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

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CONFLICTS OF INTEREST: NONE

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Unrelated: Current grant support for development of a quantitative benefit risk framework (FDA) methods for systematic reviews (AHRQ, MacArthur Foundation, USIP); consulted for the World Bank on systematic review topics.
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

Presented by: Sonal Singh, MD MPH
September 19, 2012
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.
Varenicline FDA priority review 2006

• “The serious adverse event data suggest that varenicline may be associated with ischemic and arrhythmic risks particularly over longer treatment period, although these findings are far from definitive”

However approved label contained no information on cardiovascular risk
Varenicline Timeline

May 2006
Varenicline approved by FDA

Feb 2008
FDA advisory on varenicline and neuropsychiatric effects

May 2008
ISMP report and FAA bans varenicline for airtraffic controls

July 2009
FDA requires boxed warnings on varenicline and neuropsychiatric risks

March 2010
DoD prohibits use when deployed

June /July 2011
FDA warning on CV risk among smokers with heart disease/Meta-analysis on CV risk

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
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)

Presented by: Sonal Singh, MD MPH  
Singh S et al. CMAJ 2011;183:1359-1366

September 19, 2012
Selection of DB PC RCTs for inclusion in the systematic review and meta-analysis

Articles identified through literature search: 351
- Electronic databases: 286
- Registry at www.ClinicalTrials.gov: 41
- Industry-sponsored registry at ClinicalStudyResults.org: 24

Screening of titles and abstracts: 351
- Excluded: 306
  - Reviews, commentaries, letters without original data relevant to population or intervention: 206
  - Duplicates: 63
  - Not an RCT: 29
  - No comparison group: 6
  - Crossover study: 1
  - Animal study: 1

Full-text articles reviewed for eligibility: 45
- Excluded: 30
  - Review articles: 11
  - No serious cardiovascular events or deaths: 9
  - Crossover trial: 4
  - No relevant comparators: 4
  - Study population not relevant (healthy volunteers): 1
  - Study ended early: 1

RCTs included in qualitative synthesis: 15

RCTs included in meta-analysis: 14
RCTs included in sensitivity analyses: 15*
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.

Singh S et al. CMAJ 2011;183:1359-1366
<table>
<thead>
<tr>
<th>Study</th>
<th>Duration of treatment, wk</th>
<th>Duration of study, wk</th>
<th>Primary outcome</th>
<th>Cardiac exclusions at enrolment</th>
<th>Drug and dose</th>
<th>No. of participants</th>
<th>Ages, yr, mean (SD or range)</th>
<th>Males, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol A3051080, 2010</td>
<td>12</td>
<td>26</td>
<td>Continuous abstinence rate</td>
<td>Clinically significant CVD in last 6 mo, systolic BP &gt; 150 mm Hg</td>
<td>Varenicline 1 mg bid</td>
<td>394</td>
<td>43.1 (18–69)</td>
<td>60.4</td>
</tr>
<tr>
<td>Protocol A3051095, 2010</td>
<td>12</td>
<td>24</td>
<td>Continuous quit rate, continuous abstinence rate</td>
<td>No serious or unstable disease in last 6 mo</td>
<td>Varenicline 1 mg bid</td>
<td>493</td>
<td>43.9 (18–75)</td>
<td>60.3</td>
</tr>
<tr>
<td>Fagerstrom et al., 2010</td>
<td>12</td>
<td>26</td>
<td>Continuous quit rate</td>
<td>Any serious medical condition</td>
<td>Varenicline 1 mg bid</td>
<td>214</td>
<td>43.9 (12.0)</td>
<td>88.7</td>
</tr>
<tr>
<td>Gonzalez et al., 2006</td>
<td>12</td>
<td>52</td>
<td>Continuous quit rate</td>
<td>CVD within last 6 mo</td>
<td>Varenicline 1 mg bid</td>
<td>352</td>
<td>42.5 (11.1)</td>
<td>50.0</td>
</tr>
<tr>
<td>Jorenby et al., 2006</td>
<td>12</td>
<td>52</td>
<td>Continuous quit rate</td>
<td>Clinically significant CVD in last 6 mo</td>
<td>Varenicline 1 mg bid</td>
<td>344</td>
<td>44.6 (11.4)</td>
<td>52.4</td>
</tr>
<tr>
<td>Nakamura et al., 2007</td>
<td>12</td>
<td>52</td>
<td>Continuous abstinence rate</td>
<td>Unstable CVD</td>
<td>Varenicline 1 mg bid</td>
<td>156</td>
<td>40.1 (11.6)</td>
<td>79.2</td>
</tr>
<tr>
<td>Niaura et al., 2008</td>
<td>12</td>
<td>52</td>
<td>Continuous abstinence rate</td>
<td>History of CVD</td>
<td>Varenicline 1 mg bid</td>
<td>156</td>
<td>39.0 (12.0)</td>
<td>71.1</td>
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<tr>
<td>Nides et al., 2006</td>
<td>7</td>
<td>52</td>
<td>Continuous abstinence rate</td>
<td>History of CVD</td>
<td>Varenicline 0.5 mg bid</td>
<td>52</td>
<td>41.6 (10.4)</td>
<td>52.0</td>
</tr>
<tr>
<td>Oncken et al., 2006</td>
<td>12</td>
<td>52</td>
<td>Continuous abstinence rate</td>
<td>History of CVD</td>
<td>Varenicline 1 mg bid titrated</td>
<td>130</td>
<td>42.2 (10.7)</td>
<td>48.5</td>
</tr>
<tr>
<td>Rigotti et al., 2010</td>
<td>12</td>
<td>52</td>
<td>Continuous abstinence rate</td>
<td>Excluded if unstable CVD in last 2 mo; included with stable CVD§</td>
<td>Varenicline 1 mg bid</td>
<td>129</td>
<td>43.7 (10.0)</td>
<td>48.8</td>
</tr>
<tr>
<td>Tashkin et al., 2010</td>
<td>12</td>
<td>52</td>
<td>Continuous abstinence rate</td>
<td>Unstable CVD or history of CVD in last 6 mo</td>
<td>Varenicline 0.5 mg bid</td>
<td>130</td>
<td>43.5 (10.5)</td>
<td>53.1</td>
</tr>
<tr>
<td>Tonstad et al., 2006</td>
<td>12</td>
<td>52</td>
<td>Long-term quit rate</td>
<td>CVD within last 6 mo</td>
<td>Varenicline 1 mg bid</td>
<td>250</td>
<td>57.2 (35–83)</td>
<td>62.5</td>
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<tr>
<td>Tsai et al., 2007</td>
<td>12</td>
<td>24</td>
<td>Continuous abstinence rate</td>
<td>Unstable CVD</td>
<td>Varenicline 1 mg bid</td>
<td>254</td>
<td>57.1 (34–77)</td>
<td>62.2</td>
</tr>
<tr>
<td>Williams et al., 2007</td>
<td>52</td>
<td>52</td>
<td>Long-term safety</td>
<td>Clinically significant CVD in last 6 mo</td>
<td>Varenicline 1 mg bid</td>
<td>251</td>
<td>46.6 (12.1)</td>
<td>48.4</td>
</tr>
<tr>
<td>Aubin et al., 2008</td>
<td>12</td>
<td>52</td>
<td>Continuous abstinence rate</td>
<td>Serious or unstable disease in last 6 mo</td>
<td>Varenicline 1 mg bid</td>
<td>378</td>
<td>42.9 (10.5)</td>
<td>48.4</td>
</tr>
</tbody>
</table>

Note: BP = blood pressure, CVD = cardiovascular disease, SD = standard deviation.
*All but one of the trials involved smokers; the study by Fagerstrom et al. 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.
§Prior coronary revascularization 46.2% vs. 51.5%, and stroke 4.5% v. 6.7%.
## Risk of Bias

<table>
<thead>
<tr>
<th>Study</th>
<th>Adequate sequence generation</th>
<th>Adequate allocation concealment</th>
<th>Adequate blinding of personnel and participants</th>
<th>Adequate reporting of withdrawals and loss to follow-up</th>
<th>Adequate reporting of serious adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Double-blind RCTs</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Protocol A3051080(^{16})</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Protocol A3051095(^{17})</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Fagerstrom et al.(^{18})</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Gonzales et al.(^{19})</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Jorenby et al.(^{20})</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Nakamura et al.(^{21})</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Niaura et al.(^{22})</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Nides et al.(^{23})</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Oncken et al.(^{24})</td>
<td>Unclear</td>
<td>Unclear</td>
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<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Rigotti et al.(^{9})</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Tashkin et al.(^{25})</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Tonstad et al.(^{26})</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Tsai et al.(^{27})</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Williams et al.(^{28})</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td><strong>Open-label RCT</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aubin et al.(^{29})</td>
<td>Yes</td>
<td>Unclear</td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Cardiovascular events, n/N</th>
<th>Weight, %</th>
<th>Peto OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol A3051080(^{16})</td>
<td>1/394 0/199</td>
<td>1.2</td>
<td>4.50 (0.07–2859.96)</td>
</tr>
<tr>
<td>Protocol A3051095(^{17})</td>
<td>1/493 0/166</td>
<td>1.0</td>
<td>3.81 (0.04–347.82)</td>
</tr>
<tr>
<td>Fagerstrom et al.(^{18})</td>
<td>0/214 1/218</td>
<td>1.4</td>
<td>0.14 (0.00–6.95)</td>
</tr>
<tr>
<td>Gonzales et al.(^{19})</td>
<td>2/352 2/344</td>
<td>5.4</td>
<td>0.98 (0.14–6.97)</td>
</tr>
<tr>
<td>Jorenby et al.(^{20})</td>
<td>1/344 1/341</td>
<td>2.7</td>
<td>0.99 (0.06–15.88)</td>
</tr>
<tr>
<td>Nakamura et al.(^{21})</td>
<td>1/465 0/154</td>
<td>1.0</td>
<td>3.79 (0.04–352.44)</td>
</tr>
<tr>
<td>Niaura et al.(^{22})</td>
<td>2/160 0/160</td>
<td>2.7</td>
<td>7.44 (0.46–119.40)</td>
</tr>
<tr>
<td>Nides et al.(^{23})</td>
<td>1/383 0/127</td>
<td>1.0</td>
<td>3.79 (0.04–352.09)</td>
</tr>
<tr>
<td>Oncken et al.(^{24})</td>
<td>2/518 0/129</td>
<td>1.7</td>
<td>3.49 (0.11–112.44)</td>
</tr>
<tr>
<td>Rigotti et al.(^{9})</td>
<td>25/355 20/359</td>
<td><strong>57.3</strong></td>
<td>1.28 (0.70–2.34)</td>
</tr>
<tr>
<td>Tashkin et al.(^{25})</td>
<td>5/250 2/254</td>
<td>9.4</td>
<td>2.42 (0.55–10.74)</td>
</tr>
<tr>
<td>Tonstad et al.(^{26})</td>
<td>4/603 0/607</td>
<td>5.4</td>
<td>7.48 (1.05–53.20)</td>
</tr>
<tr>
<td>Tsai et al.(^{27})</td>
<td>1/126 0/124</td>
<td>1.4</td>
<td>7.27 (0.14–366.57)</td>
</tr>
<tr>
<td>Williams et al.(^{28})</td>
<td>6/251 1/126</td>
<td>8.3</td>
<td>2.40 (0.49–11.67)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>52/4908 27/3308</strong></td>
<td><strong>100.0</strong></td>
<td><strong>1.72 (1.09–2.71)</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: \(I^2 = 0\%\)
# Sensitivity Analyses

<table>
<thead>
<tr>
<th>Sensitivity analysis</th>
<th>Statistical model</th>
<th>No. of RCTs</th>
<th>Varenicline</th>
<th>Control</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo comparator</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reciprocal of the treatment arm size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuity correction</td>
<td>Fixed (MH)</td>
<td>14(^9,16-28)</td>
<td>52/4908</td>
<td>27/3308</td>
<td>1.67 (1.06–2.64)</td>
</tr>
<tr>
<td>No continuity correction</td>
<td>Fixed (MH)</td>
<td>14(^9,16-28)</td>
<td>52/4908</td>
<td>27/3308</td>
<td>1.77 (1.09–2.88)</td>
</tr>
<tr>
<td>Use of un adjudicated cardiovascular event data from one trial</td>
<td>Peto OR</td>
<td>14(^9,16-28)</td>
<td>61/4908</td>
<td>29/3308</td>
<td>1.91 (1.25–2.94)</td>
</tr>
<tr>
<td>Exclusion of most influential study</td>
<td>Peto OR</td>
<td>13(^16-28)</td>
<td>27/4553</td>
<td>7/2949</td>
<td>2.54 (1.26–5.12)</td>
</tr>
<tr>
<td><strong>Placebo or active† comparator</strong></td>
<td>Peto OR</td>
<td>15(^9,16-29)</td>
<td>52/5286</td>
<td>30/4486</td>
<td>1.67 (1.07–2.62)</td>
</tr>
</tbody>
</table>

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.
Number Needed to Harm for CV Events

<table>
<thead>
<tr>
<th>Population</th>
<th>Source of baseline risk</th>
<th>Baseline Risk</th>
<th>Annualized Number Needed to Harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers without CVD</td>
<td>Control event rate of Meta-analysis</td>
<td>0.82%</td>
<td>167</td>
</tr>
<tr>
<td>Smokers with stable CVD</td>
<td>Control event rate of trial among smokers with CVD</td>
<td>5.8%</td>
<td>28</td>
</tr>
</tbody>
</table>

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

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

Varenicline and suicidal behaviour in the GPRD

“80,660 participants prescribed NRT (n=63,265), varenicline (n=10,973), and bupropion (n=6,422).

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 to 1.00) 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.”

Substantially more reports of suicidal behavior in patients taking varenicline have been submitted to the US Food and Drug Administration than for any other smoking cessation drug.

**Suicidal and Self-injurious Behavior**

<table>
<thead>
<tr>
<th>MedDRA Terma</th>
<th>Varenicline (n=1819) No. (%)</th>
<th>Bupropion (n=155) No. (%)</th>
<th>Nicotine (n=50) No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed suicide</td>
<td>272 (15.0)</td>
<td>19 (12.3)</td>
<td>4 (8.0)</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>1135 (62.4)</td>
<td>73 (47.1)</td>
<td>40 (80.0)</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>323 (17.8)</td>
<td>56 (36.1)</td>
<td>2 (4.0)</td>
</tr>
</tbody>
</table>

aPreferred terms from the Medical Dictionary for Regulatory Activities (http://www.meddramsso.com).

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)
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

Presented by: Sonal Singh, MD MPH  Singh S et al. CMAJ 2011;183:1359-1366
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

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]
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]
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
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.
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?
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
A Multicriteria decision analytic model for Smoking cessation agents using the Analytic Hierarchy Process
Varenicline (efficacious and safe)

Risk

CV risk

Neuropsychiatric risks

Depression

Suicide

Self harm

Efficacy

Short term abstinence

Long term CV benefit?

No RCT evidence that Varenicline provides CV benefit