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New study design holds promise for drug safety research

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As the pace of drug approvals accelerates and the U.S. Food and Drug Administration (FDA) faces potential budget cuts, a new research design from Perelman School of Medicine scientists offers a new way to successfully assess safety of newly approved drugs, as well as drugs that have been on the market for a long time and have had a marked rise in their use. The study, published in the July issue of the journal *Epidemiology*, offers benefits over typically used randomized clinical trials, as such studies are often too small to identify rare side effects or may be performed in a group of patients who do not take other types of medications or have other conditions that could skew the drug's effect in a broader group following approval. Also first-in-class drugs may not have an applicable comparator drug, and traditional follow-up studies may give inaccurate results if those who take a new drug are different from those who took the comparator drug.

In this new, unbiased, "trend-in-trend" design, researchers monitor changes in frequency of outcomes as they relate to changes in an exposure to a drug across groups that adopt the drug at different rates. This method can be used to study newly approved drugs or any drug that has a rapidly increasing or rapidly declining trend in consumption.

The trend-in-trend concept, designed by senior author Sean Hennessy, PharmD, PhD, a professor of epidemiology in the department of Biostatistics, Epidemiology & Informatics, and his colleagues, may be a welcome addition to an industry in need of support. The FDA review process for new standard drugs is accelerating - from 12 months in FY

13 to 10 months in FY 14. Drugs the FDA designate as "priority," those deemed to have a particularly significant impact - are reviewed even faster, in a median of 7.9 months in FY14. Ninety-two percent of priority classified drugs were approved in their first review cycle in FY14, up from 78 percent in FY13. Approvals for standard drugs also increased from 54 percent in FY13 to 60 percent in FY14. The U.S. approves drugs faster than Europe and Canada does. This means that drugs can have unknown safety issues at the time of approval. A fifth of all drugs receive a black boxed warning (the highest level of warning on a drug's label) after approval, and 4 percent of drugs are ultimately withdrawn for safety reasons.

The U.S. President's proposed budget includes an 18 percent cut to the department of Health and Human Services (which oversees the FDA) and calls for rolling back regulations across many industries. These changes create uncertainty for health providers and consumers about whether the agency will be able to maintain drug safeguards in place.

Using the example of the pain reliever rofecoxib, which was sold under the brand name Vioxx, and the occurrence of heart attack, the researchers reproduced that known association between the two using the new research method. When Vioxx was approved it was rapidly embraced by patients, but then quickly lost favor as safety concerns came to light, making it an ideal model to demonstrate this design.

"Epidemiologic studies can get the wrong answer if there are differences between people who take the drug and people who don't take the drug," said Hennessy, who is also a Leonard David Institute of Health Economics senior fellow. "This kind of study is immune to that bias, because it's not comparing users to non-users, it's looking at trends in the frequency of outcome as a function of trends in the frequency of exposure. Even when there are unmeasured factors that are different between groups and those factors affect the outcome - this study will

give the correct answer."

This also applies to drugs that are already popular but have not been sufficiently examined. The team has applied for a grant looking, for instance, at potential cardiac risks associated with testosterone supplementation. Testosterone became rapidly popular and then rapidly unpopular—circumstances which would allow the research team to study the cardiovascular effects of testosterone which are uncertain because of the limited number of people studied in randomized trials.

More information: Xinyao Ji et al, The Trend-in-trend Research Design for Causal Inference, *Epidemiology* (2017). DOI: 10.1097/EDE.0000000000000579

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