Evidence lacking for widespread use of costly antipsychotic drugs

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Many prescriptions for the top-selling class of drugs, known as atypical antipsychotic medications, lack strong evidence that the drugs will actually help, a study by researchers at the Stanford University School of Medicine and University of Chicago has found. Yet, drugs in this class may cause such serious effects as weight gain, diabetes and heart disease, and cost Americans billions of dollars.

"Because these drugs have safety issues, physicians should prescribe them only when they are sure patients will get substantial benefits," said Randall Stafford, MD, PhD, associate professor of medicine at the Stanford Prevention Research Center, who is senior author of the study to be published online Jan. 7 in *Pharmacoepidemiology and Drug Safety*. "These are commonly used and very expensive drugs."

Prescriptions for these drugs have risen steadily since they first came on the U.S. market in 1989, largely replacing the first generation of antipsychotics, which were mainly used to treat schizophrenia. The U.S. government's original stamp of approval for the new drugs was for treating schizophrenia, but they're used more today for other conditions, including other psychoses, autism, bipolar disorder, delirium, dementia, depression and personality disorders. And while some of these uses have recently been approved by the U.S. Food and Drug Administration, many have not.

For example, the FDA has approved quetiapine (brand name, Seroquel), the antipsychotic with the biggest U.S. sales, for treating schizophrenia

and some aspects of bipolar disorder and depression, but the drug is also often used for anxiety and dementia, among other conditions.

These new drugs accounted for more than $10 billion in retail pharmacy U.S. prescription drug costs in 2008, representing the largest expenditure for any single drug class — nearly 5 percent of all drug spending, surpassing even blockbusters like statin cholesterol medications. According to a 2004 study, a quarter of all residents of U.S. nursing homes had taken them. Among the drugs are quetiapine, aripoprazole (brand name, Abilify), olanzapine (Zyprexa) and risperidone (Risperdal), each with annual U.S. sales exceeding $1 billion.

Stafford's new study adds to concerns about the drugs, which have been the focus of thousands of lawsuits, and as a class make up the single largest target of litigation filed under the federal False Claims Act. All major companies selling new-generation antipsychotics have either recently settled cases for hundreds of millions of dollars or are currently under investigation for skewing results or using questionable marketing tactics.

In 2005, the FDA issued its strongest type of caution, the "black box" warning, for use of new-generation antipsychotics, because of increased risk of death for dementia patients.

"Most people think, 'If my doctor prescribed this, the FDA must have evaluated whether this drug was safe and effective for this use.' That's not true," said Stafford. When doctors prescribe drugs for purposes other than those approved by the FDA, it's called "off-label" use. Though it's riskier for patients, there's nothing illegal about it, and can make sense medically in some instances, Stafford said, especially if there are no approved treatments or if a patient has not responded to approved drugs.

Previous studies had shown that antipsychotic drug use is ballooning. Stafford's new study not only corroborated and updated these findings but also identified the fraction of off-label use that is based on uncertain evidence.

The researchers' first step was to analyze the results of a physicians' survey conducted by health-care information company IMS Health. The IMS Health National Disease and Therapeutic Index survey gives a snapshot of the conditions doctors treated and drugs they prescribed. About 1,800 physicians participate each calendar quarter and each is randomly assigned two days per quarter to provide data.

After identifying which antipsychotics were being used, and for what, the researchers assessed the strength of the evidence supporting those that lacked FDA approval, using efficacy ratings from the widely used drug compendium, Drugdex.

Lead author Caleb Alexander, MD, assistant professor of medicine at the University of Chicago, and colleagues conducted the analysis. Stafford supervised the project and with Alexander interpreted the data. Stanford clinical assistant professor of psychiatry Anthony Mascola, MD, provided expertise on the treatment of psychiatric conditions.

Among their findings:

- Antipsychotic treatment prescribed during the surveyed doctors' visits nearly tripled from 6.2 million in 1995 to 16.7 million in 2008, the most recent year for which they had data. During this period, prescriptions for first-generation antipsychotics decreased from 5.2 million to 1 million.

- Antipsychotic use for indications that lacked FDA approval by

the end of 2008 increased from 4.4 million prescriptions during surveyed doctors' visits in 1995 to 9 million in 2008.

- In 2008, more than half — 54 percent — of the surveyed prescriptions for the new-generation antipsychotics had uncertain evidence.

- An estimated $6 billion was spent in 2008 on off-label use of antipsychotic medication nationwide, of which $5.4 billion was for uses with uncertain evidence.

- Prescriptions for antipsychotics began dropping slightly in 2006, shortly after the FDA issued a warning about their safety.

Stafford suggests the upswing in prescriptions for antipsychotics despite the absence of good evidence for their value in many instances is the result of marketing — whether legal or illegal — and ingrained cultural tendencies. "Physicians want to prescribe and use the latest therapies — and even when those latest therapies doesn't necessarily offer a big advantage, there's still a tendency to think that the newest drugs must be better," he said.

Physicians could benefit from more feedback on what percentage of their prescriptions is for off-label uses, said Stafford. "In many cases, physicians don't realize they're prescribing off-label," he said.

In fact, in a previous survey of physicians, Alexander found that the average respondent accurately identified the FDA-approval status of drugs for a given condition just over half the time.

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