Impact of FDA safety warnings examined

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A study published today in the *Archives of Internal Medicine* examines the impact of a safety warning issued by the Food and Drug Administration for commonly prescribed antipsychotic medications. The results show the warnings resulted in a decline in usage among the elderly with dementia, yet raise the question as to whether the FDA's system of communicating these warnings is sufficiently targeted and effective.

"Because this medication class has limited evidence of benefit among the elderly with dementia and significantly increases their risk of death, the 'right' magnitude of decline in usage is not clear," said University of Rochester Medical Center neurologist Ray Dorsey, M.D., the study's lead author. "More generally, the study raises larger issues about appropriate prescribing, particularly among the elderly, and the need to improve risk communication to patients and providers."

Safety issues frequently emerge after a drug has been introduced to the market. These concerns arise either through ongoing clinical research or adverse events reported by post-market surveillance of the drug. The FDA can act upon this information in a number of ways. It can choose to remove the drug from the market or it can issue an advisory to physicians, the strongest of which is a "black box" warning which appears on the drug label.

The authors examined the impact of these warnings on a class of drugs called atypical antipsychotics. In April 2005, the FDA issued an advisory warning that elderly patients with dementia treated with these drugs were

at increased risk of death.

While atypical antipsychotic drugs have only been approved by the FDA to treat conditions such as schizophrenia and bipolar affective disorder, drugs are often used to treat conditions for which they have not been licensed. This practice is referred to as "off-label," meaning the condition is not listed on the drug's label as an approved use. In this case, the FDA warning applied to the off-label use of these drugs to treat behavioral disorders in elderly patients with dementia. The FDA issued the advisory after data from clinical studies of these drugs in this population showed a 60-70% higher death rate than those receiving a placebo.

Using a national database of office-based prescribing developed and maintained by IMS Health, Inc., the authors evaluated usage of atypical antipsychotics both before and after the issuance of the FDA warning. Prior to the advisory, use of these drugs among patients with dementia grew at an average annual rate of 16%. In the year following the advisory, their use among this population fell by 19%. Use of antipsychotics continued to decline in subsequent years, and by 2008 (three years after the FDA warning), their use among the elderly with dementia was about 50% less than before the warning.

"Given the risks of atypical antipsychotics among the elderly, these reductions in use represent an important first step," said University of Chicago Medical Center internist Caleb Alexander, M.D., co-author of the study. "All too often, these drugs have been used in settings with unclear benefits and unacceptable risks, and despite the decreases we document many elderly with dementia continue to receive these therapies."

Warnings that involve off-label use of medications create a complex set of problems for regulators and physicians. In an accompanying editorial,

it is noted that the elderly are historically under-represented in clinical trials, which places physicians in the uncomfortable position of generalizing evidence obtained from one population to another population where the risk to benefit trade-off may be different. When the risks are deemed to be significant, the FDA is then placed in a position of having to develop the right message and ensure that it reaches the target audience, which in this instance was for a usage that had not been approved by the agency.

The authors contend that the approach currently employed by the FDA needs to be supplemented with efforts such as communications that target the most frequent prescribers of the medication, as opposed to a blanket communication to all physicians, and a coordinated effort between the FDA and the drug's manufacturers to inform patients and/or their families of safety risks.

Additionally, advisories may also need to contain more specific information for providers, such as potential alternative treatments. Without such direction, particularly in instances where the medication is being used off-label and there is no clear alternative, physicians could potentially end up choosing a drug which is worse. In the case of antipsychotic medications, a potential alternative is conventional antipsychotic therapy, a treatment option that could expose patients to even greater safety risks.

"This study points to the clear need to improve the manner by which we communicate drug advisories to the public," said Dorsey. "Physicians and patients need direct and clear communication about drug risks if the goal is to restrict or modify usage and improve public health."

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