The Risk of Adverse Cardiovascular Events from Varenicline Against the Benefits in Mortality from Smoking Cessation

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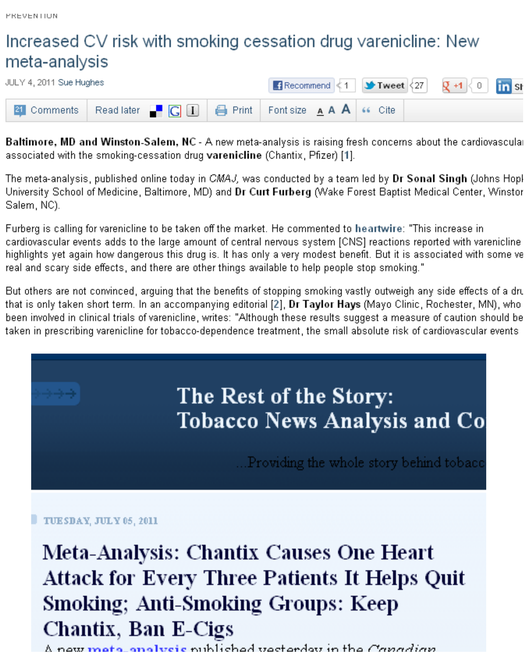
Introduction

- Smokers significantly higher mortality, tobacco cancers, and respiratory disease
- Combining behavioral counseling & pharmacotherapy highest cessation rates
- Varenicline outcomes in controlled trials significantly higher than placebo, sustained release buproprion, or single use NRT
- Meta-analysis by Singh: higher adverse CV events from varenicline, authors suggest harms outweigh benefits
- Quantification of potential varenicline benefits on patient outcomes, such as mortality, not well described



PREVENTION

Increased CV risk with smoking cessation drug varenicline: New meta-analysis

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Baltimore, MD and Winston-Salem, NC - A new meta-analysis is raising fresh concerns about the cardiovascular associated with the smoking-cessation drug **varenicline** (Chantix, Pfizer) [1].

The meta-analysis, published online today in *CMAJ*, was conducted by a team led by **Dr Sonal Singh** (Johns Hopk University School of Medicine, Baltimore, MD) and **Dr Curt Furberg** (Wake Forest Baptist Medical Center, Winstor Salem, NC).

Furberg is calling for varenicline to be taken off the market. He commented to **heartwire**: "This increase in cardiovascular events adds to the large amount of central nervous system [CNS] reactions reported with varenicline highlights yet again how dangerous this drug is. It has only a very modest benefit. But it is associated with some ve real and scary side effects, and there are other things available to help people stop smoking."

But others are not convinced, arguing that the benefits of stopping smoking vastly outweigh any side effects of a dru that is only taken short term. In an accompanying editorial [2], **Dr Taylor Hays** (Mayo Clinic, Rochester, MN), who been involved in clinical trials of varenicline, writes: "Although these results suggest a measure of caution should be taken in prescribing varenicline for tobacco-dependence treatment, the small absolute risk of cardiovascular events

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A new meta-analysis published yesterday in the *Canadian*

Aim

- To begin to calculate a balance of risks and benefits from varenicline that are meaningful to patient encounters
- To calculate the absolute risk increase from any excess cardiovascular events in varenicline users versus expected mortality reduction from varenicline-attributable tobacco cessation
- Use scenario of a 50 year old woman presenting to clinician

Method

Assumptions*

Two groups of 1,000 women smokers aged 50 one group receives standard course of varenicline, other receives placebo for cessation

Adverse cardiovascular events accrue only year 1

Mortality benefit at ten years is meaningful to patients

Initial CV risk from Framingham data

Assume that Singh reports true as published- that varenicline increases odds of an adverse CV event by 1.72

One year spontaneous cessation quit rate among placebo group is 80 of 1,000 (8.0%)

Among women smokers aged 30 to 55, current smokers have 85.6 deaths/10,000 person-years

Smoking status changes will be equal in both groups after the first year

All-cause mortality (hazard-ratio) of those who *quit* smoking for 5 to 10 years is two-thirds (0.67) that of *current* smokers

** Based on best published scientific literature*

Results

Potential Risks

- ❑ Baseline risk of an adverse CV event in a year is 0.4%, or 4 out of the 1000 women
- ❑ If Singh study true, varenicline group would have average absolute risk of CV events of 0.69%, or absolute risk increase of 0.29%., and just less than 7 of the 1000 women taking varenicline would have an adverse CV event in first year
- ❑ Number needed to harm (inverse of the absolute risk increase of 0.29%,)
  - ❑ 1 additional woman might have a adverse CV event over a year for every 345 women taking varenicline, an increase that does not increase in future years

Potential Benefits

- ❑ Placebo group
  - ❑ 80 in placebo group quit smoking & 920 continue to smoke x 10 years
    - ❑ 79 of 920 still smoking expected to die
    - ❑ 4.6 of those that quit expected to die
    - ❑ Total 83.6 expected to die over 10 years
- ❑ Varenicline group
  - ❑ 217 in varenicline group quit smoking & 783 continue to smoke x 10 years (137 additional women quit as a result of the medication)
    - ❑ 67 of the 783 still smoking expected to die
    - ❑ 12.4 of those that quit expected to die
    - ❑ Total 79.4 expected to die over ten years

Summary

- ❑ Absolute Mortality Benefit from one-time varenicline use
  - ❑ 83.6- 79.4 = 4.2 deaths
- ❑ Number needed to benefit
  - ❑ 1 additional life potentially saved over ten years for every 238 people who take one course of varenicline

Limitations

- CV events in two groups is taken at year one
- Calculations do not account for changes in smoking status over time
- Balance differs men or women of different ages

Conclusions

- Risks do not occur in a vacuum
- Clinicians could discuss benefits in more concrete terms "Just over 4 additional lives are saved over ten years at a cost of approximately 3 additional adverse cardiovascular event that would occur in the first year"
- Cost-effectiveness analysis & Markov modeling would allow broader analysis of benefits vs harms

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