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14 drugs identified as most urgently needing study for off-label use, Stanford professor says

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Physicians and policy-makers know that drugs are frequently prescribed to treat certain diseases despite a lack of FDA approval — a practice known as off-label prescribing. Yet they say the problem is so big they don't know how to begin tackling it.

But a potential game plan now exists. In a paper to be published in the December issue of *Pharmacotherapy*, a group of researchers has developed a list of 14 widely prescribed medications most urgently in need of additional study to determine how effective and safe they are for their off-label uses. Antidepressants and antipsychotics are the most prominent classes of drugs on the list, which specifically targets drugs that have high levels of off-label use without good scientific backing.

"Off-label prescribing means that we're venturing into uncharted territory where we lack the usual level of evidence presented to the FDA that tells us these drugs are safe and effective," said Randall Stafford, MD, PhD, associate professor of medicine at the Stanford Prevention Research Center, who is the senior author of the study. "This list of priority drugs might be a start for confronting the problem of off-label use with limited evidence."

Stafford collaborated on the research with lead author Surrey Walton, PhD, assistant professor of pharmacy administration at the University of Illinois-Chicago, and other researchers at UIC and the University of

Chicago.

At the top of the list was quetiapine (brand name Seroquel), an antipsychotic approved by the U.S. Food and Drug Administration in 1997 for treating schizophrenia. Not only did this drug lead all others in its high rate of off-label uses with limited evidence (76 percent of all uses of the drug), it also had features that raised additional concerns, including its high cost at $207 per prescription, heavy marketing and the presence of a "black-box" warning from the FDA, Stafford said.

Rounding out the top five were warfarin, escitalopram, risperidone and montelukast.

The most common off-label use for six of the 14 drugs on the list was for bipolar disorder. "Many of the drugs and the conditions on the list represent situations where inadequate response to treatment is common and where drug side-effects are frequent," Stafford said. "Not only are these areas where patients and physicians are naturally interested in trying off-label therapies, but areas targeted for expansion by the makers of these drugs.

"When the volume of off-label use of any drug reaches the magnitude that we're documenting, it suggests a role of the pharmaceutical industry in facilitating these types of uses," he added.

Although companies are largely prohibited from marketing off-label uses to physicians and consumers, they make use of exceptions or may market drugs illegally, Stafford said. Companies are allowed to share with physicians any published research that supports off-label uses. Several recent lawsuits have identified systematic plans on the part of some companies to market their products for off-label uses, he noted.

Previous studies have demonstrated the breadth of off-label prescribing.

A 1985 study found that of the 100 most common uses of marketed drugs, 31 of those uses did not have approval from the FDA. And a study that Stafford led in 2006 showed that of the estimated 21 percent of off-label drug uses in 2001, 73 percent did not have strong scientific support.

To get a drug approved by the FDA, a pharmaceutical company must complete three rounds of testing in human subjects to demonstrate its safety and effectiveness in treating a specific condition. Once a drug is approved and on the market, though, physicians may choose to prescribe it for any condition. But this carries unknown risks because often the drug hasn't been rigorously tested on patients with that condition.

"Many patients and physicians assume that the FDA has scrutinized all of the different ways a drug can be used, but they've only examined those uses that have gone through the approval process," Stafford said.

And pharmaceutical companies aren't often interested in spending money to investigate additional conditions that the drug might treat. Stafford said the companies may consider it risky to invest in additional testing that could show undesired results, especially when a drug is already widely used off-label.

To come up with a plan for determining which drugs were most in need of additional research for off-label use, Stafford and his colleagues convened a panel of nine experts from the FDA, the health-insurance industry, the pharmaceutical industry and academia. Based on the panel's input, the researchers identified three factors to help them prioritize the drugs that should appear on the list, including:

-- The volume of off-label drug use with inadequate evidence supporting that use (based on a large, ongoing national survey of physician prescribing patterns conducted by IMS Health, a private market-research

company).

-- The safety of the drug (based on any safety warnings issued by the FDA).

-- A composite of the drug's cost, how long it had been on the market and the amount spent marketing the drug.

After collecting the information, the researchers computed the drug rankings in each category and then came up with an overall list of the 14 drugs most in need of additional study. "Despite examining the data in a variety of ways by providing more or less emphasis on certain factors, we still came up with a very consistent list of drugs," Stafford said.

He said that in addition to prompting the FDA and other government agencies to study the priority drugs on the list, he hopes the research spurs patients to ask their doctors why they are prescribing a particular drug. "A dialogue needs to occur more frequently between physicians and patients regarding the level of evidence that supports a particular use of a drug."

Stafford also noted the societal costs associated with off-label drug use. With the prescription drug benefit now available through Medicare, taxpayers are getting the bill for costly drugs that may not be proven for the conditions they're prescribed to treat.

Source: Stanford University