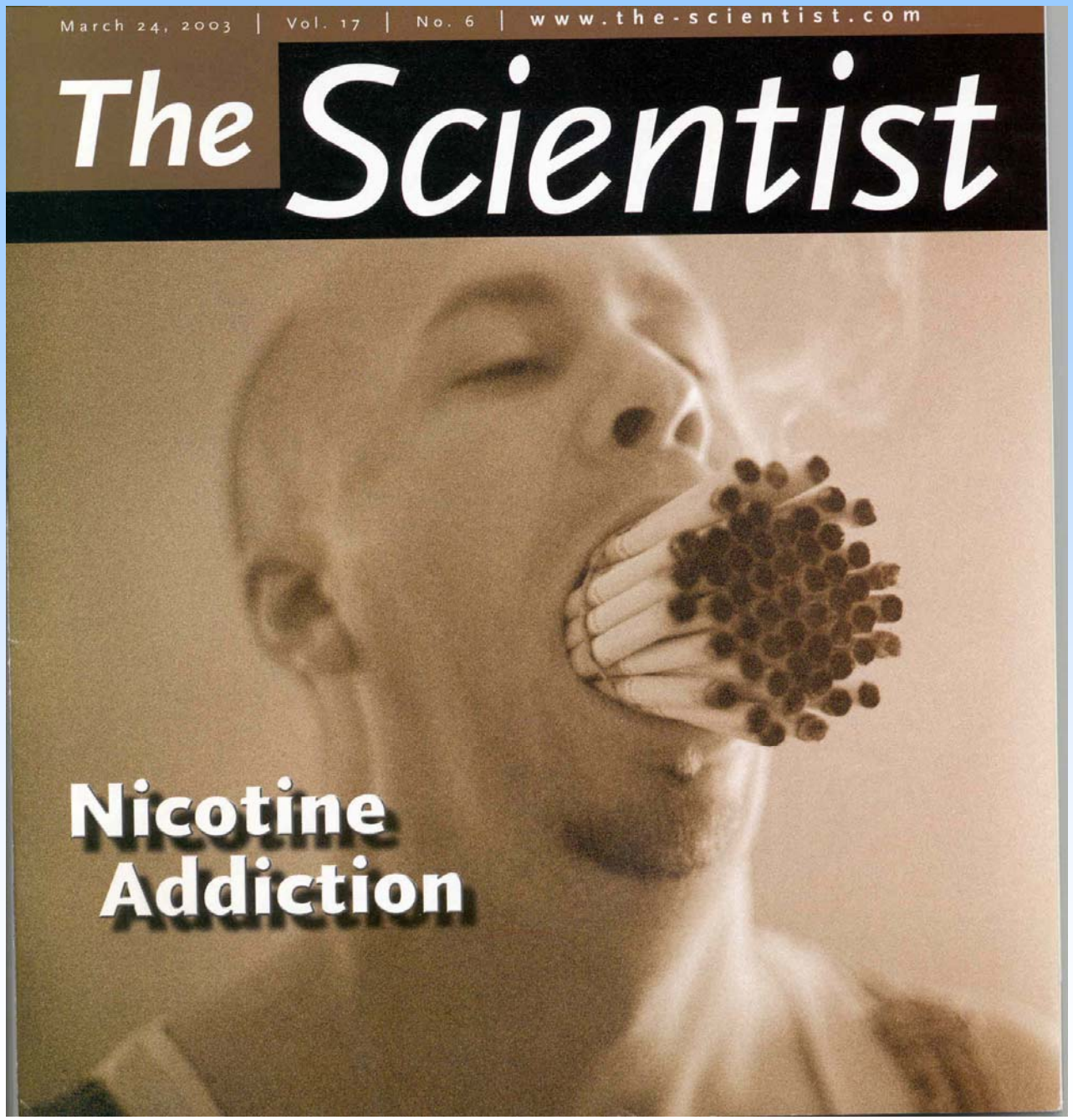
- Financial relationships past 3 years
  - I have been an investigator on research grants to Mayo Clinic provided by the following pharmaceutical manufacturers:
    - Pfizer (Chantix/varenicline)
    - Nabi (Nic Vax)
- No off-label prescribing

Learning Objectives

- Describe the efficacy of varenicline for tobacco dependence treatment
- Identify common and serious AE's associated with varenicline for tobacco dependence treatment
- Examine the risks and benefits of varenicline treatment for tobacco dependence

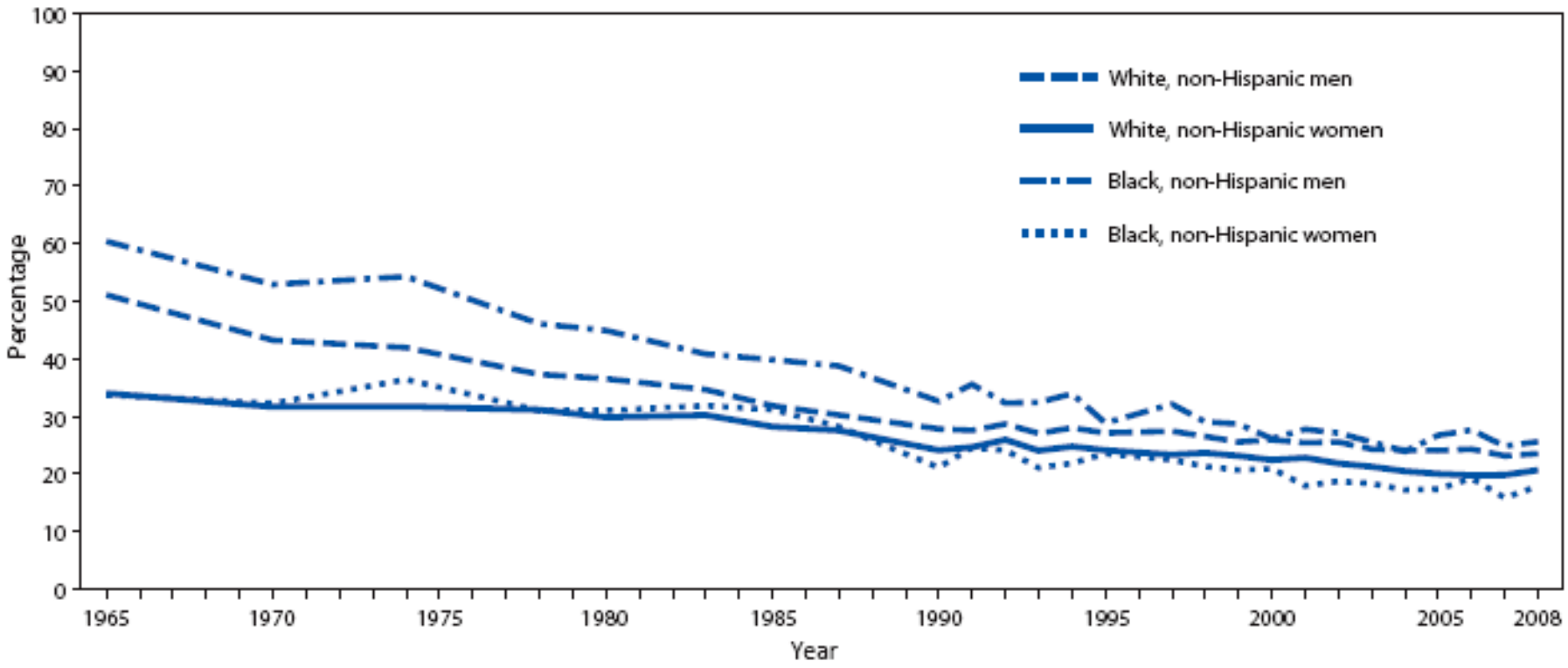
Outline

- Background
- Adverse effects of varenicline pharmacotherapy for tobacco dependence treatment
- Efficacy of varenicline for tobacco dependence treatment
- Balancing risks and benefits


March 24, 2003 | Vol. 17 | No. 6 | www.the-scientist.com
The Scientist
Nicotine Addiction

Smoking Prevalence US 1965-2008

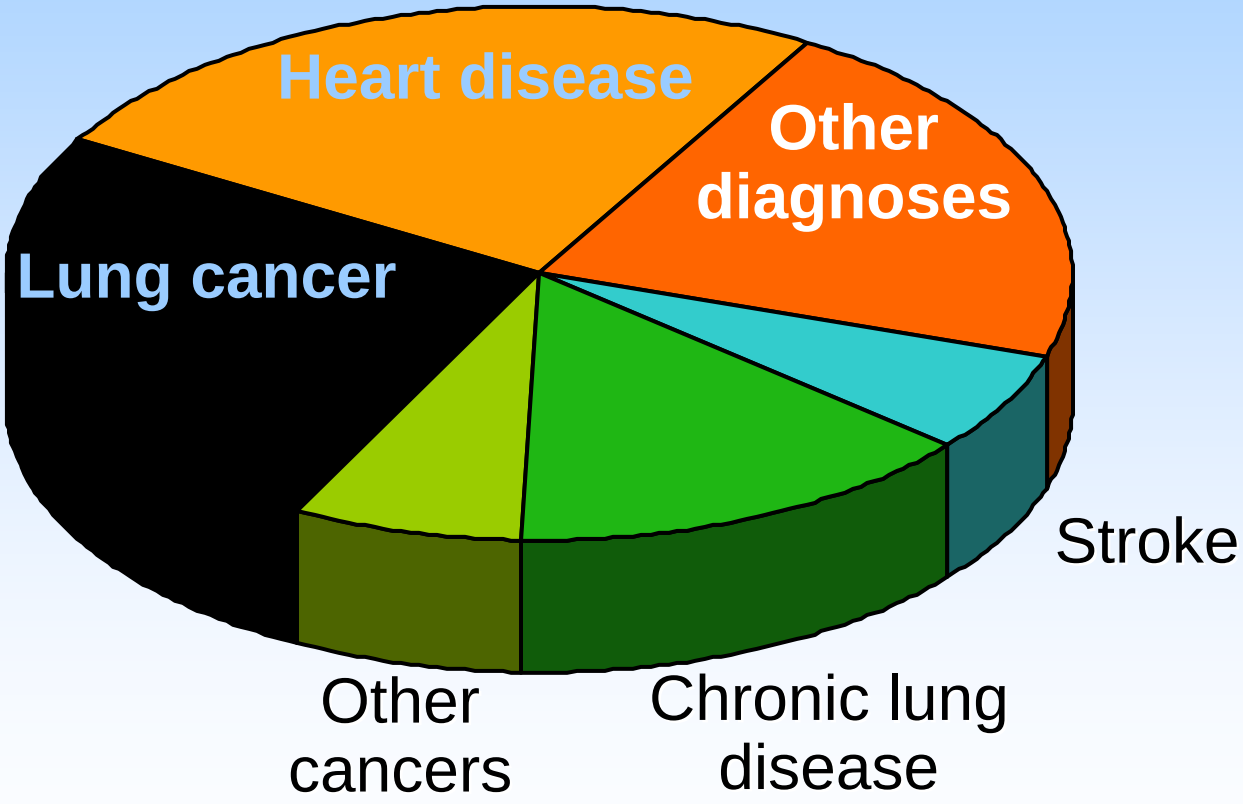
FIGURE. Percentage of adults aged ≥18 years who were current smokers,* by sex and race/ethnicity — National Health Interview Survey (NHIS), United States, 1965–2008†



CDC Health Disparities and Inequalities Report — United States, 2011

MMWR January 14, 2011, Vol 60 (suppl.)

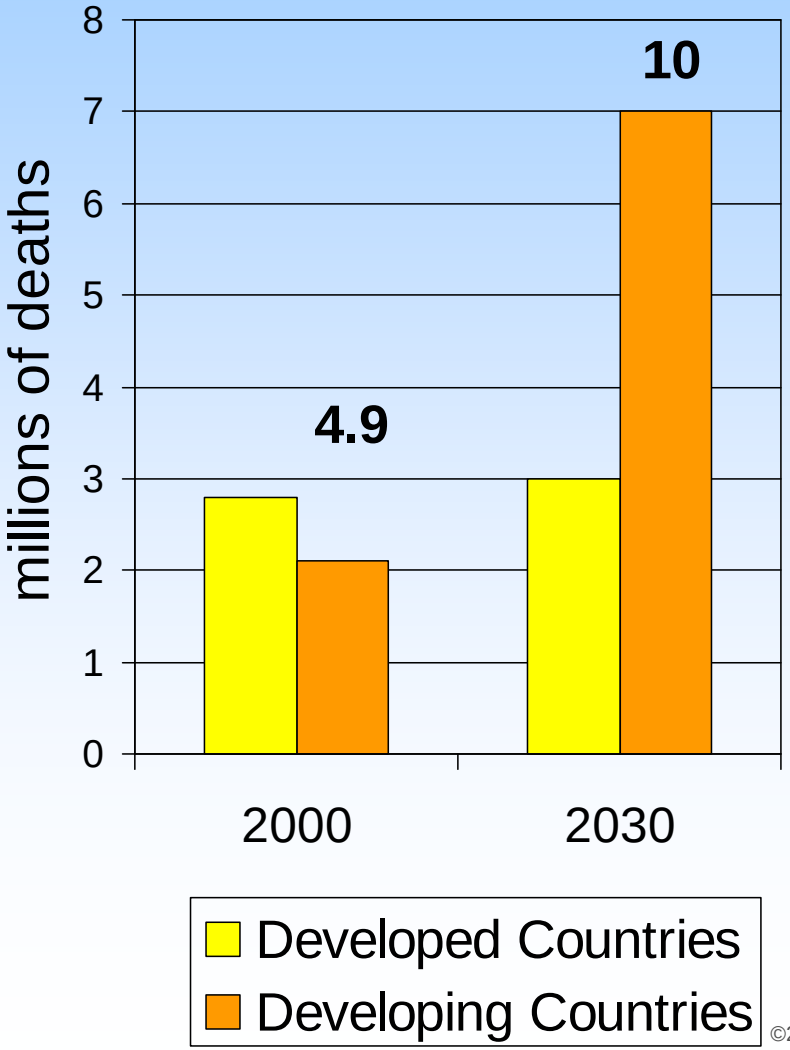
438,000 Annual Deaths Attributable to Cigarette Smoking- United States



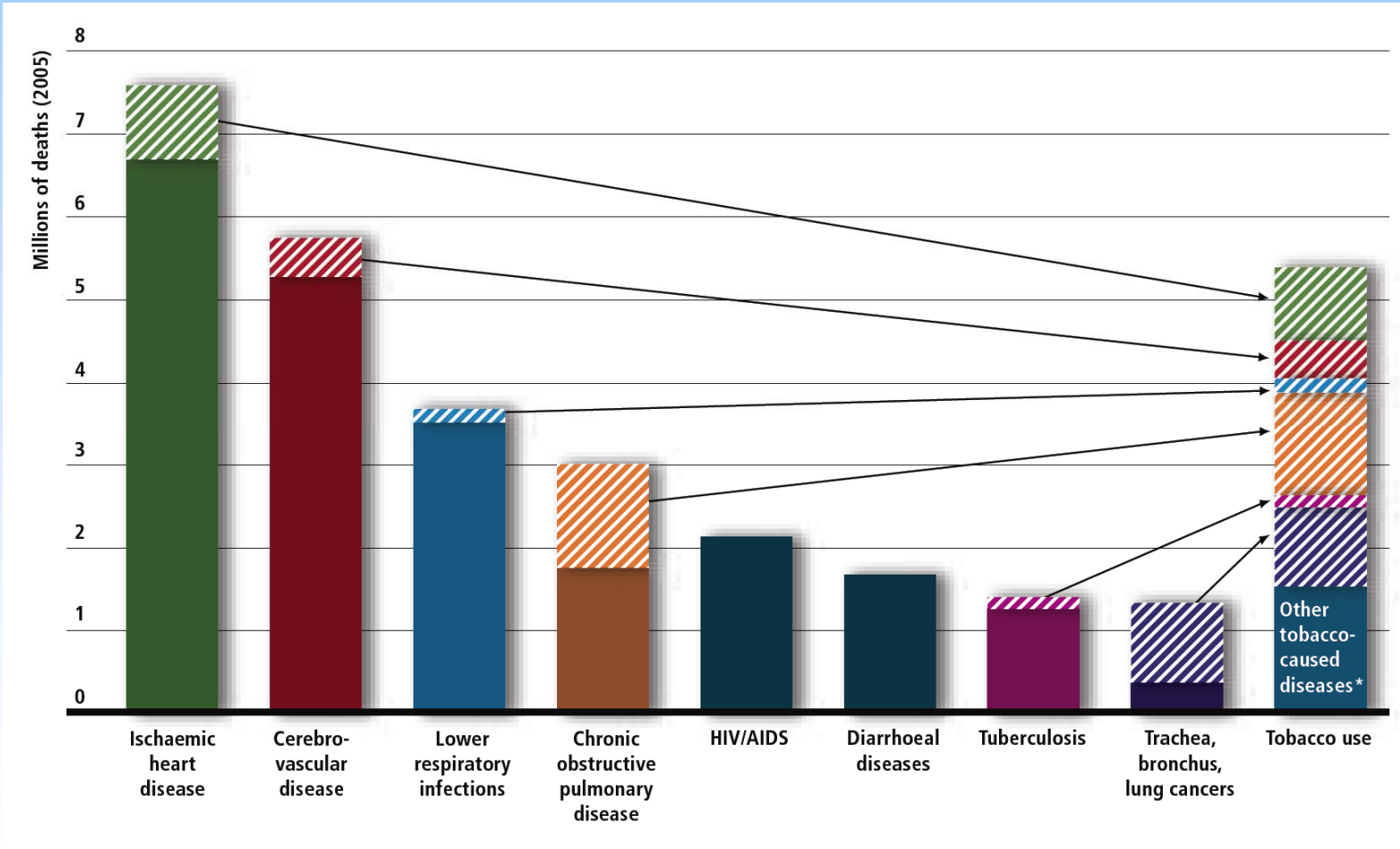
Tobacco Use: An Escalating Epidemic

By 2030:

- Leading cause of death
- 10 million annual deaths due to tobacco
- 70% of those deaths will occur in developing countries



Tobacco Is a Risk Factor for 6 of the World's 8 Leading Causes of Death

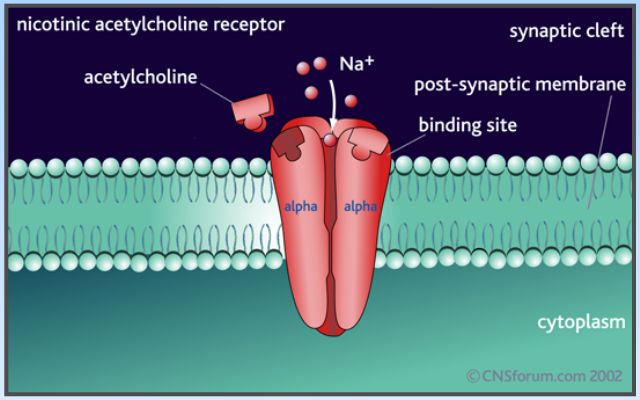


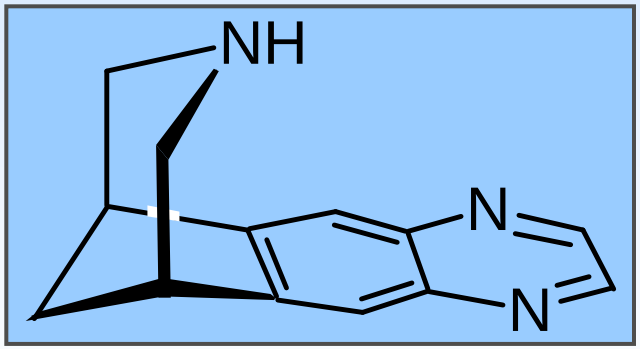
Hatched areas indicate proportions of deaths related to tobacco use.

Varenicline Adverse Effects

Varenicline Mechanism of Action

- Varenicline targets the nicotinic acetylcholine receptor (nAChR) in a unique fashion
- Partial agonist with specificity for the high-affininty α4β2 nAChR
- Agonist -- stimulates the receptor to decrease craving and withdrawal
- Antagonist—blocks the receptor to decrease the reinforcement associated with smoking
- No clinically relevant drug-drug interactions





Common Adverse Events in Clinical Trials (%)

	Varenicline	Placebo
Nausea	35.8	11.2
Insomnia	22	12.7
Abnl dreams	14.4	5
Headache	16.8	14.3
Other GI	22.5	11.8
Discontinued	12	8.1

Varenicline: FDA Warning 2008

All patients being treated with Chantix should be observed for neuropsychiatric symptoms including changes in behavior, agitation, depressed mood, suicidal ideation, and suicidal behavior. These symptoms, as well as worsening of pre-existing psychiatric illness, have been reported in patients attempting to quit smoking while taking Chantix…

Institute for Safe Medication Practices "Safety Signals"

The ISMP QuarterWatch report for May 2008 brought to FDA and the public's attention data showing strong safety signals with varenicline (CHANTIX) in the 4th Quarter 2007. Chantix accounted for more reported serious adverse events than any other prescription drug during this quarter. Other QuarterWatch reports since then have also detailed serious side effects including aggressive behavior and other neuropsychiatric symptoms. This information contributed to an FDA alert sent on July 1, 2009

CHANTIX®

(varenicline) Tablets

"Serious neuropsychiatric events, including, but not limited to depression, suicidal ideation, suicide attempt and completed suicide have been reported in patients taking Chantix."

smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking CHANTIX who continued to smoke.

"These events have occurred in patients with and without pre-existing psychiatric disease."

When symptoms were reported, most were during CHANTIX treatment, but some were following discontinuation of CHANTIX therapy.

These events have occurred in patients with and without pre-existing psychiatric disease

"Advise patients and caregivers that patients should stop taking Chantix and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior."

been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial.

(See **WARNINGS/Neuropsychiatric Symptoms and Suicidality, PRECAUTIONS/Information for Patients, and ADVERSE REACTIONS/Post-Marketing Experience**)

CHANTIX®

(varenicline) Tablets

WARNING:

Serious neuropsychiatric events, including, but not limited to depression, suicidal ideation, suicide attempt and completed suicide have been reported in patients taking CHANTIX. Some reported cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal.

"The risks of Chantix should be weighed against the benefits of its use. Chantix has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial."

depressive disorder did not participate in the pre-marketing studies of CHANTIX and the safety and efficacy of CHANTIX in such patients has not been established.

Advise patients and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many post-marketing cases, resolution of symptoms after discontinuation of CHANTIX was reported, although in some cases the symptoms persisted; therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

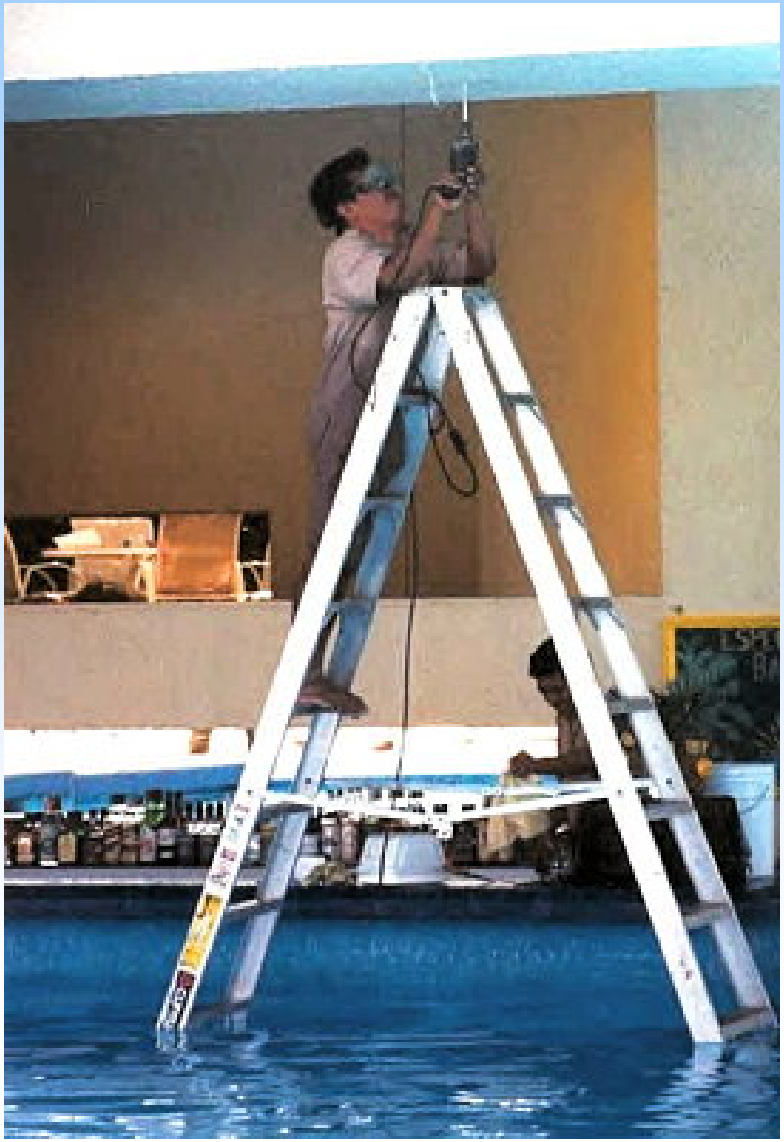
The risks of CHANTIX should be weighed against the benefits of its use. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial.

(See **WARNINGS/Neuropsychiatric Symptoms and Suicidality, PRECAUTIONS/Information for Patients, and ADVERSE REACTIONS/Post-Marketing Experience**)

Varenicline Boxed Warning

"The risk of serious adverse events while taking these products [Chantix and Zyban] must be weighed against the significant health benefits of quitting smoking. Smoking is the leading cause of preventable disease, disability, and death in the United States and we know these products are effective aids in helping people quit."

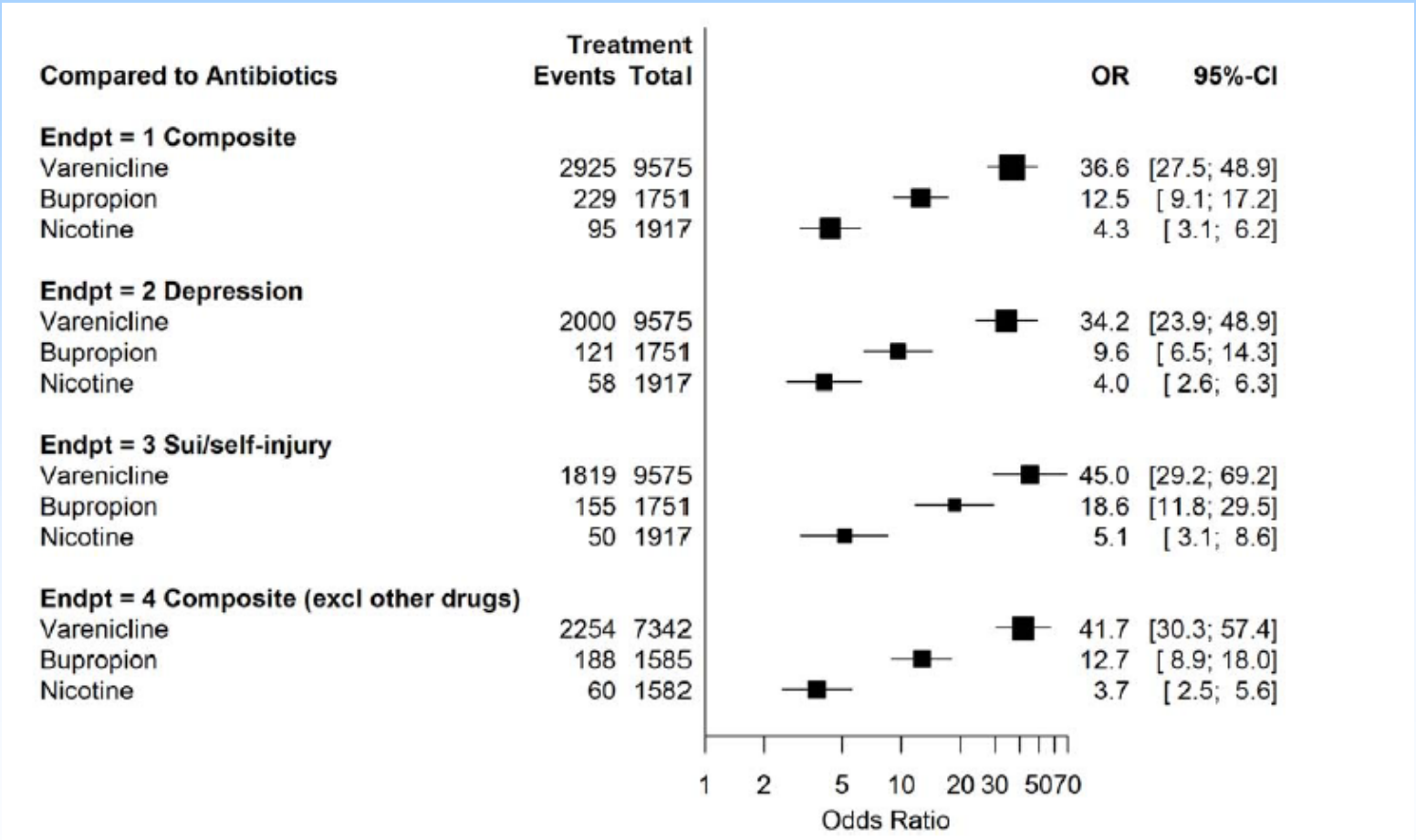
Janet Woodcock, M.D.
Director FDA Center for Drug Evaluation and Research
Press release, July 1, 2009



Varenicline and Neuropsychiatric Adverse Events

Suicidal Behavior and Depression in Smoking Cessation Treatments

Thomas J. Moore[1]*, Curt D. Furberg[2], Joseph Glenmullen[3], John T. Maltsberger[4], Sonal Singh[5]



Citation: Moore TJ, Furberg CD, Glenmullen J, Maltsberger JT, Singh S (2011) Suicidal Behavior and Depression in Smoking Cessation Treatments. PLoS ONE 6(11): e27016. doi:10.1371/journal.pone.0027016

FDA Sponsored Observational Studies of Neuropsychiatric Adverse Events and Varenicline

- Department of Veterans Affairs' (VA) Center for Medication Safety (VAMedSAFE)
- Department of Defense's (DoD) U.S. Army Medical Command's Pharmacovigilance Center (PVC)

http://www.fda.gov/Drugs/DrugSafety/ucm276737.htm

VA Study

- Retrospective cohort study to evaluate the incidence of mental health hospitalizations among veterans using Chantix or (NRT)
- Patients starting Chantix or NRT between May 1, 2006 and September 30, 2007, but with no Chantix or NRT use in the previous year, were selected and matched in a 1:1 ratio
- Main outcome was psychiatric hospitalization, with a coded primary discharge diagnosis for one of a number of psychiatric conditions
- 14,131 Chantix users and an equal number of NRT users

VA Study Results

- 14,131 Chantix users and an equal number of NRT users
  - 16 psychiatric hospitalizations in Chantix-treated patients
  - 21 in NRT patients
- No statistically significant difference in the risk of psychiatric hospitalization for Chantix users compared to NRT users (hazard ratio [HR] for Chantix/NRT = 0.76; 95% confidence interval [CI] 0.40-1.46).

DoD Study

- Retrospective cohort study comparing the acute (30-day) rates of hospitalizations for neuropsychiatric adverse events among
  - New users of Chantix (n=19,933)
  - New NRT patch (n=15,867)
  - Started therapy from August 1, 2006 to August 31, 2007
- Chantix users were matched to NRT users
- Matched sample included 11,978 Chantix users and an equal number of NRT users

DoD Study Results

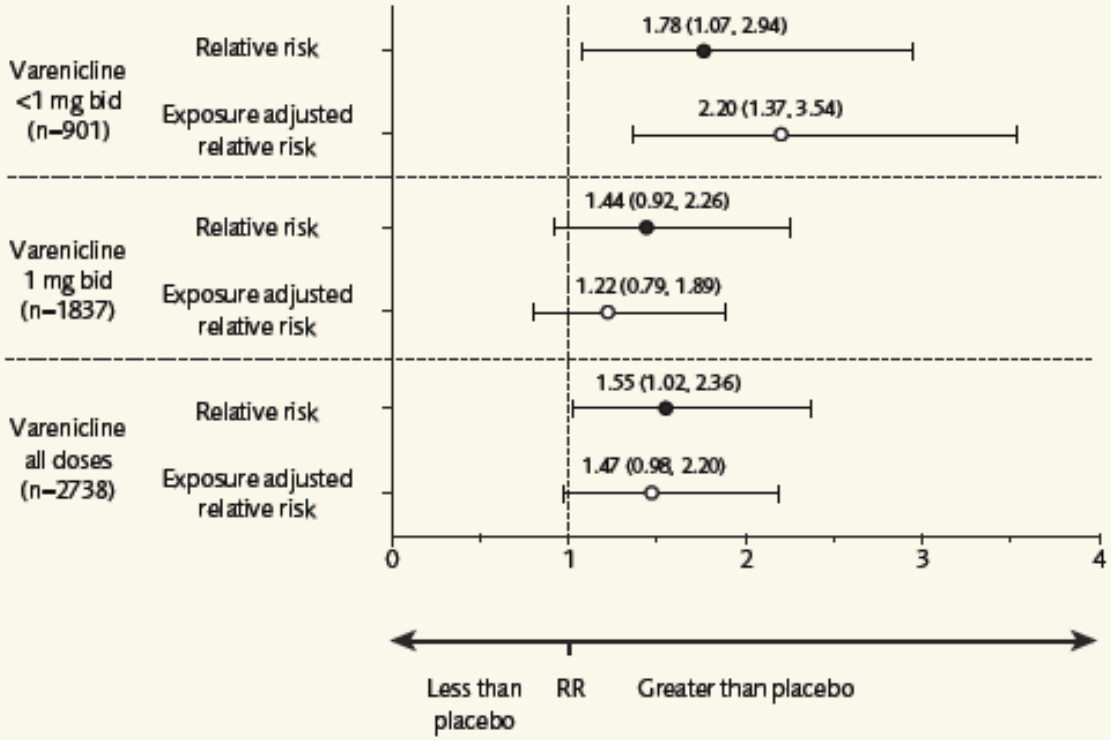
- 18 psychiatric hospitalizations among Chantix users
- 16 psychiatric hospitalizations among NRT users
- No statistically significant difference (HR for Chantix/NRT = 1.13; 95% CI 0.57-2.21) in psychiatric hospitalizations
- No significant difference in psychiatric hospitalizations for Chantix users compared to NRT users when patients with concomitant bupropion use were excluded (HR = 0.91; 95% CI 0.39-2.14)
- Most (43) of the 55 neuropsychiatric hospitalizations (18 of the 23 Chantix events and 25 of the 32 NRT events) occurred in patients with a neuropsychiatric diagnosis in the year preceding the Chantix/NRT prescription fill

FDA Study Interpretation

- No evidence of serious neuropsychiatric events occurring more often with varenicline compared with NRT
- Included patients with pre-existing mental health disorders
- Cannot exclude association of varenicline with less serious psychiatric AE's

Depression in varenicline RCT's

Figure 2. Relative risks (RR) and exposure-adjusted relative rates of depressed mood disorders and disturbances for varenicline versus placebo by dose

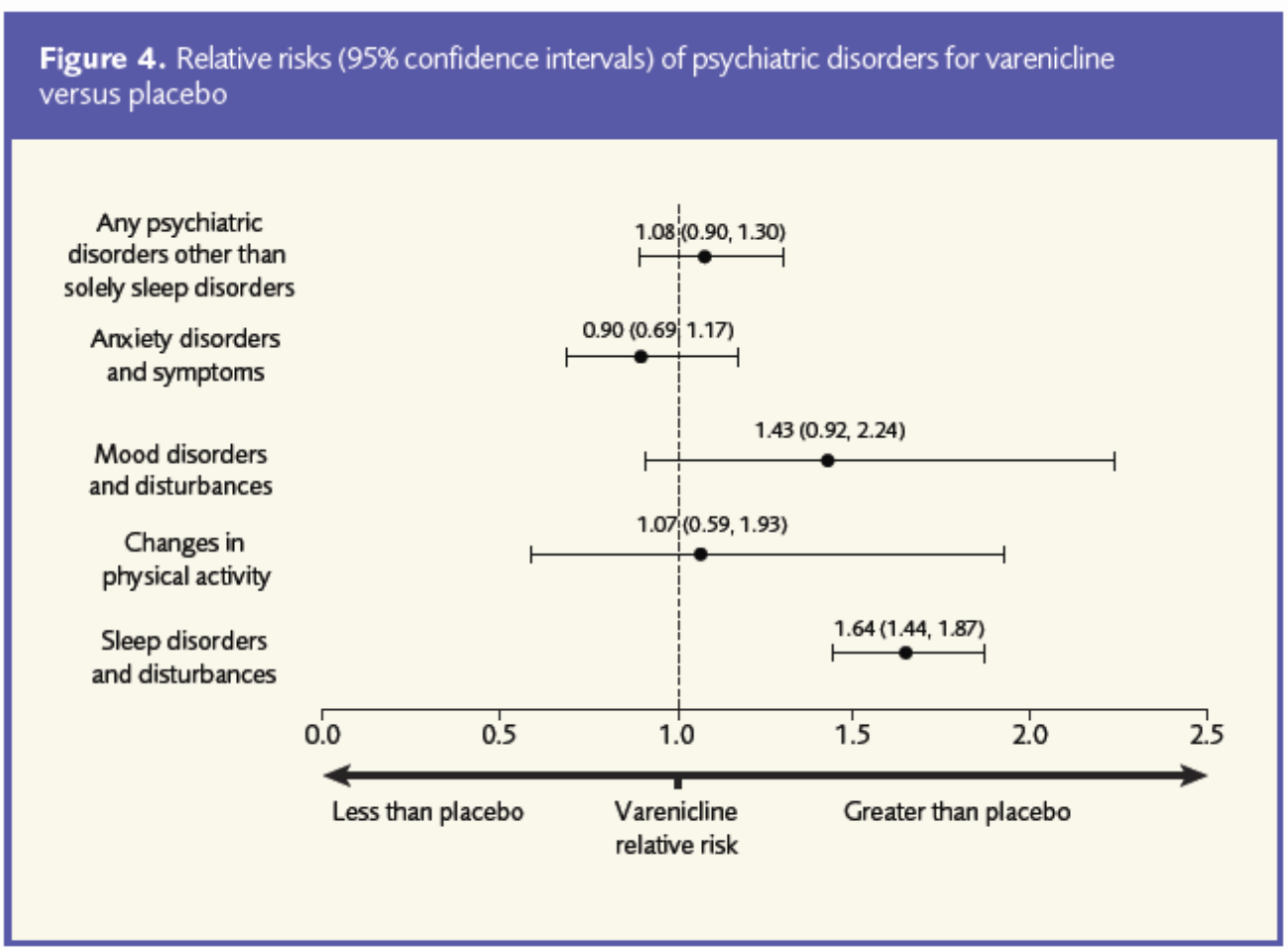


Tonstad, Flammer, Davies, Russ. 2008 SRNT Europe, Rome, Italy

Tonstad, Davies, Flammer, Russ, Hughes. Drug Safety 2010;33:289-301.

Psychiatric adverse events other than depression in Varenicline RCT's

N=2738 varenicline; 795 bupropionSR; 1655 placebo



Russ, Davies, Flammer, Tonstad. 2008 SRNT Europe, Rome, Italy

Tonstad, Davies, Flammer, Russ Hughes. Drug Safety 2010;33:289-301

Varenicline and Self-harm

Gunnel D, et al. BMJ 2009;339:b3805

Table 2 | Relative risks of fatal and non-fatal self harm, suicidal thoughts, and depression in people prescribed different smoking cessation products*

Smoking cessation product	No of events/No of people prescribed the product	Hazard ratio (95% CI)	
		Adjusted for age and sex	Fully adjusted†
Fatal and non-fatal self harm			
Nicotine replacement	141/63 265	1.0	1.0
Bupropion	9/6422	0.66 (0.33 to 1.29)	1.17 (0.59 to 2.32)
Varenicline	18/10 973	0.71 (0.43 to 1.16)	1.12 (0.67 to 1.88)
Suicidal thoughts			
Nicotine replacement	30/63 265	1.0	1.0
Bupropion	2/6422	0.69 (0.16 to 2.90)	1.20 (0.28 to 5.12)
Varenicline	5/10 973	0.94 (0.36 to 2.42)	1.43 (0.53 to 3.85)
Start of antidepressant therapy‡			
Nicotine replacement	1792/49 415	1.0	1.0
Bupropion	160/5719	0.86 (0.73 to 1.01)	0.91 (0.77 to 1.07)
Varenicline	292/9162	0.82 (0.72 to 0.93)	0.88 (0.77 to 1.00)

N=80,660

Varenicline and Neuropsychiatric Symptoms

- Advise patients and family members that this has been observed
- Ask patients and/or family to report any symptoms like this to you
- Patients with serious psychiatric comorbidity were not included in clinical trials
- No cause and effect relationship has been established

Varenicline and Cardiovascular Serious Adverse Events

Varenicline and Cardiovascular Risk-2011

The U.S. Food and Drug Administration (FDA) is notifying the public that the smoking cessation aid Chantix (varenicline) may be associated with a small, increased risk of certain cardiovascular adverse events in patients who have cardiovascular disease.

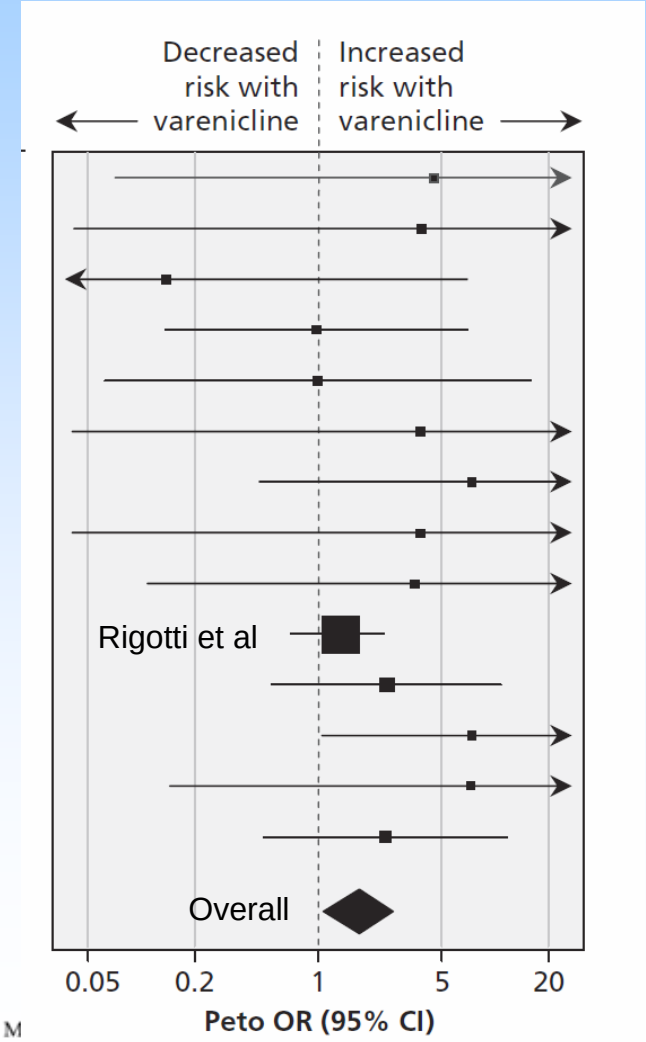
Varenicline in Stable CVD

Rigotti NA, Pipe AL, Benowitz NL, Arteaga C, Garza D, Tonstad S. Efficacy and safety of varenicline for smoking cessation in patients with cardiovascular disease: a randomized trial. *Circulation* 2010;121:221-9.

Adjudicated Cardiovascular Events During the 52-Week Study Period (≥1% in any group)

	Varenicline N=353* n (%)	Placebo N=350 n (%)
Nonfatal myocardial infarction	7 (2.0)	3 (0.9)
Need for coronary revascularization	8 (2.3)	3 (0.9)
Hospitalization for angina pectoris	8 (2.3)	8 (2.3)
New diagnosis of peripheral vascular disease (PVD) or admission for a procedure for the treatment of PVD	5 (1.4)	3 (0.9)

Varenicline and Cardiovascular Serious Adverse Events (SAE)



Overall CV SAE rates:

- Varenicline 52/4908 (1.06%)
- Placebo 27/3308 (0.82%)
- Peto OR 1.72 (95% CI 1.09 to 2.71)

Singh S, et al. Risk of serious adverse cardiovascular events associated with varenicline: a systematic review and meta-analysis. CMAJ 2011 [July 4]. doi:10.1503/cmaj110218

Varenicline and Cardiovascular Serious Adverse Events (SAE)

Hays JT. Varenicline for smoking cessation: is it a heartbreaker? CMAJ 2011 [July 4].doi:10.1503/cmaj110218

- ***Problems with the Singh et al (CMAJ 2011) meta-analysis…***
  - **Cardiovascular SAE's were rare in both groups**
    - **Only 0.82% placebo, and 1.06% varenicline**
    - **Absolute difference 0.24%**
  - **Greater numbers lost to follow-up in placebo arms**
    - **Lost opportunity to count CV events in placebo subjects**
    - **Bias in favor of fewer CV events ascertained in placebo arms**
  - **No adjudication of CV events in all but one study**
  - **The only clinical trial of varenicline efficacy among subjects with known CVD raised no safety concerns (Rigotti et al. Circulation 2010;121:221-229)**

Varenicline and cardiovascular risk

Hays JT. Varenicline for smoking cessation: is it a heartbreaker?
CMAJ 2011 [July 4].doi:10.1503/cmaj110218

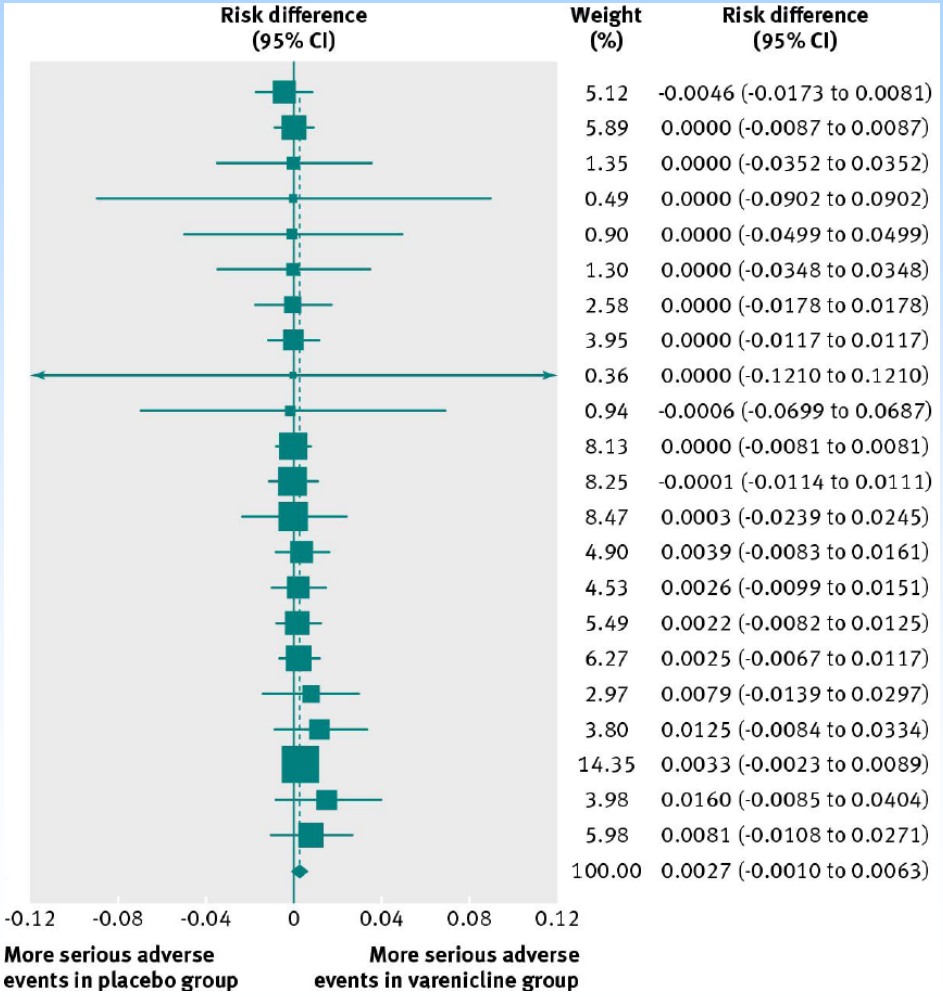
KEY POINTS

- When used as a treatment for tobacco dependence, varenicline may be associated with an increase in adverse cardiovascular events.
- The absolute increase in the rate of serious cardiovascular events associated with varenicline versus placebo is less than 1% based on analysis of more than 8200 participants involved in 13 randomized clinical trials.
- Smoking kills more than half of persistent smokers and reduces life expectancy by up to 10 years, whereas smoking cessation rapidly reduces the risk of future cardiovascular events.
- Varenicline should continue to be used with appropriate caution to limit adverse effects, while capitalizing on its benefits for smoking cessation.

Risk of cardiovascular serious adverse events associated with varenicline use for tobacco cessation: systematic review and meta-analysis

Judith J Prochaska *associate professor*[1], Joan F Hilton *professor*[2]

BMJ 2012;344:e2856 doi: 10.1136/bmj.e2856 (Published 4 May 2012)



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Risk of cardiovascular serious adverse events associated with varenicline use for tobacco cessation: systematic review and meta-analysis

Judith J Prochaska *associate professor*[1], Joan F Hilton *professor*[2]

BMJ 2012;344:e2856 doi: 10.1136/bmj.e2856 (Published 4 May 2012)

Our meta-analysis of all published, randomised controlled trials of varenicline use for tobacco cessation included 50% more studies than a previous meta-analysis by Singh and colleagues; used an unbiased summary estimate and compared findings with three other estimates; and examined events that occurred during drug treatment, which is more biologically relevant and obviates problems with differential drop out

All four summary estimates indicated no significant increase in the risk of treatment emergent, cardiovascular serious adverse events attributed to varenicline use

Varenicline and CVD Risk

- One meta-analysis with increased risk of CV serious adverse events and one with no difference
- RCT in smokers with known CVD found no significantly increased risk of CV adverse events
- FDA notes absolute increased risk of CV events
- Causal association of CVD adverse events and varenicline use remains uncertain

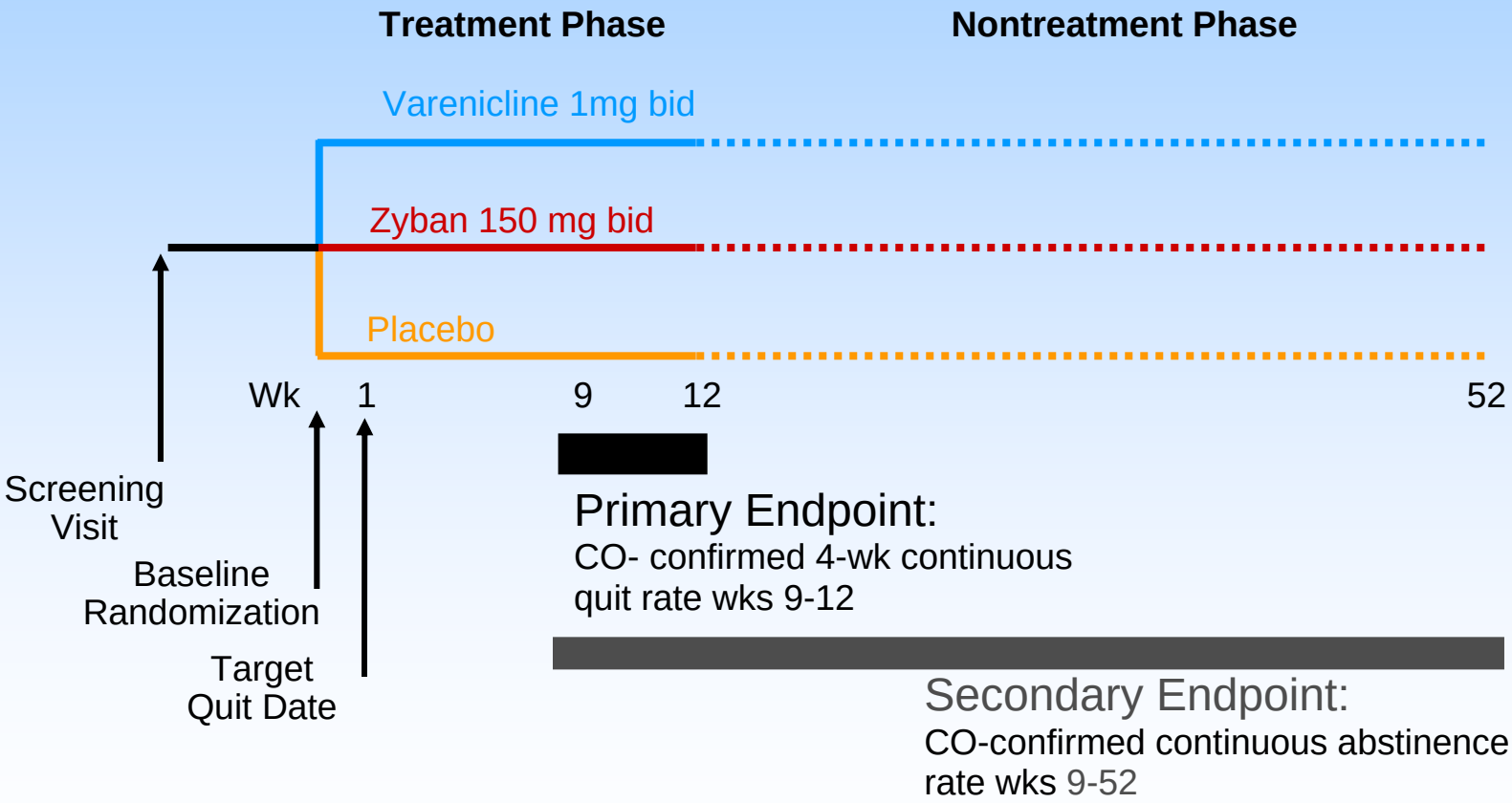
Risk is relative!

Varenicline Efficacy Overview

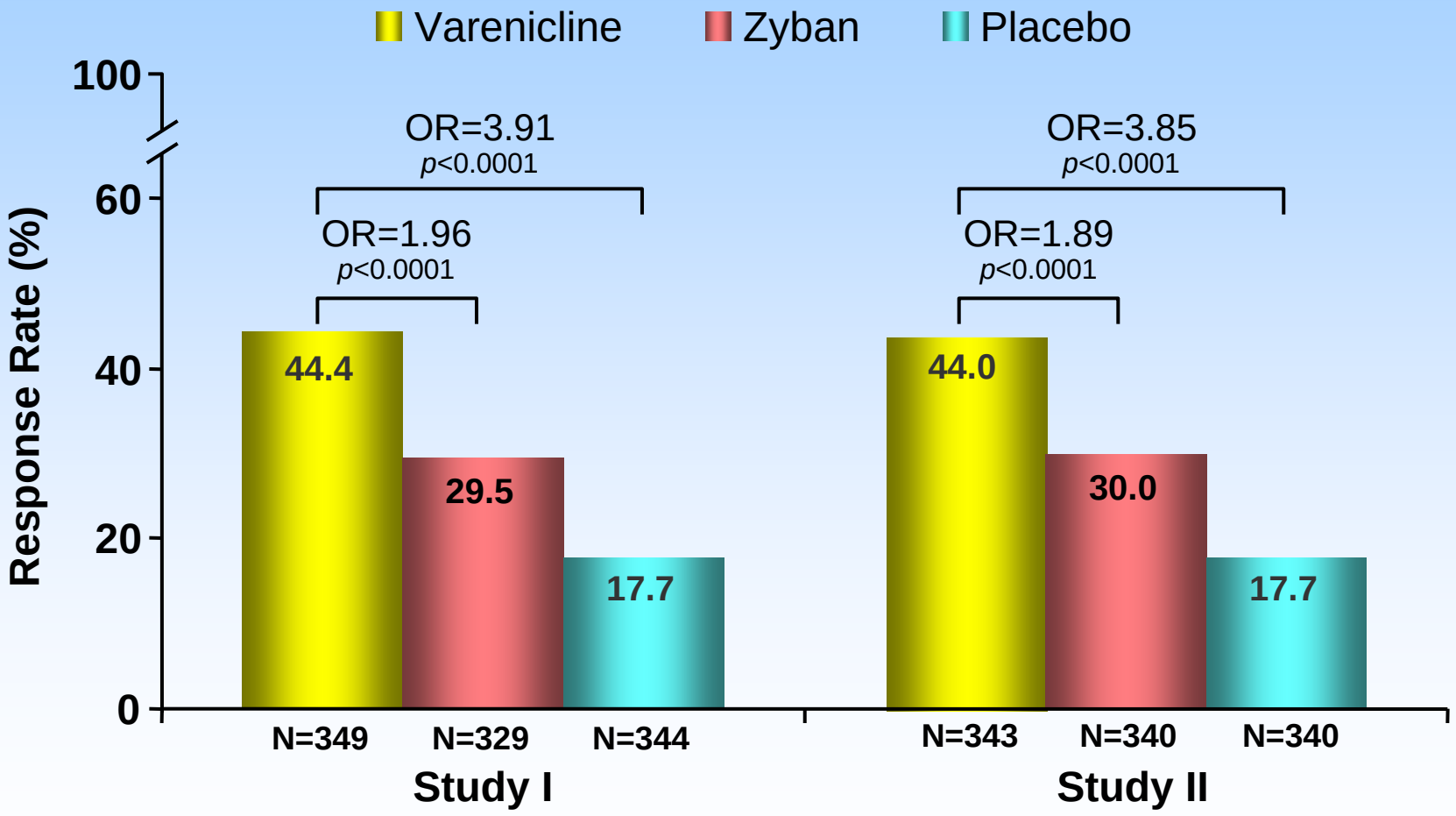
Phase 3 Trials and Meta-analyses

Varenicline Pivotal Trials Design

Subjects are 18-75 yr old, Zyban naïve, average ≥10 CPD past year

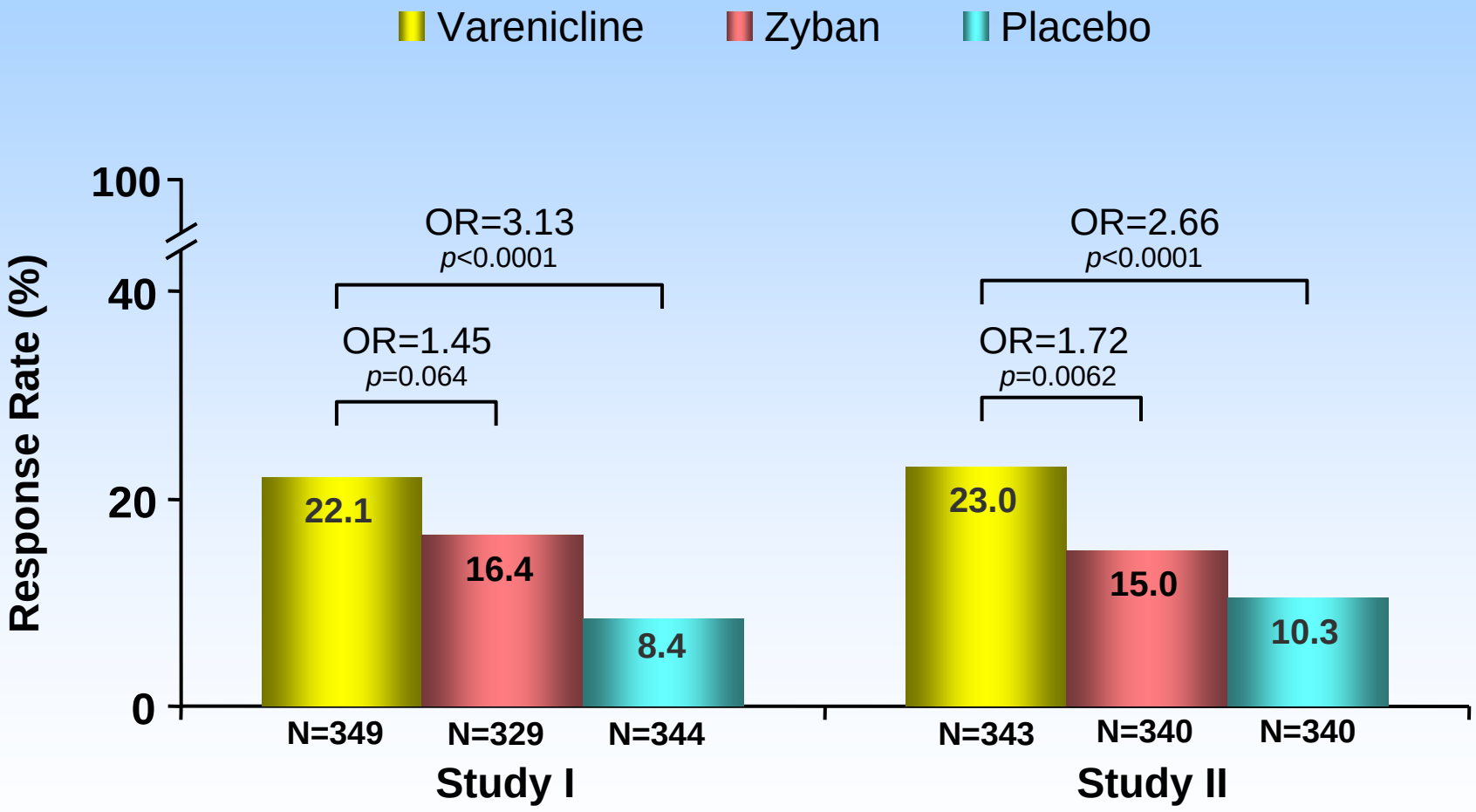


Pivotal Trials: CO-Confirmed Continuous Abstinence Rates Wks 9-12



Jorenby et al. JAMA 2006;296:56-63

Pivotal Trials: CO-Confirmed Continuous Abstinence Rates Wks 9-52



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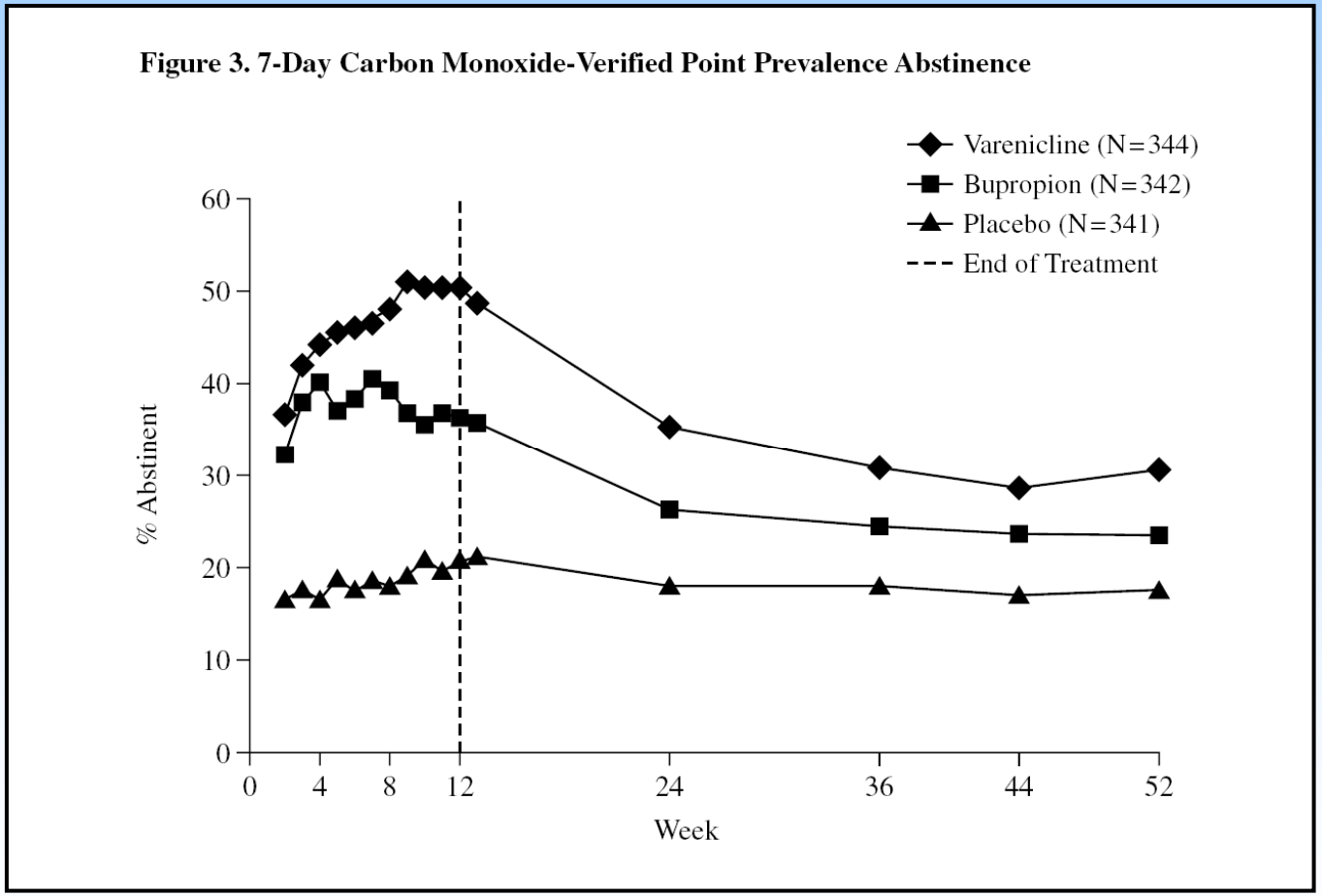
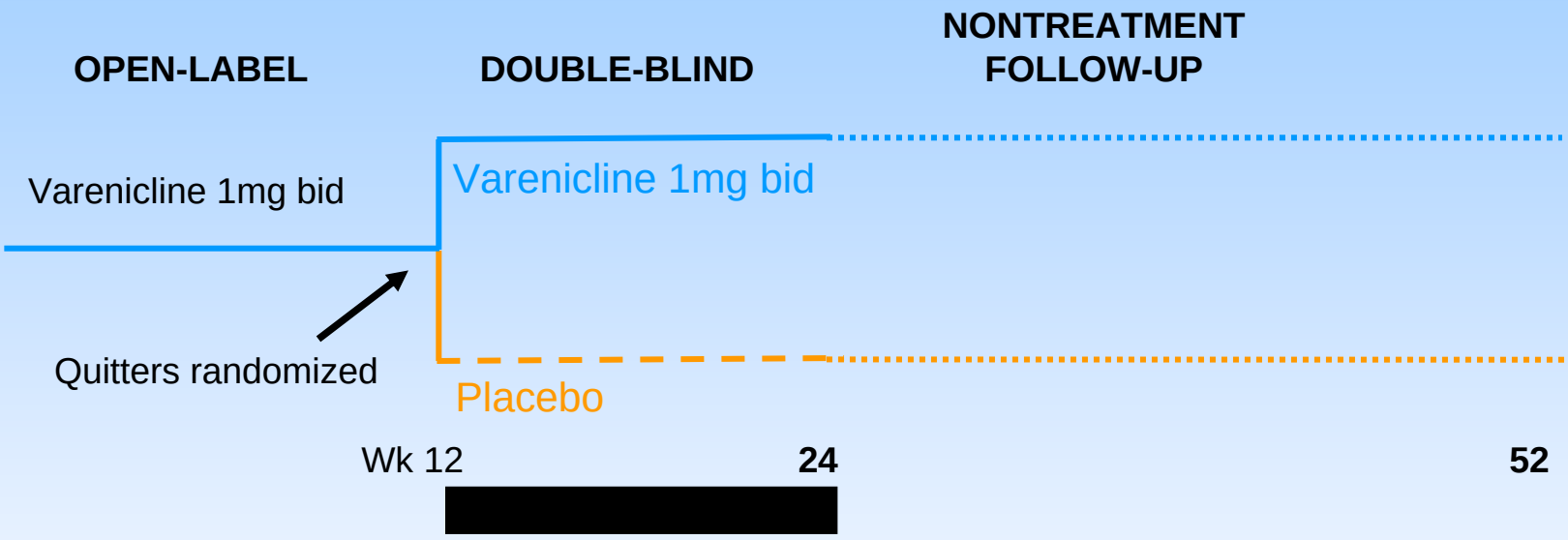
7-Day Point Prevalence Abstinence



Jorenby et al. JAMA 2006;296:56-63

Maintenance of Abstinence: Study Design



Primary Endpoint:

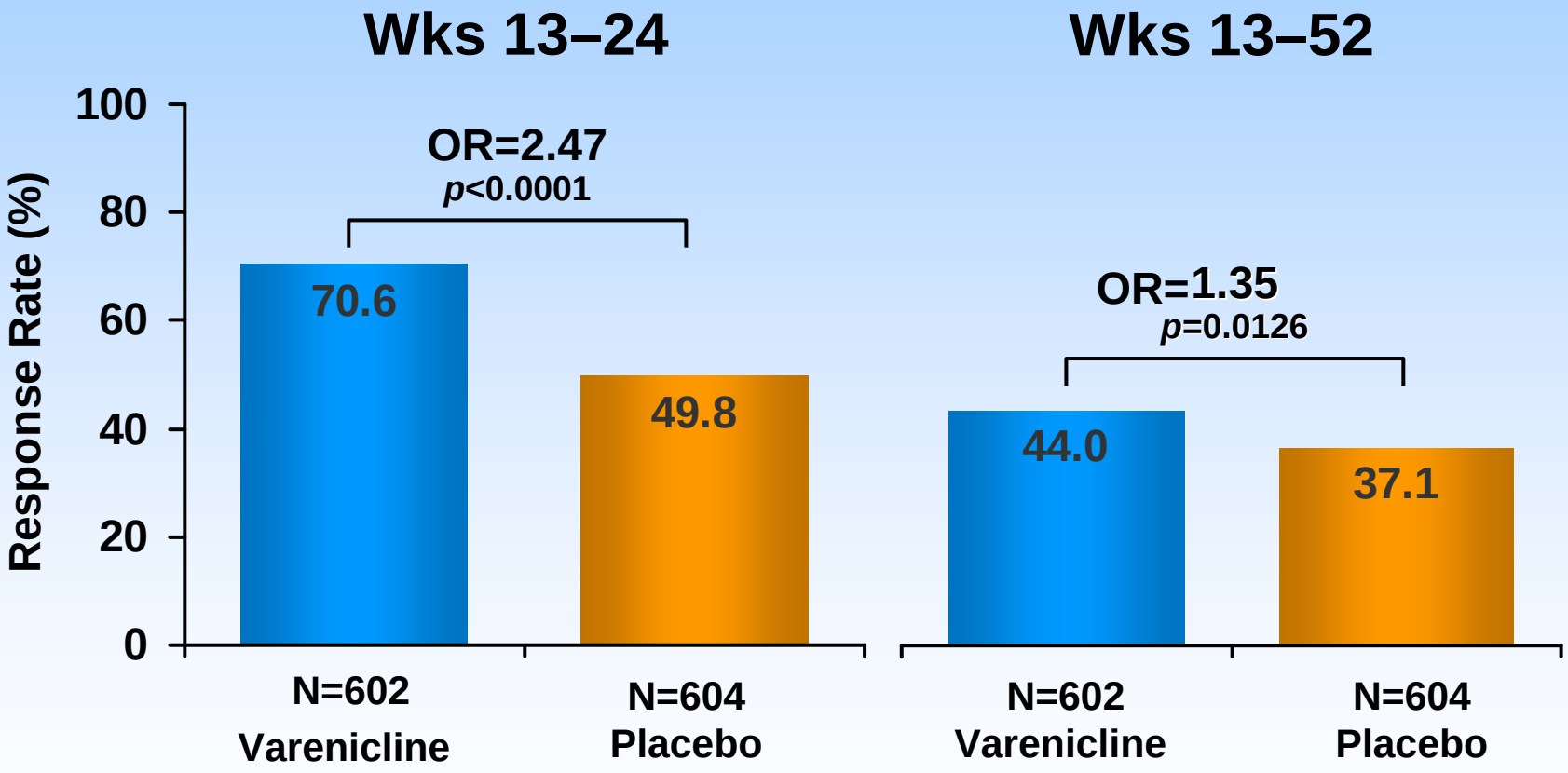
- CO-confirmed continuous abstinence rate wk 13-24

Secondary Endpoint:

- CO-confirmed continuous abstinence rate wk 13–52

Tonstad et al. JAMA 2006;296:64-71

Maintenance of Abstinence Study: CO-confirmed Continuous Abstinence Rates



Nicotine receptor partial agonists for smoking cessation

Cahill, Kate; Stead, Lindsay F; Lancaster, Tim

Cochrane Database of Systematic Reviews. Issue 2, 2011.

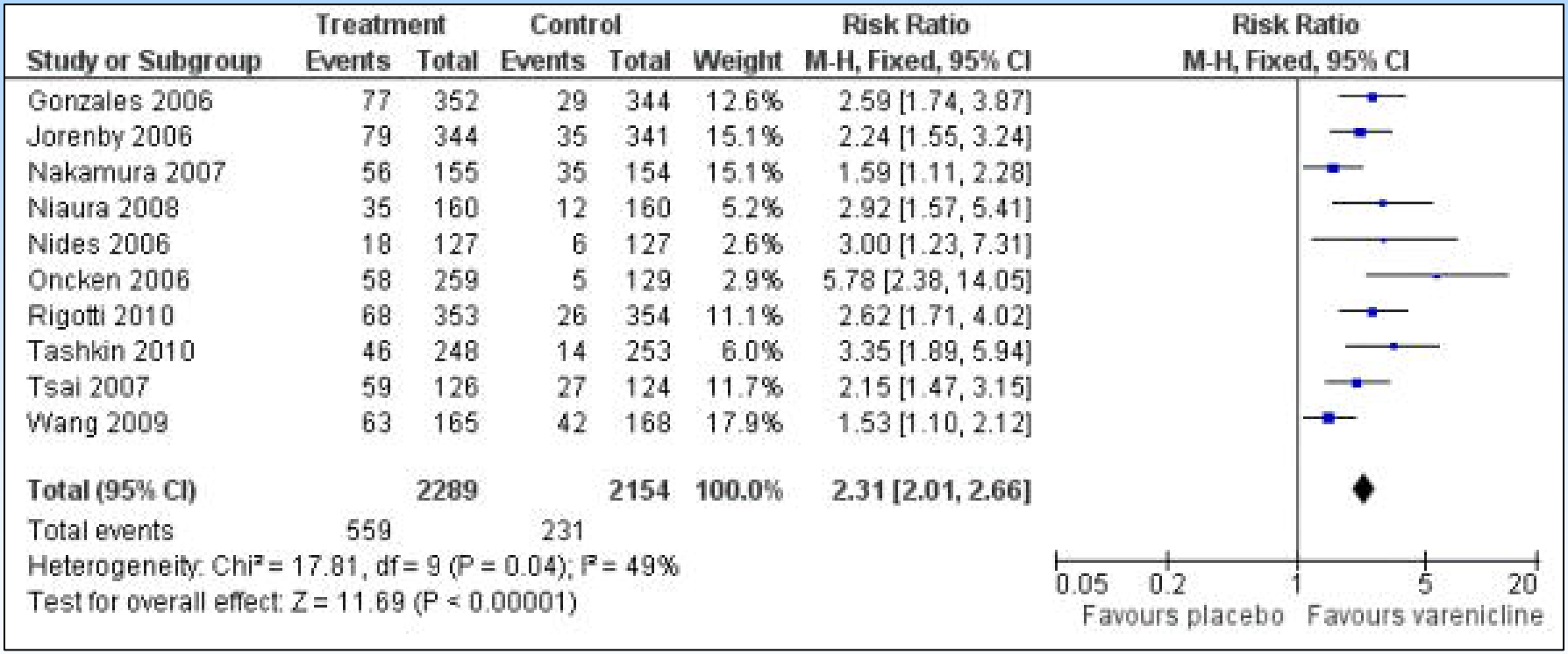


Figure 2 . Forest plot of comparison 1: Varenicline (1.0mg 2/d) vs placebo, outcome: 1.1 Continuous abstinence at longest follow up (24+ weeks)

Pharmacotherapies for smoking cessation: a meta-analysis of randomized controlled trials

Pharmacotherapy	Odds ratio (95% CrI)
Bupropion	2.12 (1.76–2.56)
Nicotine gum	1.65 (1.37–2.01)
Nicotine inhaler	2.18 (1.38–3.45)
Nicotine nasal spray	2.37 (1.57–3.60)
Nicotine patch	1.88 (1.60–2.22)
Nicotine tablet	2.06 (1.47–2.87)
Varenicline	2.55 (1.99–3.24)

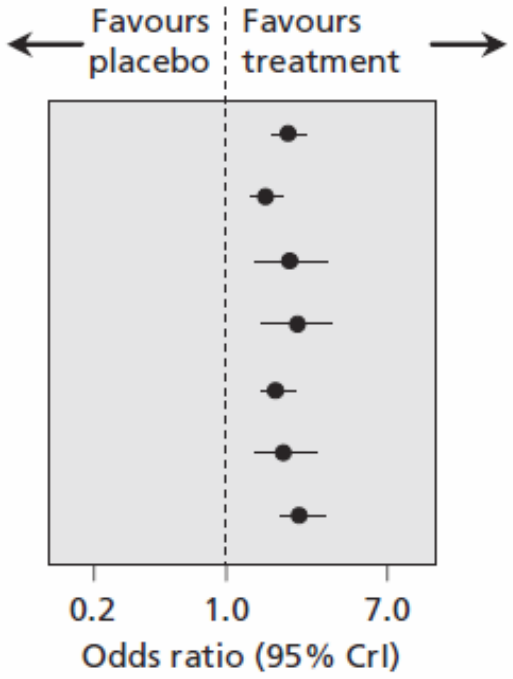


Figure 6: Summary estimates of the effect of pharmacotherapies for smoking cessation on the odds of smoking cessation. Smoking cessation is defined by the most rigorous criterion of abstinence (see Figure 2 caption for definition and ranking). Data have been adjusted for mean age, sex and mean number of cigarettes per day. CrI = credible interval.

Eisenberg MJ, et al. CMAJ 2008; 179:135-144

Varenicline Efficacy

- Varenicline 1 mg twice daily is efficacious for tobacco dependence treatment (O.R. compared with placebo about 2.5)
- Varenicline is superior to bupropion for tobacco dependence treatment (O.R. about 1.5 to 1.9)
- Meta-analyses consistently provide point estimates of efficacy (vs placebo) greater than other approved pharmacotherapies

Decisional Balance

How safe is varenicline?

How harmful is smoking?

The Toll of Smoking

The modern cigarette is the only consumer product ever produced that when used exactly as the manufacturer intended, will kill over half of its loyal customers.

The Toll of Smoking

- The leading cause of preventable death
- Over 400,000 deaths per year
- Nearly $200 billion direct and indirect health-related costs per year
- Disproportionately affects those with lower income, less education and higher burden of mental illness

Treatment Decision: Balancing Benefits, Harms and Alternatives

- What is the real risk of serious harm from varenicline treatment?
- What is the real risk of harm from continued smoking?
- Are there treatment alternatives that are nearly as effective but safer?
- Is “no treatment” a reasonable alternative?

Conclusions

- Smoking causes serious adverse health effects and a marked increased risk of premature mortality in regular users
- The only way to reduce the risk is to stop smoking
- Varenicline increases the odds of long-term smoking abstinence by 2-3 times
- Varenicline is associated with serious adverse effects in a fraction of users; causality is not established
- Alternative treatments are available of equal or lesser efficacy, but not proven to be safer

Treatment Facts

- At clinic visits with a provider…
  - 90% of smokers report being asked about smoking status
  - 70% report receiving brief counseling to quit
  - Most smokers offered treatment had tobacco related illness already
- Among smokers who attempted to stop for at least one day in the past year…
  - Only 22% used pharmacotherapy

(Fiore M, et al. Treating Tobacco Use and Dependence Clinical Practice Guideline: 2008 update)

Varenicline Prescribing

- Use in combination with behavioral treatment
- Start medication 1 week prior to target quit date
  - Days 1-3, Varenicline 0.5mg daily
  - Days 4-7, Varenicline 0.5mg twice daily
  - Day 8 to end of treatment 1.0mg twice daily
  - TQD on day 8
- Take with food
- Dose reduction with severe renal impairment
- Supplied as starter card (11X0.5mg tabs) and 4-week packs of 1 mg BID or bottles of 56
- Treat for 3 to 6 months

Additional Prescribing Information

- No dose reduction needed in…
  - Geriatric population
  - Patients with liver disease
- No important drug-drug interactions
- Reduce dose in renal impairment
  - Estimated creatinine clearance <30 ml/min reduce dose to 0.5 mg daily and titrate to
    0.5 mg BID as tolerated

Managing Adverse Effects of Tobacco Dependence Pharmacotherapy

- Review proper adherence
- Try a lower dose
  - Many of the AE's are dose dependent
  - Temporary reduction and re-challenge
  - Permanent reduction
- Alter the dosing schedule
  - Nausea- take with meals
  - Insomnia- take well before bedtime
  - Abnormal dreams- reduce or eliminate the evening dose (for patch remove at bedtime)
- Discontinue if concern about a serious AE

Managing Adverse Effects of Varenicline

- Patients should be advised to stop the drug and call their prescriber if changes in behavior or thinking occur
- Nausea: ramp-up slowly; take with food; take with 8-12 oz. water; lower the dose
- Sleep disturbance: lower the dose
- Reduce the dose if GFR is < 30

Where are we now?

- Over 40 million adults still smoke in the US
- It is a growing problem globally
- More people are receiving minimal interventions
- Most do not receive the most effective treatment: combined counseling and pharmacotherapy
- There is a growing divide between tobacco control advocates
  - Only public health approaches (e.g., taxation, plain packaging, smoke-free policies) should be supported
  - Tobacco dependence treatment along with policy change is most effective

From approval in May 2006 through July 2011, approximately 21.8 million Chantix prescriptions were dispensed and approximately 8.9 million patients received Chantix prescriptions from U.S. outpatient retail pharmacies.

