



Online article and related content
current as of February 3, 2009.

The Safety of New Medicines: The Importance of Asking the Right Questions

Alastair J. J. Wood

JAMA. 1999;281(18):1753-1754 (doi:10.1001/jama.281.18.1753)

<http://jama.ama-assn.org/cgi/content/full/281/18/1753>

Correction

[Contact me if this article is corrected.](#)

Citations

[This article has been cited 15 times.](#)
[Contact me when this article is cited.](#)

Topic collections

Public Health; Quality of Care; Patient Safety/ Medical Error; Drug Therapy; Drug
Therapy, Other
[Contact me when new articles are published in these topic areas.](#)

Related Articles published in
the same issue

The Safety of Newly Approved Medicines: Do Recent Market Removals Mean
There Is a Problem?
[Michael A. Friedman et al. *JAMA*. 1999;281\(18\):1728.](#)

Subscribe

<http://jama.com/subscribe>

Permissions

permissions@ama-assn.org
<http://pubs.ama-assn.org/misc/permissions.dtl>

Email Alerts

<http://jamaarchives.com/alerts>

Reprints/E-prints

reprints@ama-assn.org

The Safety of New Medicines

The Importance of Asking the Right Questions

Alastair J. J. Wood, MD

THE ARTICLE IN THIS ISSUE OF THE JOURNAL BY Friedman and colleagues¹ at the US Food and Drug Administration (FDA) explores the important question: “Has the number of drug withdrawals increased since the passage of the Prescription Drug User Fee Act?” This question was stimulated by an apparent spate of recent removals—5 drugs in 1 year. However, when the data were analyzed, not by the year of drug removal but by the year of drug entry into the market, the clustering of cases was not apparent. This finding is reassuring as it does not support previous criticism of the changes that followed the passage of the legislation. The rejection of 1 hypothesis should be viewed as a challenge to the scientific community and the FDA to enter into a public discussion to define what can be learned from the removal of these drugs and can be used to prevent, or more realistically, minimize the risk of future unnecessary exposure of patients to adverse drug events. Information on the 5 drugs withdrawn given in Table 7 of the article by Friedman et al¹ suggests that such a discussion would be productive.

Several conclusions are readily apparent from these data. First, a staggering 19.8 million patients (almost 10% of the US population) were estimated to have been exposed to these 5 drugs before their removal. Second, none of the drugs was indicated for a life-threatening condition nor, in many cases, were they the only drugs available for that indication. There are many unanswered questions about these drug withdrawals, which if investigated and answered would help to improve drug safety. For example, in the 11 months that bromfenac was available, it is remarkable that physicians prescribed this new nonsteroidal, known to elevate liver enzymes, to 2.5 million patients with acute pain, even though many well-tested similar drugs were available. How could a nonsteroidal for the treatment of pain, with a restriction that patients take it for no more than 10 days, be cost-effective for a pharmaceutical manufacturer to market? Why did the drug cause hepatotoxic effects? In the case of fenfluramine, an important question remains: despite more than 9 million patients having received this agent, why is the incidence of drug-associated valvular heart disease, initially reported to be 35%,² still not clear?³⁻⁷ Also, the rationale for not withdrawing ter-

fenadine from the market as soon as researchers clearly identified it as causing deaths⁸ has not been explained. It is surprising that terfenadine was removed from the market, not when the adverse effects were identified, but after the manufacturer had developed a new product to substitute for it.

That a drug may not be labeled for use in the manner that patients may use it when the adverse event occurred is not reassuring. Friedman et al state that fenfluramine’s use in the “fen-phen” combination was an “off-label use” and was used for 1 year longer than the FDA had approved.¹ They also state that “Mibefradil’s original labeling described . . . harmful interactions.” But after patient deaths,⁹ Friedman et al stated that “the FDA [had] strengthened the labeling and issued a public warning . . . after several patients experienced serious adverse events.”¹ Because bromfenac produced significant elevations in liver enzymes in trials submitted to the FDA prior to its approval, the “labeling emphasize[d] short-term use . . . and recommend[ed] monitoring hepatic enzymes.”¹ After hepatic failure was reported, the labeling was changed “to strengthen the warning of potential adverse hepatotoxic effects and to emphasize . . . short-term (less than 10 days) use.”¹

Introducing unreasonable requirements for postmarketing safety monitoring, such as frequent liver function tests for a nonsteroidal anti-inflammatory drug, transfers the costs and responsibilities from the drug manufacturer to the patients, the prescribers, and the insurance companies. Such costs should be shouldered by the manufacturers as a drug undergoes the development process. When do serial liver function tests to monitor the safety of a new nonsteroidal or oral hypoglycemic (with no formal reporting requirements) become an unreasonable imposition on patients and their physicians? Belief in the ability of such restrictive labeling to protect the public should have been severely shaken by these examples and by the evidence that even the extraordinarily stringent labeling and other educational safeguards included with the teratogenic antiacne preparation isotretinoin (Acutane) are not followed.^{10,11}

Drug safety will improve only when it is viewed as a cooperative venture between regulator, industry, and prescriber, when all parties are prepared to engage in open dialogue so they may learn from the past with a view toward

Author Affiliation: Division of Clinical Pharmacology, Vanderbilt University, Nashville, Tenn.

Corresponding Author and Reprints: Alastair J. J. Wood, MD, Division of Clinical Pharmacology, Room 532 MRBI, Vanderbilt University, Nashville, TN 37232-6602.

See also p 1728.

improving the future. The drug development process is both costly and enormously complex. When problems arise, they are unlikely to yield to overly simplistic examination. After a marketed drug is withdrawn or development of a new drug is terminated because of adverse toxic effects, an open public attempt to define what happened and why is an important element in improving the drug development and safety monitoring process. Previous proposals have included the establishment of an independent drug safety board,¹² analogous to the National Transportation Safety Board, which investigates airline crashes; however, such an open dialogue could also take place immediately under the auspices of the scientific societies dedicated to the affected discipline.

Physicians have a major role in the prevention of adverse drug reactions and should resist marketing pressures to prescribe new and potentially more toxic drugs in preference to prescribing well-established safer drugs. The majority of the adverse reports that the FDA receives come from drug manufacturers. Therefore, most of these reports are available to the manufacturer before the FDA. Drug manufacturers have a responsibility to analyze these reports thoughtfully and to act on their conclusions and not just to focus on delivering their reports to the FDA in a timely fashion. Manufacturers should behave responsibly in the promotion of new drugs for which toxicity is, by definition, currently unknown. To encourage such responsibility direct to consumer advertising should be permitted only for drugs that have undergone a monitored post-marketing testing process that would include a sufficient number of patients to provide adequate confidence in their safety for widespread clinical use. This step could help prevent the excessively rapid uptake of new drugs at a rate that exceeds the capacity available to review their safety in practice.

These issues do not attempt to catalog all of the unanswered questions surrounding these drug withdrawals; there

are many more. However, they illustrate the point that only by approaching each drug withdrawal as a learning opportunity for everyone—regulator, manufacturer, prescriber, and the public—can another 20 million Americans be prevented from being exposed to drugs that will then be removed from the market. We must use the attention focused on the recent drug withdrawals to galvanize all who are stakeholders in drug safety to initiate a new open dialogue, evaluating the roles and responsibilities of the manufacturer, the FDA, and the prescribers in improving and monitoring drug safety.

Funding/Support: Dr Wood is the recipient of US Public Health Service grants HL56251 and GM 31304.

REFERENCES

1. Friedman MA, Woodcock J, Lumpkin MM, Shuren JE, Hass AE, Thompson LJ. The safety of newly approved medicines: do recent market removals mean there is a problem? *JAMA*. 1999;281:1728-1734.
2. Johannes L. New diet-drug data spark more controversy. *Wall Street Journal*. October 1, 1997:B1.
3. Cannistra LB, Davis SM, Bauman AG. Valvular heart disease associated with dexfenfluramine [letter]. *N Engl J Med*. 1997;337:636.
4. Graham DJ, Green L. Further cases of valvular heart disease associated with fenfluramine-phentermine [letter]. *N Engl J Med*. 1997;337:635.
5. Connolly HM, Crary JL, McGoon MD, et al. Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med*. 1997;337:581-588.
6. Jick H, Vasilakis C, Weinrauch LA, Meier CR, Jick SS, Derby LE. A population-based study of appetite-suppressant drugs and the risk of cardiac-valve regurgitation. *N Engl J Med*. 1998;339:719-724.
7. Khan MA, Herzog CA, St Peter JV, et al. The prevalence of cardiac valvular insufficiency assessed by transthoracic echocardiography in obese patients treated with appetite-suppressant drugs. *N Engl J Med*. 1998;339:713-718.
8. Woosley RL, Chen Y, Friedman JP, Gillis RA. Mechanism of the cardiotoxic actions of terfenadine. *JAMA*. 1993;269:1532-1536.
9. Mullins ME, Horowitz BZ, Linden DH, Smith GW, Norton RL, Stump J. Life-threatening interaction of mibefradil and β -blockers with dihydropyridine calcium channel blockers. *JAMA*. 1998;280:157-158.
10. Lammer EJ, Chen DT, Hoar RM, et al. Retinoic acid embryopathy. *N Engl J Med*. 1985;313:837-841.
11. Koren G, Pastuszak A, Ito S. Drugs in pregnancy. *N Engl J Med*. 1998;338:1128-1137.
12. Wood AJ, Stein CM, Woosley R. Making medicines safer—the need for an independent drug safety board. *N Engl J Med*. 1998;339:1851-1854.

JAMA-EXPRESS: Rapid Peer Review and Publication

Margaret A. Winker, MD

Phil B. Fontanarosa, MD

RAPID DISSEMINATION OF RESULTS OF HIGH-QUALITY scientific investigations is desirable and now possible, prompting editors and researchers to examine ways to reduce the time from completion of a study to publication of the results.¹ Delays from study completion to article publication can occur at many stages, including by researchers in submitting the manuscript,² by editors and peer reviewers during editorial evaluation and peer review, by authors during manuscript revision, and by limitations imposed by journal space and frequency of publication.³ JAMA has made many efforts to minimize the de-

lay, with an average turnaround from submission to publication of 180 days and acceptance to publication of 60 days. For an article of substantial public health importance, however, even this time may be too long. Two journals have recently announced fast-track processing of manuscripts.^{4,5}

JAMA has had a rapid review and publication option for selected manuscripts available for some time. For example, a report of fatal adverse drug events with mibefradil was released and full text was posted on the JAMA Web site 3 days after acceptance and published in THE JOURNAL 3 weeks after acceptance.⁶ With the speed of communication afforded by the Internet both before and after publication,

Author Affiliations: Dr Winker is Deputy Editor and Dr Fontanarosa is Interim Coeditor of JAMA.