

# Review of the Clinical Literature on Psychiatric Adverse Events Associated with Varenicline in Smokers With Psychiatric Co-morbidities

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Varenicline: Where are we Today?

UCSF Tobacco-Related Disease Research Program,

September 20, 2010

## **Current Research Funding: Evins**

NIDA R01 DA021245 Smoking cessation and relapse prevention in schizophrenia  
Pfizer: Supplemental support for the NIDA funded trial: Extended Duration Varenicline for Prevention of Smoking in Schizophrenia

NIDA R01 DA030992 Trial of an alpha-7 nicotinic agonist for nicotine dependence  
Envivo Pharmaceuticals: Supplemental support for the NIDA funded Proof of Concept Trial of an Alpha-7 Nicotinic Agonist for Nicotine Dependence

NIDA U01 DA019378 Cooperative drug discovery group for nicotine dependence  
GSK: Supplemental support for NIDA funded Cooperative Drug Discovery Group for Nicotine Dependence

NIDA R21 DA030808 Cognitive remediation to improve smoking outcomes

NIDA R21 DA030523 Enhancing self-control of craving with real-time fMRI

NIDA R21 DA031925 Concurrent PET D2/D3 receptor imaging and fMRI cue reactivity in smokers

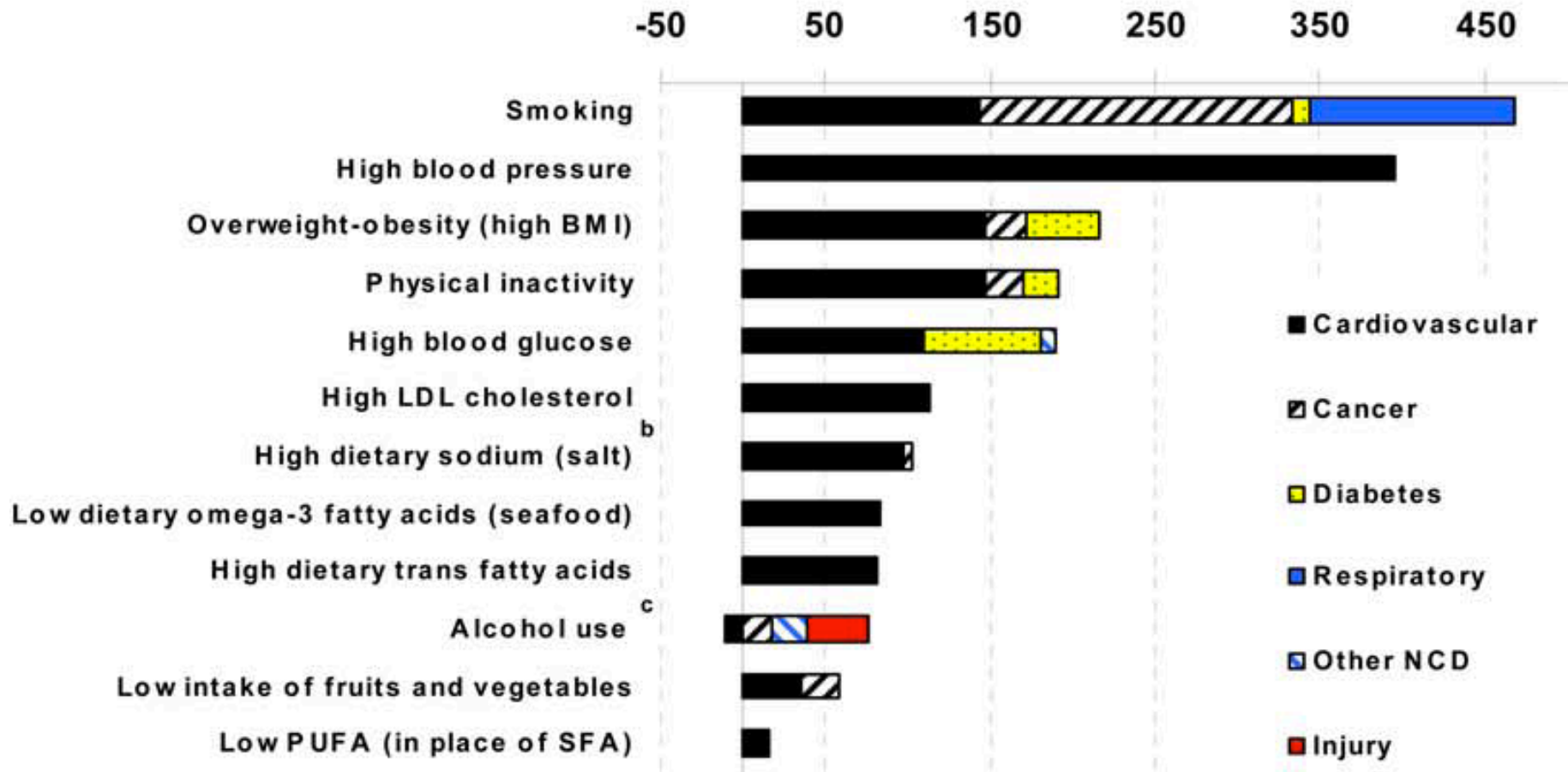
NIDA K24 DA030443 Mentoring in addiction treatment research

**Consulting Past 24 Months:** Pfizer, DLA-Piper, Boehringer-Ingelheim

Varenicline: Where are we Today?, UCSF Tobacco-Related Disease Research Program,  
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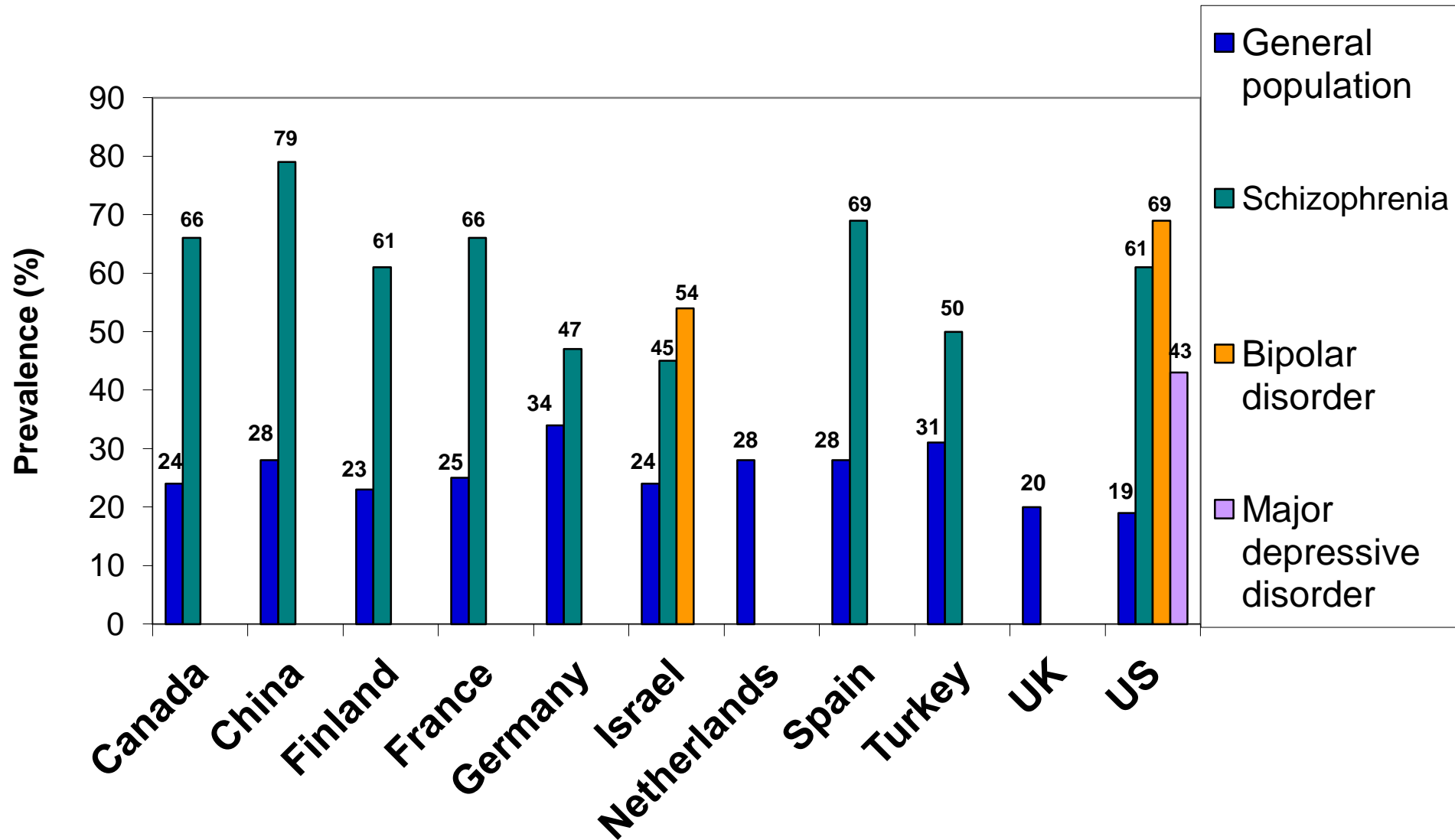
# Mortality Effects of Tobacco Smoking (US)

Cause of 435,000 (18.1%) of all Deaths in US in 2000\*



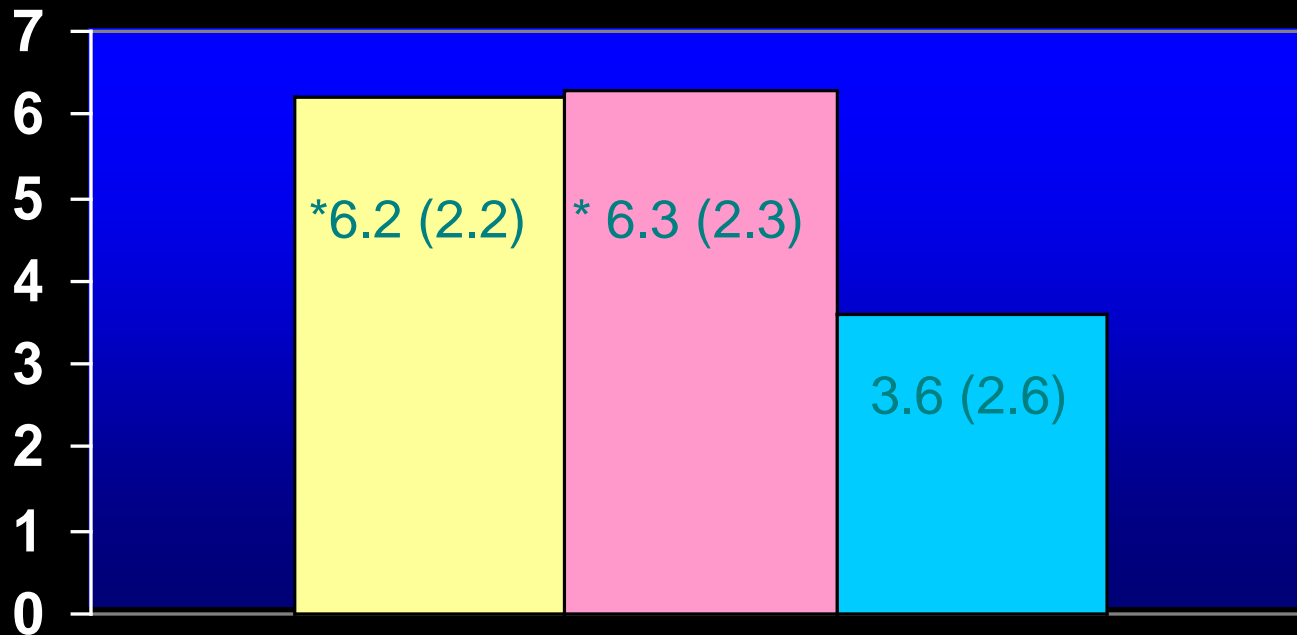
\*Mokdad, et al., JAMA 2004; Danaei, et al., PLoS Med 2009 (2003-2005)

# People with Mental Illness Are More Likely to Smoke



# Relative Severity of Dependence Fagerstrom Test for Nicotine Dependence

■ schizophrenia ■ mood disorder ■ control



\*  $p < 0.001$  vs controls



## **Smokers with mental illness are more likely to smoke heavily**

Smokers with schizophrenia are more likely to smoke, smoke more cigarettes per day, have more frequent puffs, greater puff volume, extract more nicotine per cigarette and are more heavily nicotine dependent than smokers in the general population

US: over half of cigarettes are sold to someone with a mental illness

UK: many with schizophrenia spend 1/3 of their monthly income on cigarettes

McDonald et al., 2000; McCreadie et al., 2000; Tidey, et al., 2005; Olincy, et al., 1998; Willams, et al., 2005; DeLeon et al., 2002.



## Comorbidity

**21-31% of those with nicotine dependence in the US have a current mood, anxiety, personality disorder, or other substance use disorder**

**Among those with a current non-psychotic psychiatric disorder 25-52% had nicotine dependence**

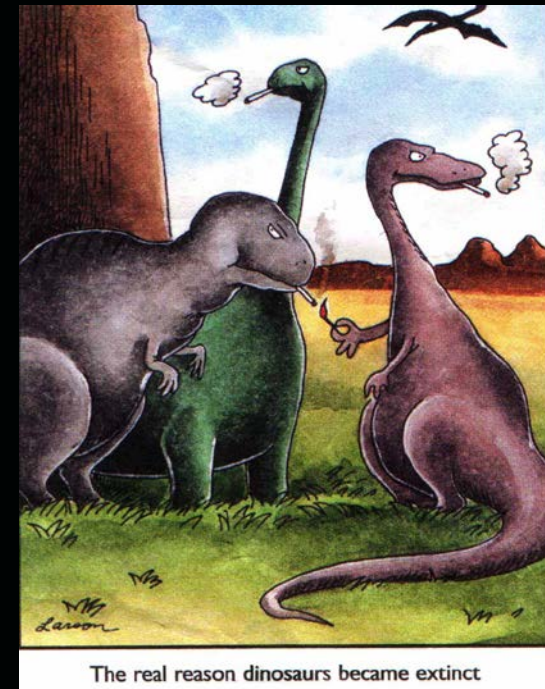
# Smoking, Schizophrenia and Mortality

People with schizophrenia die 10-25 years earlier than do those in the general population, and natural deaths account for 59% of the excess mortality.

Age-adjusted rates of death due to pulmonary disease are elevated by as much as 130% in schizophrenia.

Hannerz, Borga, & Borritz, 2001; Brown, 1997;

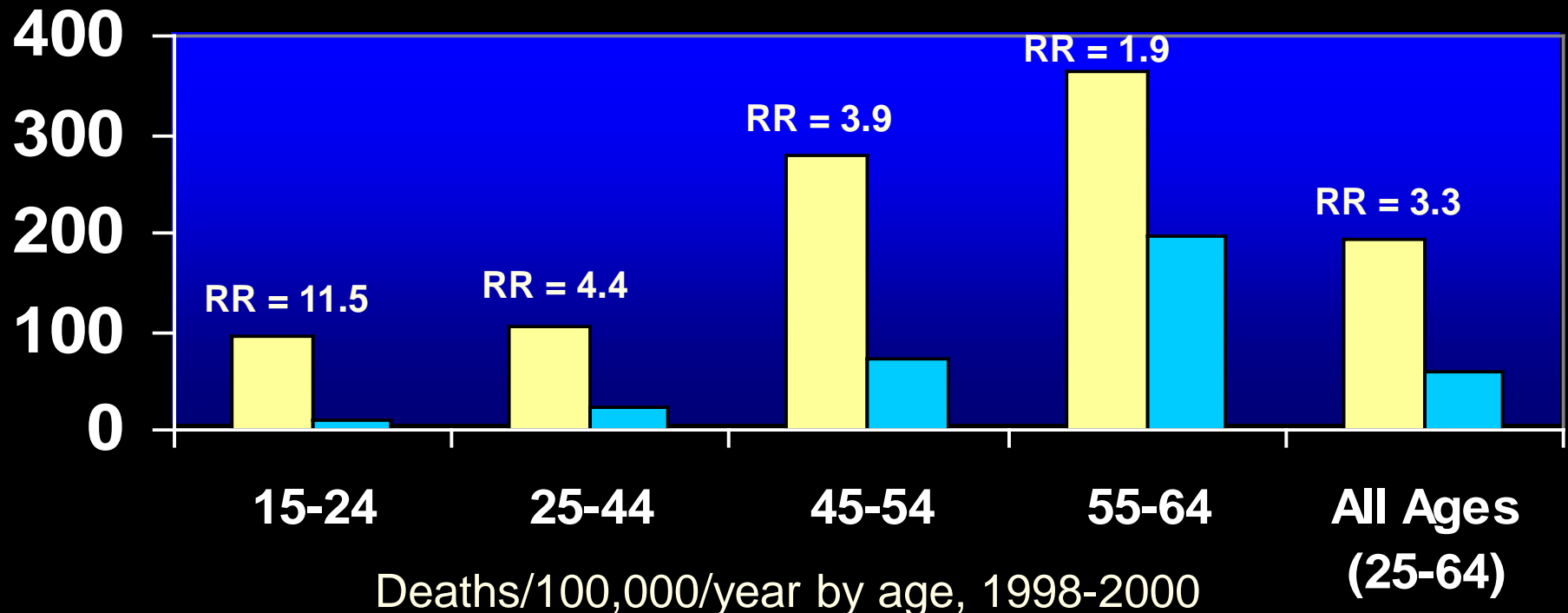
Harris & Barraclough, 1998; Joukamaa et al., 2001;  
Reviewed in: Goff, Cather, et al., 2005





# Cardiac Deaths: Massachusetts Dept of Mental Health vs. General Population

■ DMH ■ Mass



Mortality Report 2000: The Commonwealth of Massachusetts Executive OHHS, DHH; 2000.  
See also Goff et al., 2005 for 10 year cardiac risk estimates from the CATIE study

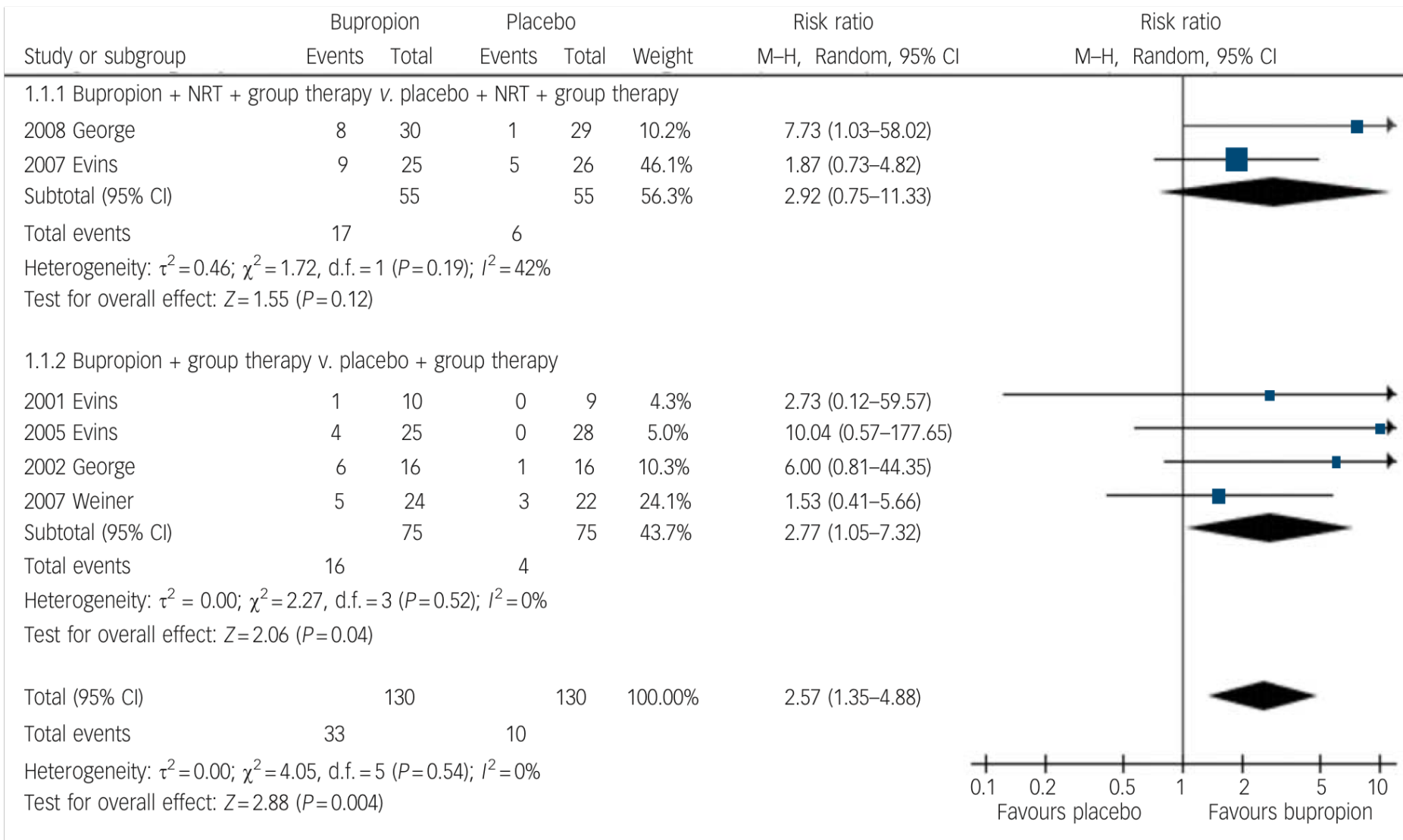
# Smokers with Major Mental Illness

- In general report that they want to quit smoking
- Are not often encouraged by their treaters to quit smoking
- Can (and should be encouraged to) quit smoking
  - Standard treatment regimens with evidence of efficacy
- Have been excluded from clinical trials

Tidey et al., 2002; George et al., 2000, 2002, 2008;  
Evins et al., 2002, 2005, 2007, 2008; Tsoi et al., 2010;  
Hall et al., 1996, 2006; Haung et al., 2005;  
Tonstad et al., 2002, Prochaska, et al., 2008, 2011



# Bupropion ± NRT Added to CBT Improves Abstinence Rates in Smokers with Schizophrenia



# Smoking Cessation Treatment for those with Depression

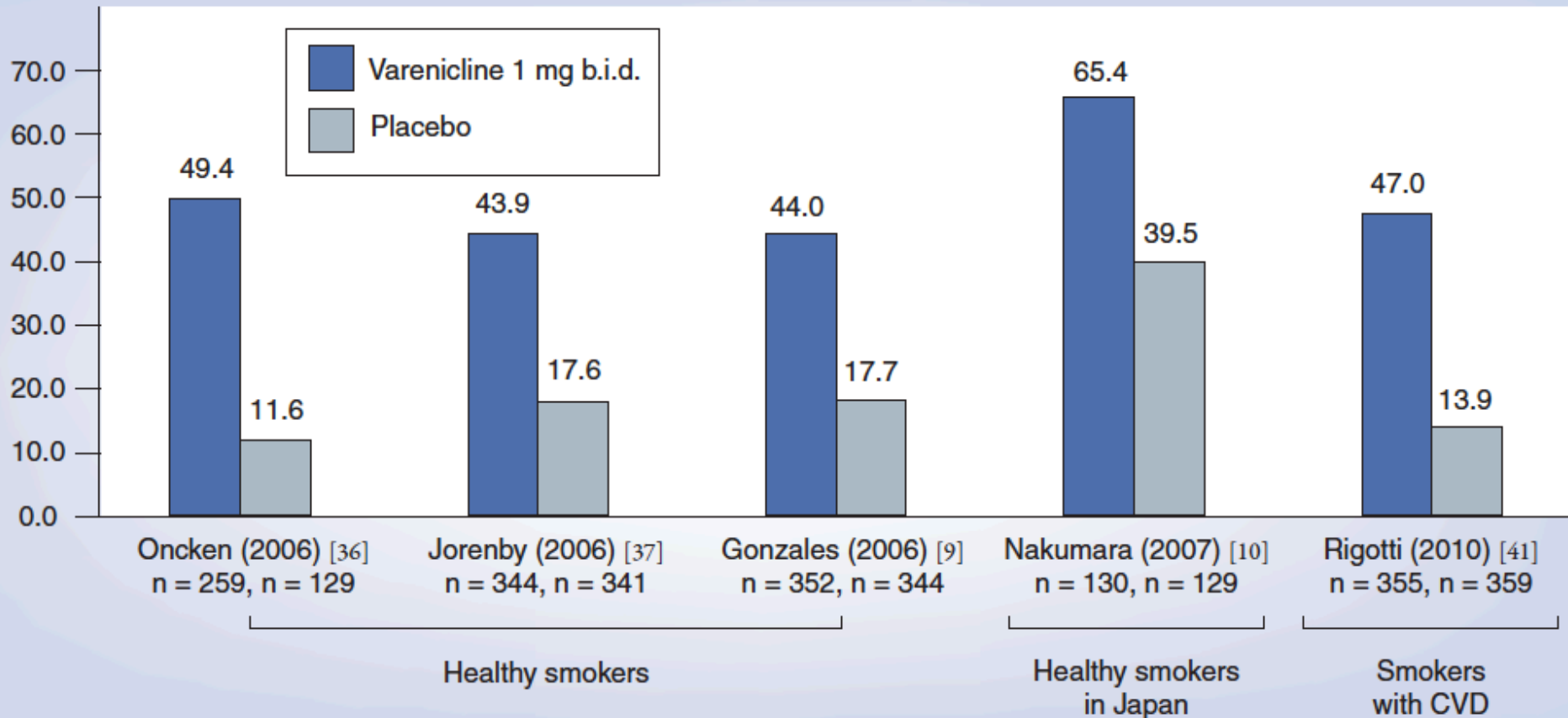
Cochrane Review Meta-analysis of RCT's of smoking cessation aids in smokers with past or current MDD

Preliminary analyses:

Behavioral mood management added to standard smoking cessation interventions effective in those with current or past MDD

Antidepressant pharmacotherapy, particularly bupropion, effective in those with past but not present MDD

# Pharmacotherapy Standard Smoking Cessation Tx: Varenicline May Offer Superior Efficacy



Varenicline superior to placebo at 12 weeks in 5 large RCT's  
Superior to bupropion in 3 Trials

Tonstad and Rollema, 2010

# Psychiatric Adverse Events

- Post marketing reports of psychiatric adverse events with varenicline. Concern that smokers with psychiatric illness were excluded from clinical trials.
- Prospective trials have not demonstrated an association between varenicline and psychiatric adverse events in smokers in the general population of 'real world smokers' or in smokers with depressive disorders or schizophrenia
- Controlled trials have not demonstrated an association between varenicline and psychiatric adverse events in smokers with schizophrenia

# Nicotine Dependence Strongly, Independently Assoc with Suicide

- Nicotine dependence independently assoc with suicidal ideation, attempts and completed suicide in mltiple large studies controlling for psychiatric illness and alcohol use. Beratis 1997; Miller 2000; Breslau 05; Bronisch 08; Donald 06; Hawton 02; Hintikka 09; Kessler 09; Martinez-Ortega 08; Tanskanen 2000
- In some studies this assoc is lost when controlling for comorbid psychiatric illnesses common in smokers also assoc with increased rates of suicide. Hemmingsson 03; Kessler 07
- In a nat. representative sample, nicotine dependence had the 3<sup>rd</sup> highest PAF for suicide attempts of any Axis I or II disorder, after MDD and BPD, higher than PTSD Bolton and Robinson 2010

# Psychiatric Adverse Events

- The nicotine withdrawal syndrome itself includes depressed mood and irritability.



# Psychiatric Adverse Events

- Case reports and pharamcovigilance reports of psychiatric adverse events with varenicline
- Prospective trials have not demonstrated an association between varenicline and psychiatric adverse events in smokers in the general population of 'real world smokers' or in smokers with depressive disorders or schizophrenia
- Controlled trials have not demonstrated an association between varenicline and psychiatric adverse events in smokers with schizophrenia

# Observational Studies – Gunnell et al., 2009

- 80,660 smokers from UK Gen. Practice Research Database
- Varenicline, NRT, or bupropion treatment
- No evidence of increased risk of depression, suicidal thoughts, or self harm during smoking cessation attempt with varenicline

	<b>Study Endpoint</b>	<b>Varenicline vs. NRT</b>	<b>Varenicline vs. Bupropion</b>
Relative Risk Varenicline vs. NRT or Bupropion	Fatal/non-fatal self-harm	1.12 (0.67-1.88)	1.17 (0.59-2.32)
	Suicidal Thoughts	1.43 (0.53-3.85)	1.20 (0.28-5.12)
	Start of Antidepressant Therapy	0.88 (0.77-1.00)	0.91 (0.77-1.07)

# Observational Studies – Boudrez et al., 2011

- 551 smokers
- 12 weeks varenicline treatment
- 64.6% successfully quit
- Most commonly reported neuropsychiatric symptoms: insomnia (2.9%), sleep disorder (2.2%), abnormal dreams (1.8%)
- “...in a real-world clinical practice setting outside a clinical trial environment, varenicline is an effective smoking cessation aid with an acceptable safety profile.” (Boudrez et al., 2011)

# Prescription Event Monitoring Studies – Harrison-Woolrych et al., 2011

- 3,415 smokers
- Varenicline treatment from April 2007 – March 2008
- Questionnaires sent to patients' physicians
- Authors documented 206 psychiatric events in 138 patients
- 38% response rate for questionnaire indicates substantial risk for reporting bias

# Observational Studies – Purvis et al., 2009

- 50 smokers, veterans
- Retrospective chart review, computerized records
- Standard 12 week varenicline treatment as part of a clinical performance initiative
- 24 patients with no preexisting mental illness and 5 with underlying mental illness reported psychiatric symptoms
- No reports of suicidal ideation, suicide attempt, or suicide
- 26% discontinued treatment due to adverse events
- Small sample

# Observational Studies – FDA-Sponsored VA Study, 2011

- 28,262 smokers, veterans
- Varenicline or NRT
- Retrospective cohort study that used propensity-matching to compare varenicline users to similar users of NRT
- No difference in psychiatric hospitalization within 30 days of initiating varenicline or NRT
- Limitation: did not include hospitalizations for PTSD

FDA Drug Safety Communication: Safety review update of Chantix (varenicline) and risk of neuropsychiatric adverse events. ([FDA.gov](https://www.fda.gov))

# Observational Studies – FDA-Sponsored DOD Study

- 23,956 smokers, veterans
- Varenicline or nicotine patch
- No difference in psychiatric hospitalization during smoking cessation attempt

# Observational Study of a Standard Clinical Intervention – Stapleton et al., 2007

- 412 smokers with and without psychiatric illness
- Varenicline or NRT
- Higher abstinence rates with varenicline vs NRT
- Varenicline equally effective in those with and without mental illness
- Symptoms of mental illness not worsened by varenicline
- No evidence of more frequent or more severe adverse events in group with mental illness



# Prescription Event Monitoring Studies— Kasliwal, 2009 (on-going)

- 2,682 smokers, Varenicline treatment
- Questionnaires completed by GP's
- Most frequent AE: nausea (35%)
- Most frequent psychiatric AE's: sleep disorder (1.6%), anxiety (1.2%), depression (1.1%), abnormal dreams (1.0%), mood change (0.6%)
- No completed suicides, two suicide attempts in patients with preexisting psychiatric illness and precipitating factor. Relation to varenicline tx undetermined
- No control group

# Prospective Open Trials – Pachas et al., 2012

- 112 stable, adult, outpatient smokers with schizophrenia and intention to quit
- 12 week varenicline treatment with weekly 1 hour group CBT sessions
- 43% (88 / 203) 14 day point prevalence abstinence at the end of treatment
- Weekly clinician ratings of symptoms: Improvement in standardized clinician ratings of psychotic symptoms, depressive symptoms and nicotine withdrawal symptoms
- No worsening of psychiatric symptoms

# Stable Psychiatric Symptoms During a Smoking Cessation Attempt with Varenicline In 100 Smokers with Schizophrenia

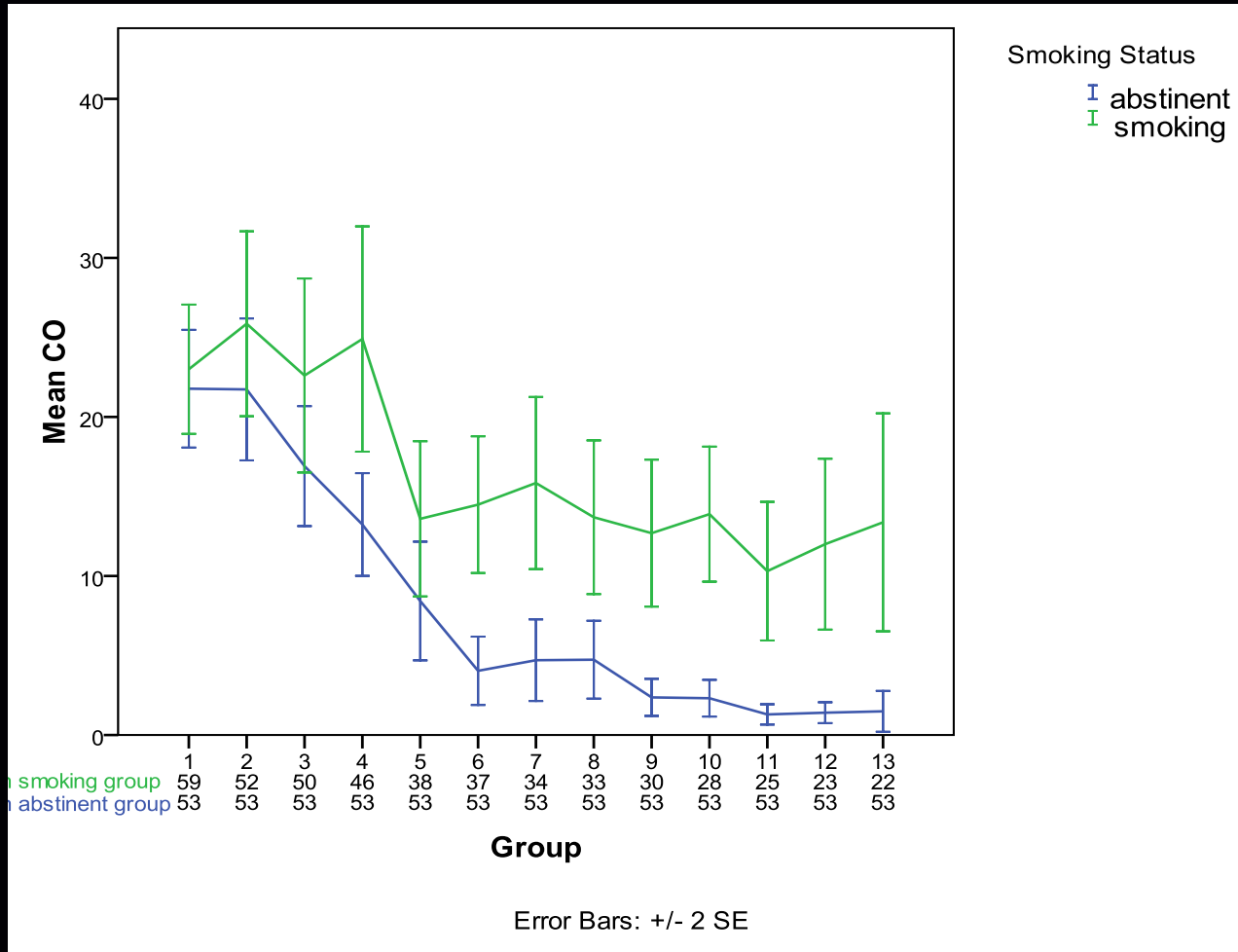
Table 2. Parameter estimates for outcomes measured weekly over 12 weeks

Outcome Variable	Intercept				Slope			Model	
	Est	SE	t or z		Est	SE	t or z		
CO	1.22	0.33	3.7	**	-0.03	0.01	-2.8	**	Poisson
Abstinent for at least the prior 7 days	-3.54	0.60	-5.9	**	0.34	0.03	12.7	**	Binary
WSWS - Total	60.92	2.54	24.0	**	-0.65	0.15	-4.3	**	Normal
Urge to Smoke subscale	12.39	0.66	18.7	**	-0.29	0.04	-7.0	**	Normal
Irritability subscale	5.24	0.44	11.9	**	-0.06	0.03	-2.1	*	Normal
Depression subscale	6.64	0.52	12.9	**	-0.04	0.03	-1.2		Normal
Increased Appetite subscale	12.22	0.65	18.7	**	0.01	0.04	0.2		Normal
Diff. Concentrating subscale	6.45	0.50	12.9	**	-0.06	0.03	-2.0		Normal
Insomnia subscale	8.25	0.61	13.5	**	-0.09	0.04	-2.4	*	Normal
Anxiety subscale	8.67	0.52	16.7	**	-0.10	0.03	-3.1	**	Normal
CDSS - Total	3.53	0.20	17.9	**	-0.14	0.01	-9.5	**	Poisson

Note: All models include "age started smoking" as a covariate, which was a statistically significant predictor of retention across the 12 weeks. CO = carbon monoxide; WSWS = Wisconsin Smoking Withdrawal Scale; CDSS = Calgary Depression Scale for Schizophrenia.

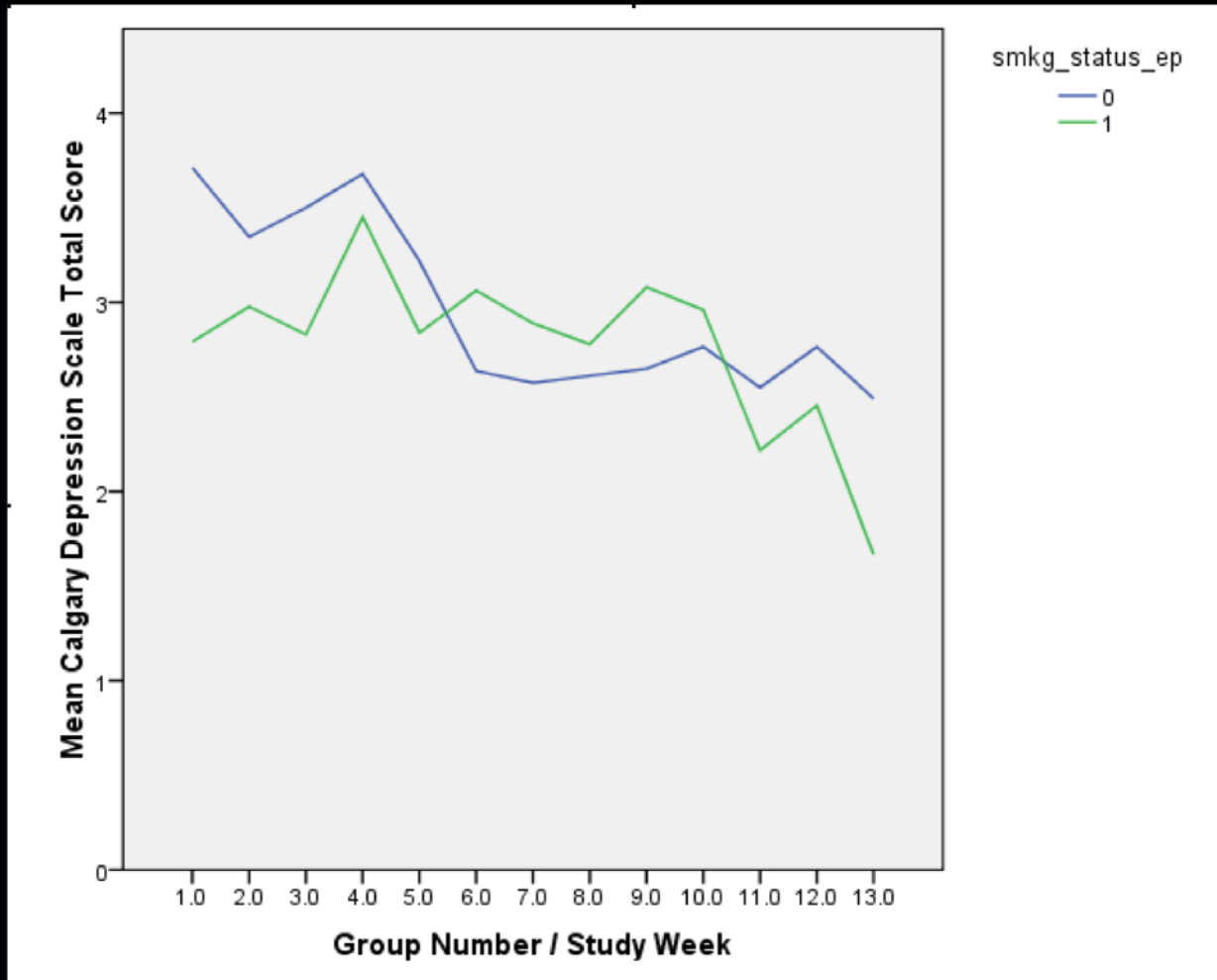
\*  $p < 0.05$ , \*\*  $p < 0.01$

# Open Label Varenicline for Smoking Cessation in 100 Outpatients with Schizophrenia



Expired carbon monoxide declined significantly during treatment in those who did and those who did not achieve abstinence

# Depressive Symptoms **Reduced** During a Cessation Attempt with Varenicline in Smokers with Schizophrenia Independent of Abstinence Status



CDSS scores reduced from baseline  
 $t = -9.5, p < 0.01$

Also significant reduction in WSWS anxiety, irritability, insomnia and urge to smoke subscales

# Prospective Open Trials – Smith et al., 2009

- 14 smokers with schizophrenia, without intention to quit
- Varenicline significantly improved performance on cognitive tests of verbal learning and memory
- Standard clinician ratings: No significant increases in psychopathology scores
- No development of clinical depression or suicidal ideation

# Secondary Data Analysis of a Randomized Trial of Behavioral Tx - McClure et al., 2010

- 542 smokers with (n=271) or without (n=271) past history of psychiatric illness (anxiety, depression, psychotic or bipolar disorder)
- Secondary data analysis of COMPASS trial
- Past history of psychiatric illness not a risk factor for adverse events during varenicline treatment
- No difference in abstinence rates between groups

# Prospective Open Trials – Philip et al., 2009

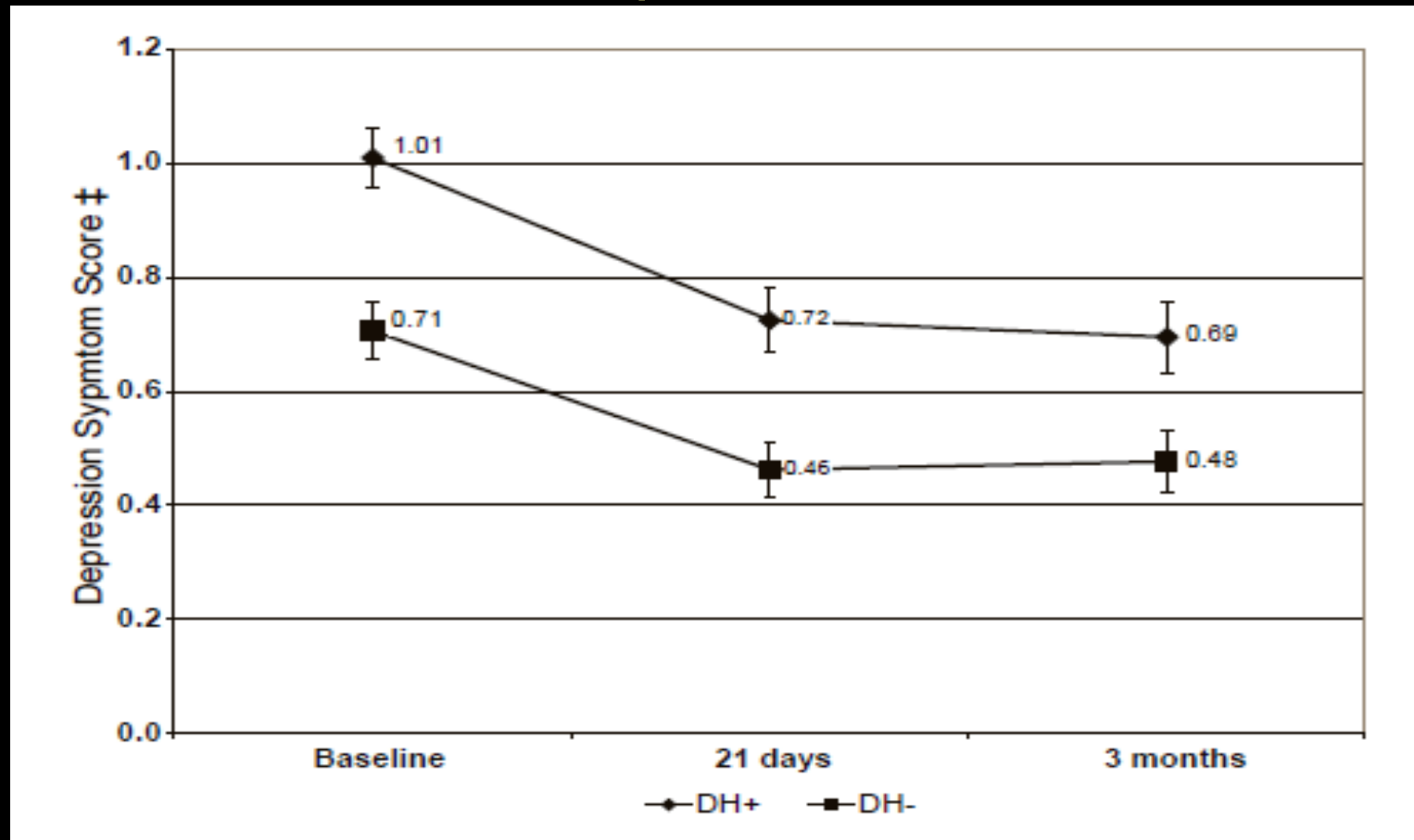
- 18 adults with treatment-resistant depressive symptoms
- Ongoing antidepressant therapy supplemented by varenicline treatment
- Varenicline improved depressive symptoms in smokers with treatment-resistant depression not trying to quit smoking
- Post-hoc analyses: Improvement in core mood items, no change in suicidality



# Secondary Data Analysis of a Randomized Trial of Behavioral Tx – McClure et al., 2009

- 1,117 smokers with or without probable lifetime history of depression
- Secondary data analysis of COMPASS trial
- All received varenicline treatment and were randomized to 1 of 3 behavioral treatment programs
- Prospective comparison of DH+ and DH- participants
- Depression and stress scores declined in both groups
- No suicide-related events
- No difference by DH in abstinence rates

# Varenicline Associated with Decreased Depressive Symptoms in Smokers with and without Prior Depression



No differential effect in (DH+) and without (DH-) history of depression

# Psychiatric Adverse Events

- Case reports and pharamcovigilance reports of psychiatric adverse events with varenicline
- Prospective trials have not demonstrated an association between varenicline and psychiatric adverse events in smokers in the general population of 'real world smokers' or in smokers with depressive disorders or schizophrenia
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# Randomized Controlled Trials – Waldo et al., 2010

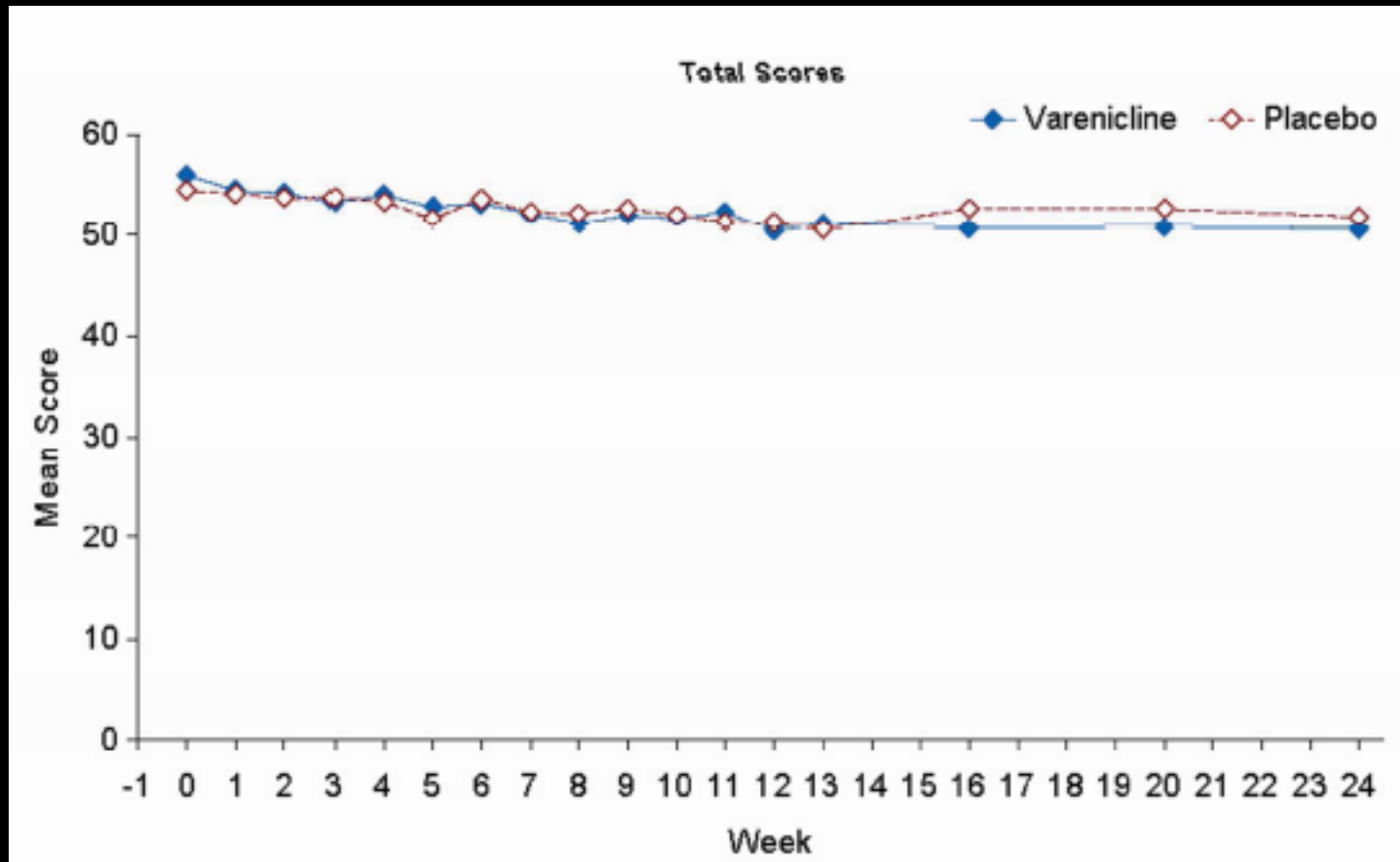
- 6 stable outpatient adults with schizophrenia
- Single dose varenicline or placebo at two visits, one week apart
- Adverse events in 3 subjects, investigators do not report systematic or prospective assessment of clinical symptoms at baseline or after single dose of varenicline or placebo
- No effect of varenicline on P50 sensory gating
- Small sample size

# Randomized Controlled Trials – Williams et al., 2012

- 127 smokers with schizophrenia or schizoaffective d.o.
- 12-weeks varenicline (n=84) or placebo (n=43) + CBT
- 7-day point prevalence abstinence at EOT:  
19% varenicline (16/84) vs. 5% placebo (2/43),  $p < 0.05$
- AE Incidence: varenicline– 87%, placebo– 84%
- Psychiatric AE's (varenicline– 37%, placebo– 33%)
- Well tolerated
- No evidence for exacerbation of psychiatric symptoms relative to placebo

# Varenicline Associated with Greater Abstinence Rates and Stable Psychiatric Symptoms in Smokers with Schizophrenia

PANSS  
Total  
Scores



# Randomized Controlled Trials – Shim et al., 2011

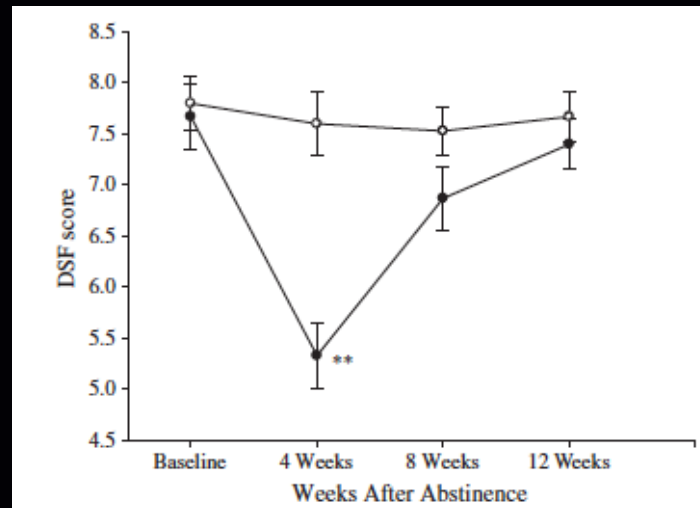
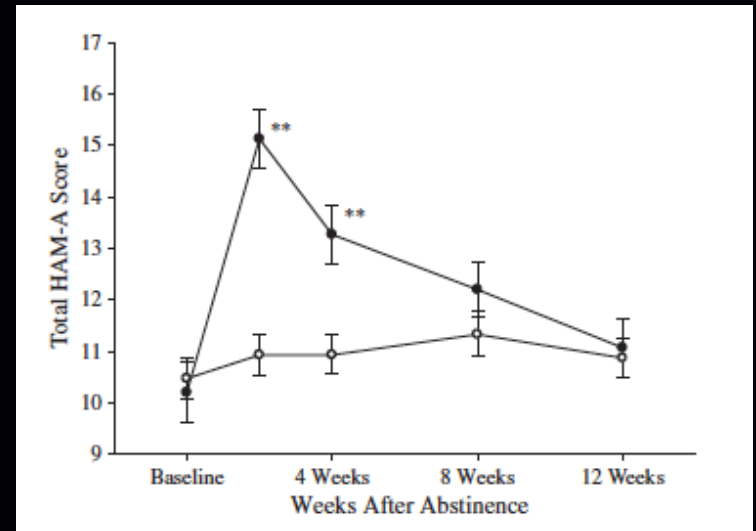
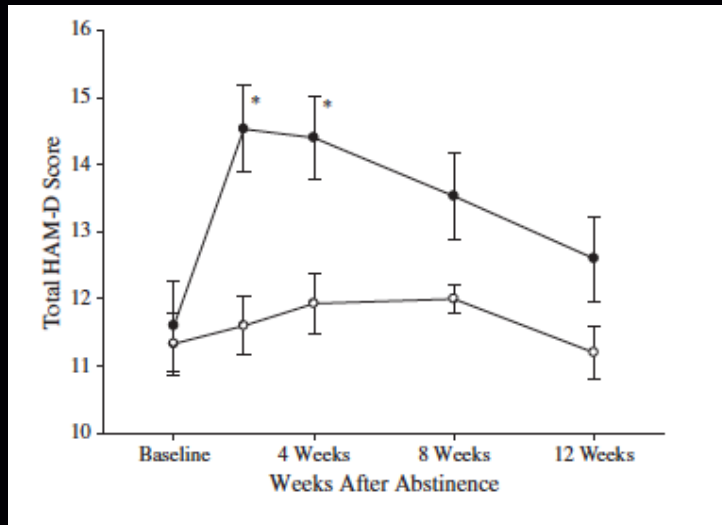
- 120 stable, treated, outpatients with schizophrenia, n=60 nonsmokers and n=60 smokers without intention to quit
- Random, double blind assignment to varenicline or placebo for 8 weeks
- Varenicline associated with improved cognitive performance: Digital Symbol Substitution Test and Wisconsin Card Sorting Test
- No significant depressive symptoms or suicidal ideation
- No treatment main effects or time x treatment interactions on assessments of psychiatric symptoms (PANSS, SANS)

# Randomized Controlled Trials – Hong et al., 2011

- 69 nonsmokers (n=26) and smokers (n=43) without intention to quit with schizophrenia or schizoaffective disorder
- Varenicline 1mg per day (n=35) or placebo (n=34) for 8 weeks
- Varenicline improved P50 sensory gating deficit in nonsmokers
- Varenicline improved startle reactivity and antisaccadic errors in both smokers and nonsmokers
- No effect of varenicline on spatial working memory, predictive and maintenance pursuit measures, processing speed, sustained attention or psychiatric symptoms



# Preliminary Evidence for Amelioration of Abstinence-associated Depressive, Anxiety, and Cognitive Symptoms in Schizophrenia by Varenicline



n = 41  
enforced abstinence  
meds self selected  
No effect of  
abstinence on  
psychosis  
DSB, Trails

# Randomized Controlled Trials – Weiner et al., 2011

- 9 smokers with schizophrenia
- Varenicline or placebo
- 3 of 4 of subjects in varenicline group and 0 of of subjects in the placebo group achieved abstinence
- No significant exacerbation of psychotic, depressive or other psychiatric symptoms
- No suicidal ideation
- Small sample

# Safety and Efficacy of Varenicline for Nicotine Dependence Treatment In Smokers with Psychiatric Co-morbidity : Conclusions

- Nausea, vomiting, insomnia, and abnormal dreams remain the most commonly reported adverse events in post marketing studies of varenicline in those with and without comorbid psychiatric illness

# Safety and Efficacy of Varenicline for Nicotine Dependence Treatment In Smokers with Mental Illness: Conclusions

- Randomized controlled trials to date support safety of varenicline in stable treated smokers with schizophrenia
- Observational studies in general population studies support safety of varenicline in smokers with past or probable history of depressive illness
- Risk of continued smoking in this population is known: high
- Little known about safety and efficacy of varenicline for those with other common psychiatric disorders with high smoking rates such as MDD, ADHD, bipolar disorder, PTSD