

# Beyond post-marketing research and MedWatch: Long-term studies of drug risks

David B Resnik

National Institute of Environmental  
Health Sciences (NIEHS)/National  
Institutes of Health (NIH)

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**Abstract:** Critics of the drug safety system have discussed many different potential reforms, ranging from mandatory registration of clinical trials to increasing the power of regulatory agencies, but few have discussed one of the most important ways of enhancing safety: increasing the number of long-term studies of medications. Long-term studies of the risks and benefits of drugs can provide useful information for regulators, healthcare professionals, and patients. Government funding agencies should lead the effort to conduct long-term studies of drugs, but private companies should also be required to lend financial support. Because cost-effectiveness is likely to be an important consideration in conducting this research, funding agencies should focus, at first, on drugs that are used to treat common, chronic conditions.

**Keywords:** drug safety, FDA, post-marketing studies, MedWatch, long-term studies

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Public interest in reforming the drug safety system in the US has surged in recent years because of health risks related to medications approved by the Food and Drug Administration (FDA), which emerged after the drugs had been on the market for several years. Harmful reactions occurred with the use of the weight loss drug dexfenfluramine (Redux) in combination with phentermine, selective serotonin reuptake inhibitors (SSRIs) used to treat children or adolescents with depression, the diabetes medication rosiglitazone maleate (Avandia), and the arthritis medications rofecoxib (Vioxx) and celecoxib (Celebrex) (Couzin 2005). Vioxx was on the market for over five years before Merck voluntarily withdrew the product due to safety (and liability) concerns. Officials from Merck had evidence as early as November 1999 that Vioxx increases the risk of heart attacks and strokes. Merck reported this information to the FDA, but the company continued to market the drug without informing consumers or physicians about these risks. The FDA did not require Merck to change the labeling on Vioxx until 2002, when evidence concerning the cardiovascular risks of the drug continued to mount. The FDA also required the labeling to include a black box warning. In September 2004, Merck decided to pull the drug from the market. An estimated 88,000 Americans had heart attacks while taking Vioxx, 38,000 of whom died. Over 13,000 lawsuits involving Vioxx have been filed against Merck (Prakash and Valentine 2006). The Vioxx debacle triggered a Congressional inquiry into drug safety and the structure of the FDA. Several bills to address the issues have been drafted, but no legislation has passed thus far (Couzin 2005).

In the subsequent debate regarding drug safety, researchers, policy analysts, and healthcare professionals identified many different problems that can compromise the quality and integrity of drug approval and oversight, including insufficient public funding of the FDA, over-reliance on user fees to support the FDA, conflicts of interest on FDA advisory panels, management problems at the FDA, lack of transparency and openness in industry-sponsored studies, and inadequate post-marketing research

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Correspondence: David B Resnik  
National Institute of Environmental  
Health Sciences (NIEHS)/National  
Institutes of Health (NIH), Box 12233,  
Mail Drop NH 06, Research Triangle Park,  
NC 27516, USA  
Tel +1 919 541 5658  
Fax +1 919 541 3845  
Email resnikd@niehs.nih.gov

and surveillance (Fontanarosa et al 2004; IOM 2006; Okie 2005; Avorn 2007; McClellan 2007; Angell 2004; Resnik 2007). Critics also put forth a number of different proposals for improving the drug safety system, such as increasing public funding for the FDA, enhancing the FDA's regulatory authority, restructuring drug safety review within the FDA, mandatory registration of clinical trials, increasing the number of subjects in Phase II and Phase III trials, limiting direct-to-consumer advertising of drugs, and placing newly approved drugs on probationary status pending the outcome of post-marketing studies (IOM 2006; Strom 2006).

There is insufficient space in this commentary to evaluate all of these various proposals for reforming the drug safety system: I refer the reader to discussions by other author (IOM 2006; Strom 2006). Instead, this short essay will develop and defend a proposal for improving drug safety that is seldom mentioned in current policy debates: initiating more long-term studies of the risks of medications. A "long-term" study is one that gathers data on research subjects for 5 years or more. The US drug safety system is not designed to detect the long-term risks of medications. A typical Phase I trial may last 60 days or less, a Phase II study may take from a few months to a couple of years, and a Phase III trial usually last a couple of years at most (Centerwatch 2007). Although a new drug may go through 7 or more years of human testing before it is approved, this usually encompasses several separate studies, each of which might last anywhere from a few months to a couple of years. Most drug safety data from clinical trials and post-marketing studies are collected from subjects who have been exposed to a medication for less than a few years. However, some health risks do not materialize until a person has been exposed to a substance for 5, 10, 15 or more years. For example, the average pack-a-day smoker will not develop lung cancer until they have smoked for at least 25 years (CDCP 2005). Some adverse health outcomes occur many years after a brief exposure to a substance. For example, a person who inhales asbestos particles during a construction job might develop mesothelioma many years after this exposure (NCI 2007).

The medical literature contains some well-designed, useful studies of the long-term risks of medications, but even more long-term studies are warranted. For an example of one, consider the research conducted by Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group. The DAD investigators conducted a prospective observational study of 23,437 patients infected with HIV. They analyzed data on myocardial infarction (MI) and exposure to protease inhibitors and other anti-HIV medications, controlling for various factors than can affect the risk of MI, such as age,

sex, body-mass index, blood pressure, smoking status, and blood cholesterol levels. 93.6% of the subjects in the study had taken protease inhibitors by the end of the study, with a median exposure of 6.9 years. The investigators found that the people exposed to protease inhibitors for 6 or more years are almost four times more likely to have an MI, as compared with people not exposed to protease inhibitors. They found that exposure to nonnucleoside reverse-transcriptase inhibitors did not increase the risk of MI (Friis-Møller and the DAD Study Group 2007).

The main argument for conducting additional studies of the long-term risks of drugs is that the information gained from this research can play an important role in health promotion and disease prevention. The FDA could use data from long-term drug studies to require changes in labeling or medication guidance, or even withdraw a drug. For example, the FDA changed its medication guidance and product labeling concerning SSRIs in response to studies showing that these drugs can increase the risk of suicidal thinking and behavior in children and adolescents (FDA 2007a, 2007b). Physicians and patients can use the data from long-term studies to make decisions related to treatment or prevention. The knowledge gained from the DAD Study Group, for example, will play an important role in helping patients to reduce the risks of taking protease inhibitors and other anti-HIV medications. Patients who take protease inhibitors can try to counteract their increased risk of an MI by engaging in activities that can help to lower that risk, such as exercising, not smoking, and taking cholesterol-lowering drugs (if medically indicated). Some patients may decide to not take protease inhibitors, if other options for therapy are available.

Regulatory agencies do not currently have effective and reliable mechanisms for obtaining information about the long-term risks of drugs. As noted earlier, clinical trials gather data concerning risks that materialize from taking a drug for a couple of years, at most. The two mechanisms for collecting safety data after a drug is approved, post-marketing studies and the MedWatch program, are not systematic, thorough, or reliable. The FDA does not require companies to conduct or publish post-marketing studies. Consequently, drug manufacturers fail to complete post-marketing that they have agreed to perform more than 50% of the time, and they may fail to publish studies (Fontanarosa et al 2004). Moreover, even when post-marketing studies are performed and published, they last no more than a couple of years.

Under the MedWatch program, physicians and companies report adverse drug reactions (ADRs) to the FDA, which

records and analyzes the data. Though companies are required by law to report ADRs they learn about, physicians are not. Since physician reporting constitutes a major source of information for MedWatch, data collection under this program is sporadic and incomplete. Additionally, there may be adverse outcomes related to drugs that physicians and companies do not even think about reporting because they do not regard these outcomes as ADRs. For example, if a patient who has been taking a diabetes medication for ten years develops liver cancer, a physician will probably not view this health outcome as related to the medication, even though this may constitute evidence that the medication increases the risk of liver cancer.

With regard to the drugs mentioned at the beginning of this commentary, there is, admittedly, no direct evidence that long-term studies would have prevented the harms that occurred. However, long-term studies could have alerted researchers and regulators to some of the problems with these drugs before post-marketing studies sponsored by pharmaceutical companies or the MedWatch program had indicated a cause for concern. First, since companies are not required to publish the results of their post-marketing research, they could decide to suppress results that demonstrate the harmful effects of their drugs. Indeed, there is some evidence that Merck suppressed or delayed publication of its post-marketing studies on Vioxx (Prakash and Valentine 2006). A company would not have the authority to stop or delay the publication of a long-term study sponsored by an independent institution or agency. Second, since reporting of adverse drug reactions under MedWatch is not systematic, thorough, or reliable, it might take a long time for data generated from this program to demonstrate statistically significant and harmful effects of a drug. A long-term study could detect these effects much earlier. Thus, while long-term studies cannot prevent tragedies like Vioxx, Redux, and Avandia, they can help to minimize harm to the public.

One of the problems with conducting long-term studies of drugs is that they can be difficult to design and implement. For ethical and practical reasons, experimental methods, such as randomized controlled trials (RCTs), are usually not a legitimate option for long-term medication studies. Subjects randomly assigned to a particular treatment regimen for 5 or more years or to a control placebo group (if allowed by the medical condition, drug, and study design) may decide to opt out of the study when a better treatment becomes available, or when they want to switch medications for some other reason (Levine 1988). In addition, following subjects for a long time can be logistically difficult because the subjects might

change phone numbers, addresses, pass away, or simply lose interest in the study. Any of these situations would lead to a high attrition rate, which could compromise the validity of the study (Gallin 2002). Additionally, experimental studies can be prohibitively expensive, because the sponsor would need to pay for the medication for 5 or more years.

Since an RCT might not be a legitimate option for a long-term drug study, investigators may have to use an observational (versus interventional) study design that can be either prospective or retrospective, conducted after FDA approval of the drug (Blair and Taylor 2007). Prospectively, investigators can collect and analyze data from both exposed and unexposed groups at regular intervals on the variables of interest, such as demographic characteristics, health status, morbidity, mortality, and so on. The DAD Study Group used a prospective cohort study design to examine the effects of anti-HIV medications. Other observational methods that might prove useful in long-term drug studies include retrospective cohort studies, and prospective and retrospective case-control studies (Blair and Taylor 2007).

Observational methods also have some problems. It can be difficult to identify subjects that meet all study inclusion criteria. Retrospective observational methods might also require data abstraction from medical records that might not be complete or standardized across medical centers and reference laboratories. Furthermore, it can be difficult to identify and control all of the factors that may affect the research subjects, and unknown factors might confound the data, giving investigators the impression that two variables are related when they are not. For example, if a cancer rate increases for several measurement intervals in a row while a subject is taking an experimental drug, it may appear that the drug is causing the cancer rate to increase, when, in fact, a confounding factor such as age, is responsible for the increased cancer rate. Another confounding factor may be the person's disease status: as a person's disease progresses, this may have some influence over the medications he chooses to take or his body's response to those medications (Hughes and Williams 2007).

Even when investigators have been able to eliminate or account for confounding factors, it may be difficult to develop statistically significant associations between the characteristic being investigated and specific health outcomes, due to the large number of different variables. To show that exposure to a chemical increases the risk of cancer, for example, the analysis of the data must account for factors such as age, genetics/family history, smoking status, exposure to radiation and other chemicals, diet, and so on. Investigators

can overcome this problem by using statistical methods that can account for many different variables, such as testing for confounders, analysis of variance, or multiple regression, and by ensuring that the sample size is large enough to yield the desired level of statistical significance (Blair and Taylor 2007).

Increasing the sample size creates other practical problems, however, since the sample size may need to be very large (5,000 or more subjects) to achieve the goals of the study. The DAD Study Group gathered data on 23,437 people exposed to antiretroviral drugs (Friis-Møller and the DAD Study Group 2007). Investigators from a National Institute of Environmental Health Sciences (NIEHS) project known as the Sister Study, plan to enroll 50,000 breast cancer-free sisters of women who have had breast cancer to understand how different environmental factors may increase the risk of this disease (NIEHS 2007). Increasing the size of study also increases its complexity and cost, and large observational studies can be very expensive and difficult to administer (Blair and Taylor 2007). Cost need not be a deterrent to conducting long-term drug studies, but it does require research sponsors to make prudent choices concerning funding. To make effective use of limited resources, it may be wise to focus, at first, on drugs used to treat common, chronic diseases, such as arthritis, diabetes, hypertension, anxiety, and depression, since many people take drugs to treat these diseases for many years. When enough research has been conducted on common, chronic diseases, investigators can examine rarer ones.

The topic of money brings up another important problem concerning long-term drug studies: who will pay for them? Biomedical research and development (R and D) is supported primarily by private industry, which funds about 62% of biomedical R and D while the government funds about 31%. The remaining 7% of R and D funding comes from private foundations and universities (Resnik 2007). Pharmaceutical companies have no incentive to pay for long-term, post-marketing studies that could link their medications to health risks. Once a drug is already on the market, a company's main reason for funding additional research would be to compare the drug with competing drugs, or to determine whether the drug can be safely used in a manner different from its original approved use, eg, to treat a different medical condition or different population (Angell 2004).

If pharmaceutical companies are not likely to voluntarily sponsor long-term studies of drugs, then the financial burden falls on the government, unless the Congress or regulatory agencies decide to require companies to sponsor long-term

studies. In the US, the National Institutes of Health (NIH) is the main source of government support for biomedical research. Leaders of the NIH set funding priorities based on input from scientists, healthcare professionals, patient advocacy groups, members of the public, and, of course, politicians (Resnik 2001). NIH leaders use the disease burden concept to decide how much R and D to allocate toward specific diseases or research areas. Disease burden is multi-faceted concept that attempts to capture that total burden that a disease places on society. It includes mortality, morbidity, loss of quality of life years, and social and economic costs (Resnik 2001).

While it is difficult to estimate the burden related to the long-term adverse effects of medications, there is some evidence that it is substantial. First, as noted earlier, Vioxx, Redux, and many other medications have caused considerable harm after going on the market. If the cardiovascular problems related to Vioxx had occurred after five or more years of exposure to the drug instead of less than two, the medical community might have never learned about the risk of Vioxx, or it might have learned about these risks only after thousands more people had been harmed. If drug-related harms can emerge after only a couple of years of exposure, it is likely that harms can emerge after a longer period of exposure. Second, ADRs are one of the leading causes of ill-health in the US, killing more than 100,000 people each year and seriously injuring more than 2 million (Public Citizen 2007). Though most ADRs are due to improper drug dosage or administration, dangerous drug interactions, and allergic responses drugs, it is likely that many are due to the long-term effects of drugs on the body.

These sobering facts form the threads of a sound policy argument for investing government funds in studies of the long-term effects of drugs: the government should spend money on this research to reduce the health burdens caused by the adverse effects of medications. Leaders of the NIH institutes with an interest in this problem, such as the NIEHS, the National Institute of General Medical Sciences (NIGMS), the National Heart, Lung and Blood Institute (NHLBI), and the National Cancer Institute (NCI) should each set aside some funds to jump-start research into the long-term studies of drugs. They may ask Congress for additional funds to cover this research, if necessary. Funds from different agencies could be pooled together to form an inter-agency group to assess evidence, develop research strategies and review research proposals. Additionally, private companies should be required to help fund this research by making a contribution to the

government's efforts. Drug approval could be contingent upon a commitment to contributing a percentage of funds to long-term drug studies.

In conclusion, long-term studies of the risks of drugs can and should play an important role in the drug safety system. Information gained from long-term drug studies can be useful to regulators, healthcare professionals, and patients. Though these studies are conducted from time to time, more are needed. Government funding agencies, such as the NIH, should lead the effort to conduct long-term studies of drugs, but private companies should also lend financial support. Because cost-effectiveness is likely to be an important consideration in conducting this research, funding agencies should focus, at first, on drugs that are used to treat common, chronic conditions. The funds used to conduct these studies will be money well spent.

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