

Phenylpropanolamine Banned Based on What?

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The greatest impact of a single epidemiologic study I can recall.

A single study:

WN Kernan et al. Phenylpropanolamine and the Risk of Hemorrhagic Stroke. *New England Journal of Medicine*, 343(25):1826-32, 21 December 2000, (released at nejm.com about three months earlier).

(Only previous epi study was very limited. Showed protective association with substantial uncertainty.)

Motivation for study:

Case reports, primarily associating diet pills with stroke in young women.

Stated Conclusions:

PPA, in the form of cold medicine (decongestant) and diet pills (appetite suppressant) is associated with an increased risk of subarachnoid or intracerebral hemorrhage (stroke).

Primary Result:

Popular drug gone: U.S. FDA removes PPA from diet pills and very popular decongestant formulations.

Secondary Results:

Large number of lawsuits likely.

I get annoyed.

To answer the ethical question of whether the ban was a good idea, we need to know:

How sure are we that there is a harm? (What is the distribution of point estimates?)

Benefits of ban: How big is the health hazard in *absolute* terms?

Costs of ban: What is the cost to consumers of changing to other drugs (new health risks) and/or losing benefits of treatment?

In sum, what is the expected value of change on net welfare?

How sure are we that there is a harm?

Key finding (emphasized the article, press releases, news, and policy discussions):

Target population = women, 18-49, selected geography.

Exposure = use of PPA within ~3.5 days.

Effect = hemorrhagic stroke w/o selected relevant diagnosis.

	Cases	Noncases
Exposed	21	20
Nonexposed	355	713

adj OR = 1.98
 95% c.i. = (1.00, 3.90)

How Robust Is the Result?

How big an error would cause half the observed association? Any of these plausible errors:

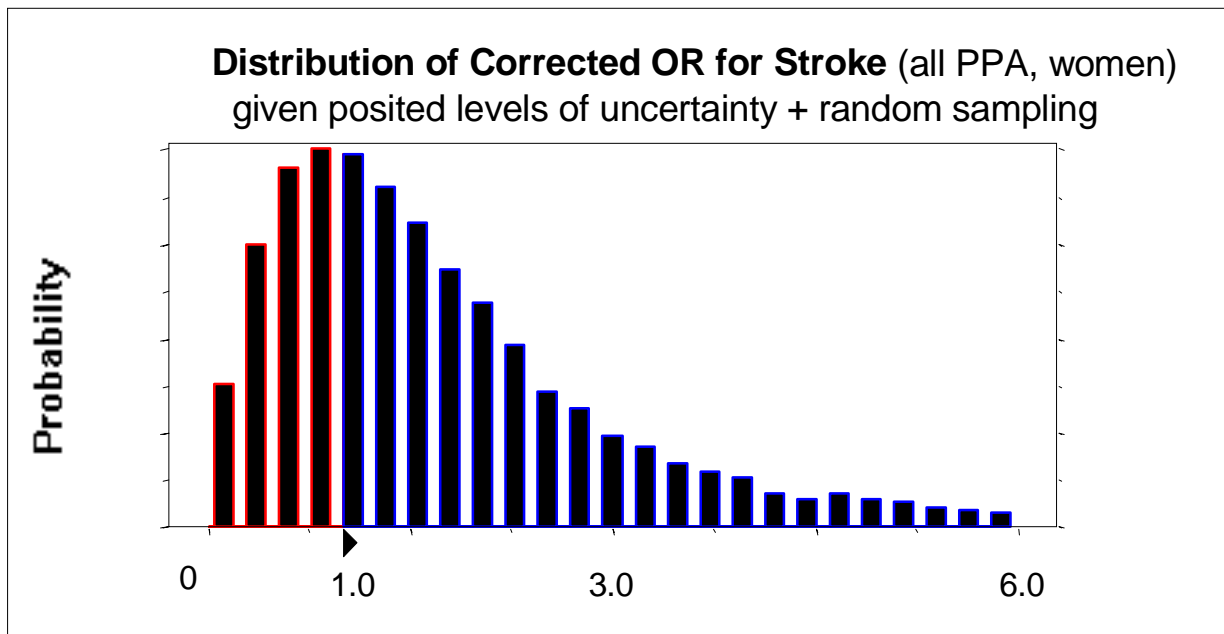
- Exposure specificity for cases 1.5% worse than controls (e.g. .985 and 1.00) because of bias toward finding a cause.
- Control exposure sensitivity of .75 (with all other measurement perfect) because of lack of motivation to think hard about answers.
- Control selection bias: exposed individuals answer the phone at 3/4 the rate of unexposed because of illness or weight loss behavior.
- Severe stroke victims (not studied) have lower exposure by 3 percentage points.
- Plausible residual confounding (details omitted).

A combination of these could plausibly explain the result. The message to the public that the finding is 95% certain is clearly wrong.

Very rough cut at distribution of true OR using Monte Carlo Uncertainty Quantification Methods

If we believed these distributions (all uniform for simplicity):

- $Se \in [.9, 1.0]$ $Sp \in [.95, 1.0]$ for exposure measurement.
- Control selection bias: [.0005, .0012] of exposed, compared to .001 of total.
- Case selection bias: [.5, .6] of exposed, compared to .54 of total.
- No confounding.



(Serves primarily to illustrate the limited robustness of the point estimate.)

Results show a positive association is fairly likely.

Is that enough to justify a major policy response?

We are always uncertain. This is ok! We can and should still make decisions.

What is not ok is not actually considering the costs and benefits.

Target population = men, 18-49.

adj OR = 0.62 It's protective!

Thumbnail of the ethical calculus

-Benefits of the ban

Rate of hemorrhagic stroke for 18-49 year old women =

$$1.8 \times 10^{-7} / \text{woman} \cdot \text{day} \quad (\text{i.e., very low})$$

(all numbers for U.S.)

Accepting the estimate of OR=2,

⇒ ~ 1 extra stroke for each 5½ million days of taking PPA

-Costs of the ban

Next best alternative for consumers and resulting net loss:

Suffer with a nasal congestion.

Switch to pseudoephedrine.

Go without a diet pill.

Switch to ephedra and analogs, caffeine, various weirdness, etc.

So, back of the envelope cost-effectiveness analysis:

Optimistically posit:

3/4 of users find an alternative drug they like just as much (based on acute benefits and costs).

These alternatives create only half the risk of major CV events.

The 1/4 who do not find a substitute would pay only \$10/daily dose to have a safe and effective drug.

⇒ ban costs *women* the equivalent of \$22 million/stroke averted

⇒ costs society the equivalent of **\$44 million/stroke averted**

Way high.

This result (i.e., that it is very high) is quite robust.

Even if these numbers were wrong such that:

Odds Ratio = 3.0, double the effect,
AND *no offsetting side effects* from other drugs,
AND w.t.p. of people who want the drug was
only \$5/day,

This is would still be extremely costly,
even if every prevented stroke were fatal.

So, Why is PPA Gone?

FDA and women's health.

Producers did not manage to fight effectively for it.

Consumers have no effective advocates for their non-health interests, other than the producers.

An Ethical Failing

Public health community does not adequately consider ethical obligation to people's overall well-being.

"Ban something because it has a downside" is a terrible excuse for a public policy ethic.

FDA's position that the beneficial effects cannot justify the side effects is no better.

(By that logic, we should ban video stores.)

There is no substitute for proper cost-benefit analysis.

And that still ignores:

- distributional concerns,
- illiberalism.