Varenicline and cardiovascular and neuropsychiatric events: Do Benefits outweigh risks?

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CONFLICTS OF INTEREST : NONE

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Objectives

1. Synthesize the evidence on cardiovascular effects associated with varenicline
2. Synthesize the evidence on neuropsychiatric adverse events associated with varenicline
3. Benefit Risk Assessment of varenicline to inform policy decisions

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Background

- Smoking is a chronic heterogenous condition in which patients quit and relapse.
- Smokers at an increased risk of both cardiovascular (CV) events and depression.
- Varenicline, bupropion and five different formulations of nicotine replacement products approved for smoking cessation in the United States.

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Varenicline FDA priority review 2006

- *" The serious adverse event data suggest that varenicline may be associated with ischemic and arrythmic risks particularly over longer treatment period, although these findings are far from definitive"*

However approved label contained no information on cardiovascular risk

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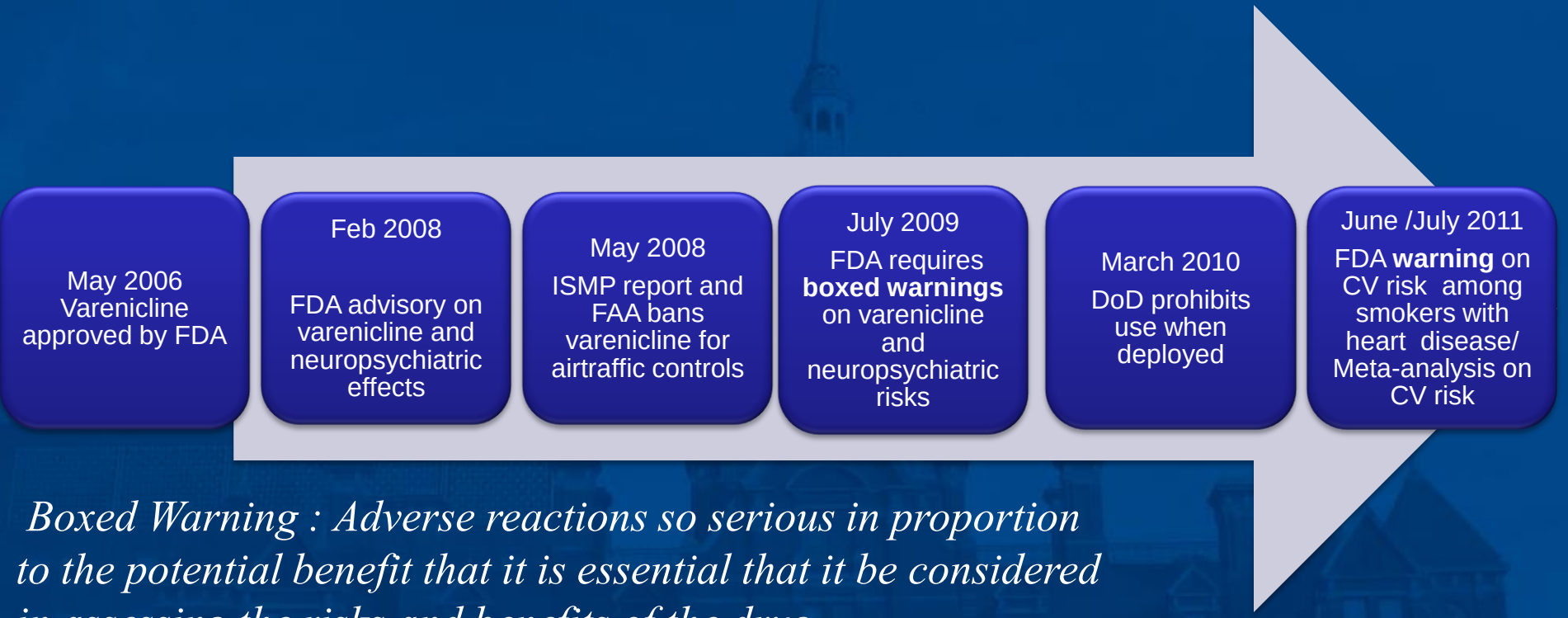
Howard Josefberg FDA safety review of varenicline on approval May 2006

Varenicline Timeline



Boxed Warning : Adverse reactions so serious in proportion to the potential benefit that it is essential that it be considered in assessing the risks and benefits of the drug

Warning :*Clinically significant adverse reactions with reasonable evidence of a causal association*

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Emerging evidence on cardiac risk

- 224 case reports of potential heart rhythm disturbances in spontaneous post-marketing reports to the FDA in 2008
- Spontaneous reports of myocardial infarction prompted addition of these report to the label
- The biological mechanisms could include vasospasm and autonomic dysregulation but not well studied.

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[Moore et al. Institute of Safe Medication Practice Report, 2008]

Outcomes and Analytic Plan

• Primary Outcome : Any serious ischemic or arrhythmic cardiovascular event reported during the double blind period of the trial [composite]

•Secondary outcome : All cause mortality

•Analytic plan specified that all events for the entire duration of the trial are counted (Intention to Treat Analysis)

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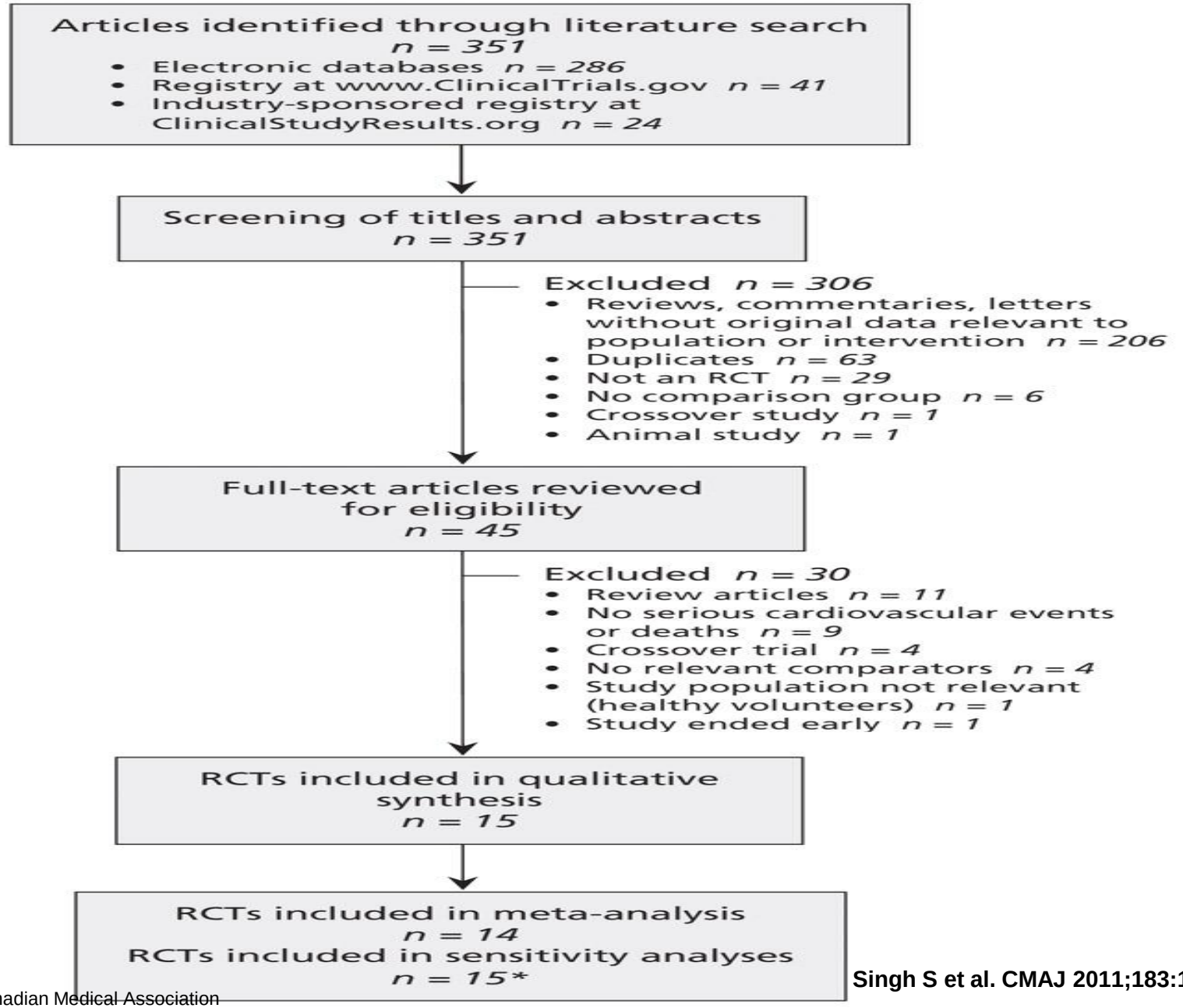
Selection of DB PC RCTs for inclusion in the systematic review and meta-analysis



Singh S et al. CMAJ 2011;183:1359-1366

Meta-analysis Database

- 14 DB, PC RCTs-13 trials enrolled smokers; one RCT enrolled smokeless tobacco users.
- **13 trials excluded patients with a history of CVD; one RCT included participants with stable CVD but excluded those with unstable CVD**.
- Sample sizes from 250 to 1210.
- The primary outcome was the continuous abstinence rate (CAR) in 12 trials the **long-term quit rate in 1 trial and long-term safety in 1 trial.**
- Duration of treatment ranged from **7 weeks to 52** weeks, and the total duration of study, including treatment and follow-up, ranged from 24 to 52 weeks.

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RCTs of Varenicline vs Placebo

Study	Duration of treatment, wk	Duration of study, wk	Primary outcome	Cardiac exclusions at enrolment	Drug and dose	No. of participants	Age, yr, mean (SD or range)	Males, %
Protocol A3051080, 2010[16]	12	26	Continous abstinence rate	Clinically significant CVD in last 6 mo, systolic BP > 150 mm Hg	Varenicline 1 mg bid	394	43.1 (18–69)	60.4
					Placebo	199	43.9 (20–71)	60.4‡
Protocol A3051095, 2010[17]	12	24	Continous quit rate, continous abstinence rate	No serious or unstable disease in last 6 mo	Varenicline 1 mg bid	493	43.9 (18–75)	60.3
					Placebo	166	43.2 (18–72)	60.0
Fagerstrom et al., 2010[18]	12	26	Continous quit rate	Any serious medical condition	Varenicline 1 mg bid	214	43.9 (12.0)	88.7
					Placebo	218	43.9 (12.0)	89.9
Gonzales et al., 2006[19]	12	52	Continous quit rate	CVD within last 6 mo	Varenicline 1 mg bid	352	42.5 (11.1)	50.0
					Bupropion 150 mg bid	329	42.0 (11.7)	58.4
					Placebo	344	42.6 (11.8)	54.1
Jorenby et al., 2006[20]	12	52	Continous quit rate	Clinically significant CVD in last 6 mo	Varenicline 1 mg bid	344	44.6 (11.4)	55.2
					Bupropion 150 mg bid	342	42.9 (11.9)	60.2
					Placebo	341	42.3 (11.6)	58.1
Nakamura et al., 2007[21]	12	52	Continous abstinence rate	Unstable CVD	Varenicline 1 mg bid	156	40.1 (11.6)	79.2
					Varenicline 0.5 mg bid	156	39.0 (12.0)	71.1
					Varenicline 0.25 mg bid	153	40.2 (12.3)	72.7
					Placebo	154	39.9 (12.3)	76
Niaura et al., 2008[22]	12	52	Continous abstinence rate	History of CVD	Varenicline 1 mg/d	160	41.5 (11.3)	50.3
					Placebo	160	42.1 (11.7)	53.5
Nides et al., 2006[23]	7	52	Continous abstinence rate	History of CVD	Varenicline 0.3 mg/d	128	41.9 (10.6)	50.0
					Varenicline 1 mg/d	128	42.9 (10.5)	43.7
					Varenicline 1 mg bid	127	41.9 (9.8)	50.4
					Bupropion 150 mg bid	128	40.5 (10.8)	45.2
					Placebo	127	41.6 (10.4)	52.0
Oncken et al., 2006[24]	12	52	Continous abstinence rate	History of CVD	Varenicline 1 mg bid titrated	130	42.2 (10.7)	48.5
					Varenicline 1 mg bid nontitrated	129	43.7 (10.0)	48.8
					Varenicline 0.5 mg bid titrated	130	43.5 (10.5)	53.1
					Varenicline 0.5 mg bid nontitrated	129	42.9 (10.1)	45.0
					Placebo	129	43.0 (9.4)	51.9
Rigotti et al., 2010[9]	12	52	Continous abstinence rate	Excluded if unstable CVD in last 2 mo; included with stable CVD§	Varenicline 1 mg bid	355	57.0 (8.6)	75.2
					Placebo	359	55.9 (8.3)	82.2
Tashkin et al.,† 2010[25]	12	52	Continous abstinence rate	Unstable CVD or history of CVD in last 6 mo	Varenicline 1 mg bid	250	57.2 (35–83)	62.5
					Placebo	254	57.1 (34–77)	62.2
Tonstad et al., 2006[26]	12	52	Long-term quit rate	CVD within last 6 mo	Varenicline 1 mg bid	603	45.4 (10.4)	50.2
					Placebo	607	45.3 (10.4)	48.3
Tsai et al., 2007[27]	12	24	Continous abstinence rate	Unstable CVD	Varenicline 1 mg bid	126	39.7 (9.3)	84.9
					Placebo	124	40.9 (11.1)	92.7
Williams et al., 2007[28]	52	52	Long-term safety	Clinically significant CVD in last 6 mo	Varenicline 1 mg bid	251	48.2 (12.3)	50.6
					Placebo	126	46.6 (12.1)	48.4
Aubin et al., 2008[29]	12	52	Continous abstinence rate	Serious or unstable disease in last 6 mo	Varenicline 1 mg bid	378	42.9 (10.5)	48.4
					Nicotine transdermal patch	379	42.9 (12.0)	50.0

Note: BP = blood pressure, CVD = cardiovascular disease, SD = standard deviation.
*All but one of the trials involved smokers; the study by Fagerstrom et al.[18] involved users of smokeless tobacco. Additional study characteristics are available in Appendix 2 (www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.110218/-/DC1).
†Investigators enrolled smokers with mild to moderate chronic obstructive pulmonary disease.
‡The proportion of males in study overall; the proportion in each study arm was not reported.
§The proportion of patients with cardiac disease in varenicline versus placebo groups was angina 53.2% v. 47.9%, myocardial infarction 45.9% v. 52.4%, prior coronary revascularization 46.2% v. 51.5%, and stroke 4.5% v. 6.7%.

Risk of Bias

Study	Adequate sequence generation	Adequate allocation concealment	Adequate blinding of personnel and participants	Adequate reporting of withdrawals and loss to follow-up	Adequate reporting of serious adverse events
Double-blind RCTs					
Protocol A3051080[16]	Unclear	Unclear	Yes	Yes	Yes
Protocol A3051095[17]	Unclear	Unclear	Yes	Yes	Yes
Fagerstrom et al.[18]	Yes	Yes	Yes	Yes	Yes
Gonzales et al.[19]	Yes	Yes	Yes	Yes	Yes
Jorenby et al.[20]	Yes	Yes	Yes	Yes	Yes
Nakamura et al.[21]	Yes	Yes	Yes	Yes	Yes
Niaura et al.[22]	Yes	Yes	Yes	Yes	Yes
Nides et al.[23]	Yes	Yes	Yes	Yes	Yes
Oncken et al.[24]	Unclear	Unclear	Yes	Yes	Yes
Rigotti et al.[9]	Yes	Yes	Yes	Yes	Yes
Tashkin et al.[25]	Unclear	Unclear	Yes	Yes	Yes
Tonstad et al.[26]	Yes	Yes	Yes	Yes	Yes
Tsai et al.[27]	Yes	Yes	Yes	Yes	Yes
Williams et al.[28]	Unclear	Unclear	Yes	Yes	Yes
Open-label RCT					
Aubin et al.[29]	Yes	Unclear	Y		Yes

*Details of the methodology of the studies are available in Appendix 3 (www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.110218/-/DC1).

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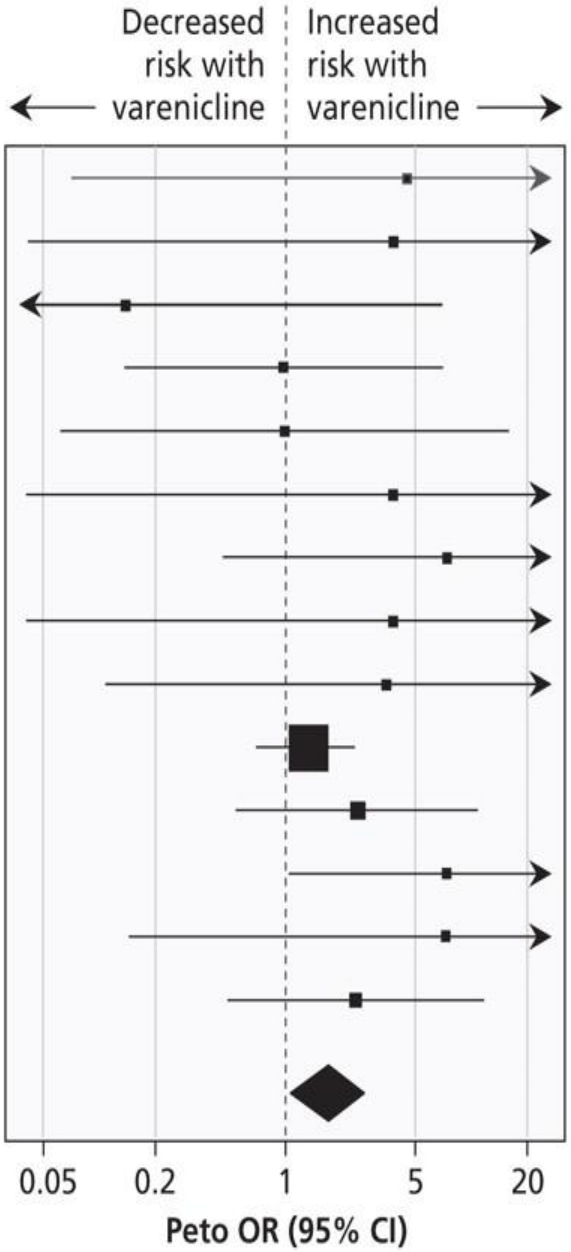
Meta-analysis of DB RCT of the risk of serious adverse CV events with varenicline.

Study	Cardiovascular events, *n/N*		Weight, %	Peto OR (95% CI)
	Varenicline	Placebo		
Protocol A3051080[16]	1/394	0/199	1.2	4.50 (0.07–285.96)
Protocol A3051095[17]	1/493	0/166	1.0	3.81 (0.04–347.82)
Fagerstrom et al.[18]	0/214	1/218	1.4	0.14 (0.00–6.95)
Gonzales et al.[19]	2/352	2/344	5.4	0.98 (0.14–6.97)
Jorenby et al.[20]	1/344	1/341	2.7	0.99 (0.06–15.88)
Nakamura et al.[21]	1/465	0/154	1.0	3.79 (0.04–352.44)
Niaura et al.[22]	2/160	0/160	2.7	7.44 (0.46–119.40)
Nides et al.[23]	1/383	0/127	1.0	3.79 (0.04–352.09)
Oncken et al.[24]	2/518	0/129	1.7	3.49 (0.11–112.44)
Rigotti et al.[9]	25/355	20/359	57.3	1.28 (0.70–2.34)
Tashkin et al.[25]	5/250	2/254	9.4	2.42 (0.55–10.74)
Tonstad et al.[26]	4/603	0/607	5.4	7.48 (1.05–53.20)
Tsai et al.[27]	1/126	0/124	1.4	7.27 (0.14–366.57)
Williams et al.[28]	6/251	1/126	8.3	2.40 (0.49–11.67)
Overall	**52/4908**	**27/3308**	**100.0**	**1.72 (1.09–2.71)**

Heterogeneity: $I^2 = 0\%$



Sensitivity Analyses

Sensitivity analysis	Statistical model	No. of RCTs	Group; no. of events, *n/N*		OR (95% CI)
			Varenicline	Control	
Placebo comparator					
Reciprocal of the treatment arm size					
Continuity correction	Fixed (MH)	14[9,16–28]	52/4908	27/3308	1.67 (1.06–2.64)
No continuity correction	Fixed (MH)	14[9,16–28]	52/4908	27/3308	1.77 (1.09–2.88)
Use of unadjudicated cardiovascular event data from one trial	Peto OR	14[9,16–28]	61/4908	29/3308	1.91 (1.25–2.94)
Exclusion of most influential study	Peto OR	13[16–28]	27/4553	7/2949	2.54 (1.26–5.12)
Placebo or active† comparator	Peto OR	15[9,16–29]	52/5286	30/4486	1.67 (1.07–2.62)

Note: CI = confidence interval, OR = odds ratio, MH = Mantel–Haenszel test, RCT = randomized controlled trial.
*Statistical heterogeneity was I^2 = 0% for all sensitivity analyses.
†Bupropion or nicotine replacement therapy

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Number Needed to Harm for CV Events

Population	Source of baseline risk	Baseline Risk	Annualized Number Needed to Harm
Smokers without CVD	Control event rate of Meta-analysis	0.82%	167
Smokers with stable CVD	Control event rate of trial among smokers with CVD	5.8%	28

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Limitations

- Studies underpowered to detect differences in individual endpoints of MI and stroke
- Lack of data on time to event
- Small numbers and imprecision

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Neuropsychiatric effects of varenicline

*…." **RRs 1.42 (0.96, 2.08)** for depressed mood disorders …. However, among three trials that were excluded from the analysis because of their open-label design, **two cases of suicidal ideation and one completed suicide** were reported in patients who had been treated with varenicline. "*

INTERPRETATION : " *There was no significant increase in overall psychiatric disorders "*

only applicable to smokers without psychiatric comorbidities

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Tonstad S, Davies S, Flammer M, Russ C, Hughes J. Psychiatric adverse events in randomized, double-blind, placebo-controlled clinical trials of varenicline: a pooled analysis Drug Saf. 2010 1;33(4):289-301

Varenicline and suicidal behaviour in the GPRD

“ 80,660 participants prescribed NRT(n=63 265), varenicline (n=10 973), and bupropion (n=6422).

RESULTS: HR for self harm for varenicline was 1.12 (95% CI 0.67 to 1.88), 1.17 (0.59 to 2.32) for bupropion compared to NRT. No increased risk of depression (HR 0.88 (0.77 to1.00) or suicidal thoughts (1.43 (0.53 to 3.85) with varenicline

CONCLUSION: Although a twofold increased risk of self harm with varenicline cannot be ruled out…., these findings provide some reassurance concerning its association with suicidal behaviour.”

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Gunnell D, Irvine D, Wise L, Davies C, Martin RM.Varenicline and suicidal behaviour: a cohort study based on data from the General Practice Research Database.BMJ. 2009 Oct 1;339:b3805.

From: New Reports Examine Psychiatric Risks of Varenicline for Smoking Cessation

JAMA. 2012;307(2):129-130. doi:10.1001/jama.2011.1924

Suicidal and Self-injurious Behavior

MedDRA Term[a]	Varenicline (n=1819) No. (%)	Bupropion (n=155) No. (%)	Nicotine (n=50) No. (%)
Completed suicide	272 (15.0)	19 (12.3)	4 (8.0)
Suicidal ideation	1135 (62.4)	73 (47.1)	40 (80.0)
Suicide attempt	323 (17.8)	56 (36.1)	2 (4.0)

[a]Preferred terms from the *Medical Dictionary for Regulatory Activities* (http://www.meddramsso.com).

Source: Moore TJ, Furberg CD, Glenmullen J, Maltsberger JT, Singh S. Suicidal behavior and depression in smoking cessation treatments. *PLoS ONE*. 2011;6(11):e27106.

Challenges in detecting safety signals in trials

- EXCLUSION : Exclude high-risk participants
- POORASCERTAINMENT : Rely on participant reports of adverse events rather than active ascertainment
- CENSOR: Arbitrary censoring participants for analysis. Do not follow participants or count them
- OPTIMAL INFORMATION SIZE: Conclude drug is "safe" in statistically underpowered analyses despite overall small database (Type 2 error)

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Singh S, Loke YK : Drug Safety Assessment in Clinical Trials-Methodologic Challenges and Opportunities. Trials 2012.

Ongoing safety studies

-FDA mandated individual patient data meta-analysis of varenicline and cardiovascular events (AEs and all SAEs)

-Several more clinical trials of varenicline have been completed at clinicaltrials.gov but few published

-- 12 week smoking cessation study (with 52 week followup) among smokers with mental disorders (CATS) scheduled for completion in 2017..Monitor CV outcomes

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Efficacy of Varenicline on Abstinence

- Placebo : RR for continuous abstinence (CA) at 6 mo for varenicline vs placebo =2.31 (95% CI] 2.01 to 2.66). (10 trials, 4443 people) ; typical quit rates of 7.5% for behavioural counselling NNT =10 for varenicline
- Pooled RR for varenicline vs bupropion at 1 y 1.52 (95% CI 1.22 to 1.88; 3 trials, 1622 people). NNT=20 for bupropion and NNT = 23 for NRT
- Varenicline to nicotine patches found no statistically significant difference in 7-day reported abstinence at 52 weeks

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Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. Cochrane Database Syst Rev. 2010 8;(12):CD006103.

Smoking cessation interventions and CV benefit in Long Term Trials

- No long term abstinence data on varenicline
- NRT is the only smoking cessation product known to reduce CV risk and all cause mortality in the Lung Health Study in a clinical trial.
- Usual care arm had an 18% higher risk of death at 14.5 years compared to those given NRT- hazard ratio, 1.18 [95% CI, 1.02 to 1.37]

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. Ann Intern Med. 2005 ;142(4):233-9

Evidence gaps

- All treatment effects on benefit and harm from RCT [Ideal]
- RCTs underpowered to detect rare and serious effects such as completed suicide (<1/1000)
- Probability of an outcome is no measure of its importance
- All treatment effects from a thorough review of all sources of evidence including observational studies of harm [pragmatic]

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Evidence gaps : Heterogeneity of patient preferences

- How many suicides and short term adverse cardiovascular events should be traded off for *potential* long term health benefit?

- Are patients less tolerant of treatment induced risks than behavioural risks?

-- Will patients trade-off higher risks for more efficacy?

- Are risks and benefits concentrated in subgroups (quitters vs non-quitters)?- requires IPD analysis

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Clinical Implications

-Clinicians should determine the best available options after eliciting **patient preferences** for various outcomes in a shared decision making context

-Should varenicline be a second line agent among smokers?

-Close monitoring of patients for mental disorders and CV events

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Policy Implications

- Underpowered safety studies cannot provide reassurance on safety .
- Better tools are needed to generate independent, reliable and *valid* estimates of the balance of benefit and harm to facilitate evidence based and transparent policy decisions
- Should the approval of smoking cessation products for a long term chronic condition (in which smokers quit and relapse) be based on short term efficacy trials ?

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Does the benefit of varenicline outweigh its risks?

- Baseline risk of the patient for CVD and psychiatric comorbidities
- - Importance patients assign to these outcomes
- How one weighs evidence from various sources
- Benefits and risks of alternatives.
- Transparent assumptions about data and potential benefit and risk

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A Multicriteria decision analytic model for Smoking cessation agents using the Analytic Hierarchy Process

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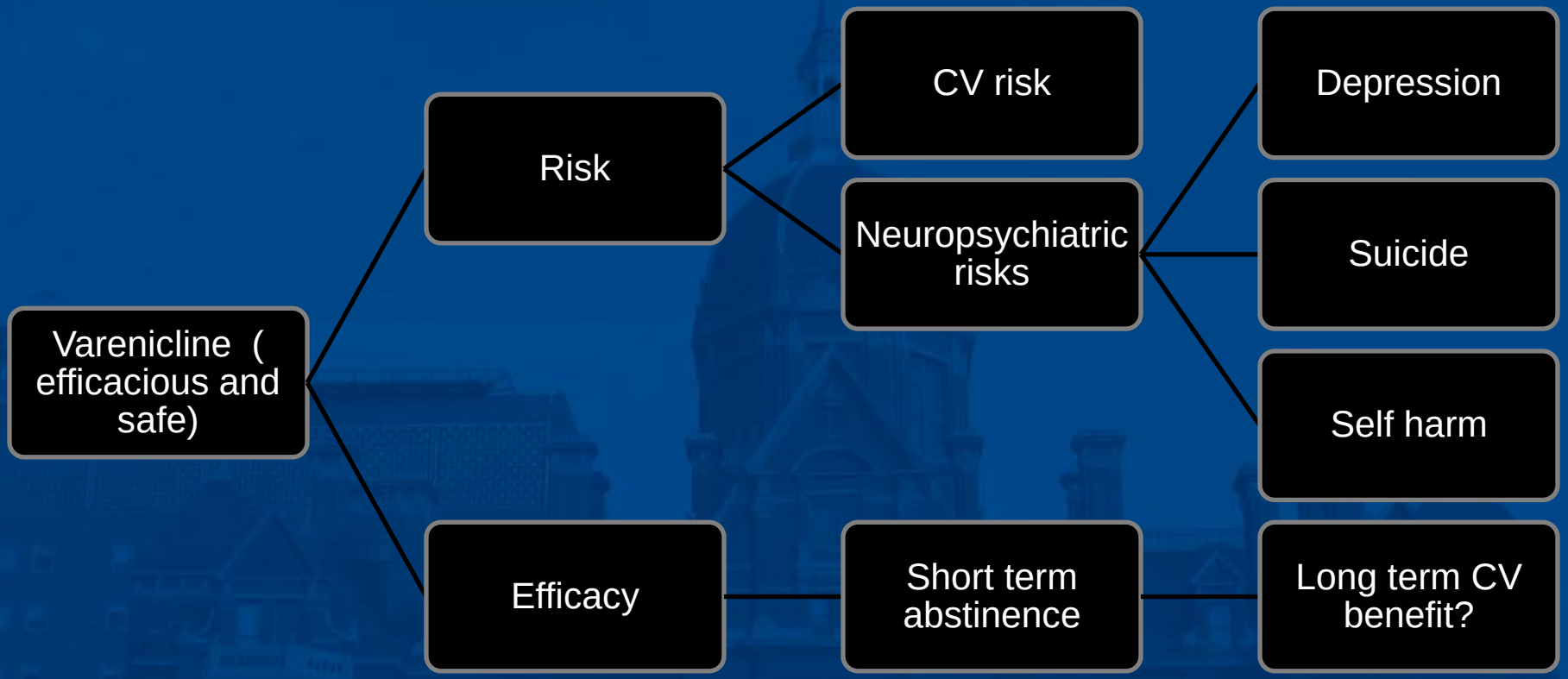
Multicriteria Decision Analysis Model



No RCT evidence that Varenicline provides CV benefit

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