Off-label use: Oft not evidence based

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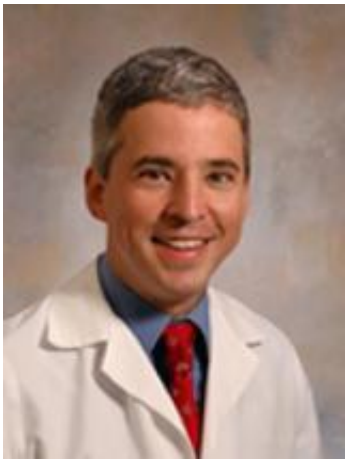

"Our research shows that some off-label prescribing might be driven by mistaken beliefs about FDA approval and the level of evidence supporting off-label drug use," said G. Caleb Alexander, MD, MS, assistant professor of medicine at the University of Chicago Medical Center. Credit: The University of Chicago Medical Center

In a recent national survey, a substantial minority of physicians erroneously believed that certain off-label uses of prescription drugs were approved by the Food and Drug Administration. This mistaken belief could encourage them to prescribe these drugs, despite the lack of scientific evidence supporting such use.

"Off-label prescribing is common, but researchers have not always known why. Our research shows that some off-label prescribing might be driven by mistaken beliefs about FDA approval and the level of

evidence supporting off-label drug use," said G. Caleb Alexander, MD, MS, Assistant Professor of Medicine at the University of Chicago Medical Center and corresponding author of the research, which will be published under an embargo in *Pharmacoepidemiology and Drug Safety* on August 21, 2009. "The results indicate an urgent need for more effective methods of informing physicians about the level of evidence supporting off-label drug use—especially for common off-label uses that are ineffective or carry unacceptable risks of harm."

Overall, physicians were able to correctly identify the FDA-approval status of just over half (mean 55%) of the 22 drug-indication pairs (i.e., a particular drug prescribed for a particular condition) that were included in the survey.

In many cases, the proportion of physicians who erroneously believed a particular drug was FDA approved for a specific indication was higher among physicians who had prescribed the drug for that indication.

For example, 26% of all physician respondents erroneously believed that lorazepam was FDA approved for chronic anxiety. That figure rose to 33% for physicians who had prescribed lorazepam for chronic anxiety.

And 13% of all physician respondents erroneously believed that quetiapine (Seroquel®) was FDA approved for dementia with agitation. That figure rose to 19% for physicians who had prescribed quetiapine for dementia with agitation. At the time of the study there was even an FDA-advisory specifically urging caution regarding the off-label use of quetiapine in patients with dementia.

The survey of 1,199 physicians (599 primary care physicians and 600 psychiatrists) was conducted in 2007-2008 and included 22 drug-indication pairs. The indications varied in their FDA approval status from on-label use to off-label use supported by medical evidence to off-

label use deemed to be ineffective. (The level of evidence supporting or not supporting each specific use was based on Drugdex, an independent drug compendium.)

The FDA makes it clear that they regulate the marketing of prescription drugs, not prescribing. The agency approves drugs for marketing with an official "label" that stipulates an indication, dose, intended population, duration of use, and other specifications. However, physicians and other licensed prescribers are free to prescribe any approved drug for any indication, whether or not the indication is included on the drug's FDA-approved label.

"Some physicians and health care experts maintain that physicians should know the evidence, not the FDA labeling. However, knowledge about FDA labeling can be important because FDA approval of a drug for a specific indication indicates a clear threshold of evidence supporting that use," said Donna Chen, MD, Assistant Professor of Biomedical Ethics, Public Health Sciences, and Psychiatry at the University of Virginia. Dr. Chen is the lead author of the research, entitled "U.S. physician knowledge of the FDA-approved indications and evidence base of commonly prescribed drugs: results of a national survey".

A study published in the *Archives of Internal Medicine* by other investigators in 2006 indicated that approximately 21% of drug uses in the United States occur for off-label purposes, with 73% of those cases lacking scientific evidence of the drug's effectiveness. The highest rates of off-label use were for anticonvulsants (74%), antipsychotics (60%) and antibiotics (41%).

"We hope our research will increase awareness of off-label prescribing and highlight the pressing need for more evidence-based use of prescription drugs," Alexander said. "Although some off-label uses are

well-supported, many are not. New ways are needed to help physicians tap the scientific evidence supporting various prescription drug uses."

Some disadvantages of off-label use

- May diminish public expectation that drugs will be evaluated for safety and efficacy before use
- Blunts industry incentives to perform studies required for FDA label changes
- Drugs used off label may have unrecognized safety and efficacy problems
- Promotes use of drugs in populations (e.g., children, the elderly) for which they have not been tested

Source: G. Caleb Alexander, MD, MS, Assistant Professor of Medicine at the University of Chicago Medical Center

Some advantages of off-label use

- Allows for clinical innovation, especially for patients who do not respond to standard treatments
- May be only available option for uncommon conditions or for patient populations that have not been studied
- Allows physicians to anticipate growing evidence of efficacy prior to formal evaluation

- Increases return on investment for pharmaceutical firms

Source: G. Caleb Alexander, MD, MS, Assistant Professor of Medicine at the University of Chicago Medical Center

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