LDI Clinical Brief

Leonard Davis Institute of Health Economics Volume 13, Number 7 • Summer 2008

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Drug Safety and Surveillance: the Case of Avandia

Editor's note: A year ago, a meta-analysis published in The New England Journal of Medicine sounded alarms about the cardiovascular safety of the popular diabetes drug Avandia (rosiglitazone). The study caused both policymakers and the public to question the Food and Drug Administration's ability to ensure the safety of drugs brought to the marketplace, and evoked memories of Vioxx, the painkiller withdrawn from the market in 2004 because of its link to heart attacks. A year after the Avandia story broke, this Clinical Brief revisits the controversy, summarizes a new study of the cardiovascular safety of diabetes drugs, and analyzes the policy implications for the drug approval process.

Avandia lowers blood glucose, but its effects on other outcomes is not known

Avandia was first marketed in 1999 as an oral treatment for Type 2 diabetes. It was adopted quickly, becoming the top selling oral diabetes drug in the U.S. in 2006. Avandia, and its sister drug Actos (pioglitazone), belong to the drug class thiazolidinediones (TZDs), which reduce insulin resistance. [The first TZD, Rezulin (troglitazone) was removed from the market for causing liver disease.] TZDs can be used alone or with other hypoglycemic drugs to improve glycemic control in diabetic patients.

- As with other diabetes drugs, Avandia was approved for marketing on the basis of its ability to lower blood glucose. Its effects on longer-term outcomes, such as microvascular complications or cardiovascular disease, were unknown. Premarketing studies were not designed to examine these outcomes.
- Because TZDs can cause fluid retention, Avandia was not recommended for patients with symptomatic heart failure. In August 2007 the FDA requested that both Avandia and Actos carry a stronger "black box" warning against its use in patients with heart failure.
- After approval, some signals suggested that Avandia might increase the risk of myocardial ischemia that might lead to heart attacks, but the evidence was inconclusive. A post-marketing clinical safety trial of 4,400 patients was eventually launched, with results to be available in 2009. In May 2007, a meta-analysis combining the results of 42 clinical trials of Avandia found a 43% percent increased risk of heart attack among patients taking the drug, mostly compared to a placebo. However, the analysis combined studies of various designs and goals, and included some studies of non-diabetic patients. The article prompted the FDA to convene a panel to review the evidence and recommend any action.

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- In July 2007, the panel acknowledged the possibility of elevated risk of heart attacks with Avandia, especially when used in combination with insulin, but voted overwhelmingly to keep the drug on the market. In November 2007, Avandia's labeling was changed to include the results of the meta-analysis, as well as the FDA's determination that there was not enough evidence that Avandia posed an increased risk for myocardial ischemia, especially compared to other approved drugs to manage diabetes.

New study compares cardiovascular outcomes among patients on different diabetes drugs

To compare cardiovascular outcomes associated with different diabetes treatments, Margolis and colleagues used The Health Information Network (THIN), a medical records system set up in 2002 in the United Kingdom. THIN contains records from about 300 UK general practices, and includes 4.78 million patients, of which 2.26 million are currently active. The investigators identified patients with at least two records for Type 2 diabetes between January 2002 and January 2006 who were at least 40 years old.

- The investigators studied two cohorts within the database: individuals diagnosed with diabetes at any time, and a sub-cohort of those diagnosed after 2002. There were 63,579 individuals in the first cohort, with median diabetes duration of 6.5 years, and 13,576 in the sub-cohort.
- The primary outcome of interest was the onset of serious cardiovascular disease after exposure to an oral diabetic medication. These outcomes included myocardial infarction, unstable angina, cardiac death, as well as coronary artery procedures such as angioplasty or bypass surgery.
- The investigators adjusted for confounding factors such as age, sex, body mass index, and prior history of cardiovascular disease.

Lower, not greater, risk of heart attacks found with Avandia use

Overall, the analysis revealed that diabetic patients using TZDs had a lower risk of myocardial infarction and other myocardial ischemic events, compared to users of other therapies used to treat diabetes. Conversely, those who used insulin and sulfonylureas had a higher risk of myocardial infarction, a risk that emerged or increased with longer use.

- Of the 63,579 individuals in the long-term cohort, 5,644 experienced one of the cardiovascular outcomes. After adjusting for other factors, the investigators found an increased risk of serious cardiovascular disease associated with insulin (hazard ratio, 1.2) and decreased risk associated with both TZDs (hazard ratio, 0.5).
- Of the 13,576 individuals in the more recently diagnosed cohort, 744 experienced one of the cardiovascular outcomes. After adjusting for other factors, the investigators found an increased risk of serious cardiovascular disease associated with insulin (hazard ratio, 2.4), sulfonylureas (hazard ratio, 1.4) and decreased risk associated with both TZDs (hazard ratio, 0.8).
- Risk increased as total duration of therapy increased for insulin, sulfonylureas, and biguanide, but decreased with duration for both TZDs. No additional risk was associated with combinations of drugs.
- This study does not definitively answer whether Avandia increases or decreases the risk of cardiovascular events, but it does emphasize that careful studies are necessary after a drug is marketed to learn about unexpected risks.

Drug safety in perspective

In June 2007, Strom submitted testimony about the Avandia controversy to a Congressional oversight committee. In it, he discussed the scientific issues of Avandia safety regarding myocardial infarction, and cautioned against an exaggerated response to the meta-analysis.

- Strom said that the meta-analysis raised a signal of concern, but that other available studies had not confirmed the findings. He noted that the post-marketing trial was underway to more definitively answer the question, and that the FDA, physicians, and patients could reasonably await these results. He also mentioned the significant risk to patients of quickly withdrawing a drug that was helping to control their blood glucose.
- Strom emphasized that many adverse reactions will not be known at the time of approval, and that such a situation is not evidence that the FDA has failed. Generally, a drug is studied in roughly 2000-3000 patients before approval—meaning that adverse reactions that occur once per 100 patients will be known at the time of marketing. In contrast, adverse reactions that occur once per 1000 patients will not be known at the time of marketing. "The problem is that these studies take a long time to conduct, and we have to ask whether we should deny patients access to the drug while these studies are underway. My view is that these studies should be done, and the drugs should be available while they are being done, but only selectively to patients that really need them. The situation we have now is that new drugs are overused too early."

A proposal to improve the drug safety system

The Avandia controversy highlights the holes in the U.S. drug safety system, which does not accommodate the need for studies after a drug is marketed. Until recently, the FDA did not have the regulatory or enforcement authority to require such data. Pharmaceutical manufacturers have little incentive to provide these data. Strom outlined his vision of systemic changes that would improve the ability of the FDA to ensure drug safety.

- Conditional approval. Initial drug approval should at first be conditional. During this time, marketing, especially direct-to-consumer marketing, should be restricted. Conditional approval would be removed only when sufficient numbers of individuals have been investigated to ensure the detection of rare side effects and to answer drug safety questions that emerged pre-marketing or thereafter. This way, drug use immediately after marketing would be restricted to those who truly need the drug, in whom the risk/benefit balance in the face of uncertainty is more favorable.
- Empowered FDA. Strom and others noted that the FDA could not require post-marketing studies or labeling changes; rather, any changes were subject to negotiation between the FDA and the manufacturer. Congress addressed this issue in September 2007, at least in part, when it gave the FDA the regulatory authority to require post-marketing data, enforcement authority to fine manufacturers if necessary, and new resources set aside for drug safety.

POLICY IMPLICATIONS

At this point, the link between Avandia and ischemic cardiac outcomes remains unknown. The results of the meta-analysis that raised public concerns have not been confirmed by subsequent studies. The new study described in this brief, although retrospective in nature, found a reduced risk associated with Avandia. While the Avandia question remains unsettled, the episode does serve as a cautionary tale about existing flaws in the system.

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POLICY IMPLICATIONS

- Congress and the public must be given a better perspective on the benefits and risks from pharmaceutical products. Drugs are not without risk, and a drug's balance of risks and benefits becomes less favorable as the drug is marketed to wider populations with less specific need. Many risks can be determined only after a drug is marketed to these wider populations.
- The system must provide pharmaceutical manufacturers with incentives to provide postmarketing information, rather than disincentives. A conditional approval designation would prompt drug sponsors to gather post-marketing safety information quickly.
- The FDA should fully use its new regulatory authority to address some of the post-marketing safety questions that will inevitably arise. The additional resources devoted to drug safety, while critically important, remain inadequate. In 2008, the FDA will collect an additional $25 million in user fees (from the drug industry) for post-marketing safety, which will increase by $10 million per year through 2012. The Institute of Medicine estimates that 10 safety signals per year could be evaluated extramurally at an annual cost of $10-$60 million. The FDA's budget increase is dwarfed by the $188.5 billion spent on prescription drugs in the U.S. in 2004 and the $11.9 billion spent on pharmaceutical advertising in the same year.

This Clinical Brief is based on the following article: D.J. Margolis, O. Hoffstad, B.L. Strom. Association between serious ischemic cardiac outcomes and medications used to treat diabetes. Pharmacoepidemiology and Drug Safety, August 2008 (published online July 9, 2008 at http://dx.doi.org/10.1002/pds.1630); B.L. Strom. Statement for the hearing of the United States House of Representatives Committee on Oversight and Government Reform, June 7, 2007. Available at: http://republicans.oversight.house.gov/Media/PDFs/20070607StromTS.pdf. See also B.L. Strom. How the US drug safety system should be changed. Journal of the American Medical Association, May 3, 2006, vol. 295, pp. 2072-5.

Published by the Leonard Davis Institute of Health Economics, University of Pennsylvania, 3641 Locust Walk, Philadelphia, PA 19104.
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This Clinical Brief and the Margolis study it describes were supported by Grant Number UL1RR024134 from the National Center for Research Resources. The opinions expressed are those of the authors and not the funding agency. Dr. Margolis reports no potential conflicts of interest. Dr. Strom is currently involved in a sponsored research agreement with Takeda Pharmaceutical through the Trustees of the University of Pennsylvania. They manufacture pioglitazone. The primary outcome of that study and those reported here are not the same.

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Clinical Brief

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Leonard Davis Institute
of Health Economics
University of Pennsylvania

Nonprofit Organization
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Permit No. 2563
Philadelphia, PA 19104