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Off-Label Drug Study Yields Off-the-Wall Results

By Josh Bloom — November 5, 2015

[1]The *JAMA* headline alone raised a number of red flags: "Association of Off-Label Drug Use and Adverse Drug Events in an Adult Population." At the very least, the recent *Internal Medicine* on-line article [2] suggests a problem.

And you can bet the delivered message will be something along these lines: That off-label use of prescription drugs is more dangerous than using them as intended.

Is this correct? Is it even possible?

I say no.

Tewodros Eguale, MD, PhD, of McGill University, and colleagues, tried to answer this non-question with a retrospective study of 46, ¯021 patients from primary care clinics in Quebec, Canada, by analyzing data from the Medical Office of the XXIst Century electronic health record during a five-year period beginning in January 2005.

As is the case with any retrospective study, it is virtually impossible to establish cause and effect. Yet, the group claims that when drugs were used off-label, there were 50 percent more adverse drug events (ADE) than when they were used for the FDA-approved use. Sort of.

(Note: Once a drug is approved by the FDA for a particular use, it can be prescribed for any other use. This is very common, and there a number examples where off-label use to treat a particular condition is actually an improvement over existing drugs that were approved for that condition.)

Even a brief look at the abstract reveals this is nonsense: "[The study examined] [a]dverse drug events in off-label use with and without strong scientific evidence."

And, "The rate of ADEs for off-label use (19.7 per 10, ¯000 person-months) was higher than that for on-label use. ... However, off-label use *with strong scientific evidence had the same risk* for ADEs as on-label use."

Translation: A lousy study showed an increase in ADEs with off-label use, but a good study showed no difference at all.

My comment: Duh.

Why was this paper even published? From the beginning, even the *premise makes no sense.* Here's why:

1. Let's say that you use L-DOPA, a drug (and a lousy one at that) for Parkinson's Disease. One of the side effects is nausea. If it is prescribed off-label for toenail fungus -- and it isn't -- is it going to produce any more nausea? (Hint: No). If so, this would lead to the insane conclusion that the Parkinson's somehow protected those with the disease from nausea. Please.
2. If this were true, it would really mess up clinical trials. In Phase I, any drug seeking approval is given to healthy volunteers, and they are monitored very closely for all biochemical and physical effects that might suggest toxicity. In Phase II, the drug is given to people with a disease, infection or condition, to see if it works. Are people who are (by definition) *sicker* than the control group really going to have *fewer* side effects? No. Whatever is going on here is not real.
3. The only way that this could be true is if the off-label use was a larger dose than that for the for the approved condition. This is extremely unlikely. In fact, it is likely to be the opposite.

Although the title of the paper doesn't contradict the conclusion from the study more common that you'd think it really should have read "Adverse Drug Effects Are No More Or Less Common When a Drug is Used Off-label."

Or, maybe something just as obvious, like "Gravity Works."
