

**COMMENTARY**

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# Why are there deadly drugs?

Joel Lexchin<sup>1,2,3</sup>

## Abstract

Some drugs eventually have to be removed from the market because of a negative benefit-to-harm ratio, including an excess of mortality. Drug safety is the result of multiple factors, commencing with how clinical trials are designed, the information generated by and/or hidden through these trials, trial analysis by drug regulatory authorities (DRAs) and the amount of information that DRAs choose to release, the amount of published information regarding drug safety, the effectiveness of postmarket surveillance systems in recognizing and reporting adverse drug reactions, and the structure of DRAs such as the United States Food and Drug Administration and its equivalent in other countries. This commentary will look at each of these issues in order to highlight the problems in the current approach to drug safety and finally indicate how some of these deficiencies should be addressed.

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All drugs will cause death in some people at some point, but only a very few drugs are removed from the market for this reason. In a research article published in *BMC Medicine*, Onakpoya and colleagues [1] provide the first systematic examination of drugs withdrawn from the market because of a link to mortality. Their study highlights a number of issues that bear further examination. Why do so few withdrawals occur in African countries as opposed to European ones and why are many drugs not withdrawn worldwide? Second, they find that we are getting better at recognizing drug-related mortality but no better at dealing with the problem. While we wait to take action on these drugs, millions of people are being exposed to potentially deadly medications [2]. Although the article deals with drugs that lead to death at both therapeutic doses and overdoses, this commentary only deals with the former group.

## Where do withdrawals occur?

The question of where withdrawals occur points to a problem that has long been recognized; only a few developing countries have a well-functioning drug regulatory

authority (DRA) [3] and pharmacovigilance systems in these countries are generally rudimentary [4]. Dealing with these problems is something that the global community needs to tackle, but the lead agency in this regard, the World Health Organization, is affected by a lack of resources [5].

## Factors involved in recognizing and dealing with potentially unsafe drugs

The finding that we are recognizing problems more quickly but failing to deal with them any faster suggests that some elements in the drug safety system are improving whereas others are not seeing any progress. Drug safety is the result of multiple factors starting with how clinical trials are designed, what information these trials generate and what may be hidden, how the trials are analyzed by DRAs, what is published and what is not, how well the postmarket surveillance system functions, and the structure of DRAs such as the United States Food and Drug Administration (FDA) and its equivalent in other countries.

## Recognizing dangerous drugs in clinical trials

It is well known that clinical trials are primarily designed to show that a drug is efficacious and not to detect anything other than relatively common safety problems. Who is included and excluded from clinical trials is

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important. If certain groups of people are not included then, when doctors prescribe for them, they have little or no information about what kind of side effects may occur. That typically means a lack of knowledge of how the drug will behave in people who are taking other medications, who have other chronic conditions, or who may not metabolize the drug in a well understood manner, i.e., children or the elderly. Clinical trials typically enroll, at most, about 5,000 patients and, therefore, any side effect, serious or trivial, that occurs in fewer than about 1 in 1,700 people will not necessarily be observed.

There have been a number of documented instances where pharmaceutical companies failed to provide mortality data to the FDA in a timely manner minimizing the appearance of a mortality risk and producing an apparent decrease in the danger associated with the drug [6,7].

Are reviewers within DRAs picking up on safety signals in clinical trials? In most of the world the answer is that we do not know. Drug safety reports are publicly available on the FDA website, but are redacted to remove confidential information. Woloshin and Schwartz have called on the FDA to make information more accessible by creating “*standardized executive summaries of drug reviews that quantify the benefit and important harms found in the phase III trials*” and that highlight remaining uncertainties [8]. Documents from some regulatory agencies that are supposed to outline the clinical basis behind the approval of new drugs do not disclose all the relevant information necessary to adequately assess the safety of the products [9,10]. Speeding up reviews of new drug submissions may get new drugs onto the market faster, but at the expense of more safety problems once they are being used by patients [11,12].

### **Under-reporting of drug safety information**

Safety information is routinely under-reported in published reports of randomized clinical trials. In one assessment of publications in six high-impact general medical journals, no information on severe adverse events and withdrawal of patients owing to an adverse event was given in 27.1% and 47.4% of articles, respectively. Restrictions in the reporting of harm-related data appeared in under one-third of articles [13]. Similar findings have been reported in other specialty journals [14].

There is significant under-reporting of adverse drug reactions. A systematic review of 37 studies from 12 countries found that the median under-reporting rate was 94% [15]. Even for extremely serious reactions, such as toxic epidermal necrolysis, under-reporting may be as high as 96% [16]. When reports contain insufficient detail, then doctors (and patients) have a false sense of

security about the safety of the products that they are prescribing and using. The number of serious and fatal adverse drug reactions reported to the FDA between 1998 and 2005 went up 2.6- and 2.7- fold, respectively; reported serious events increased four times faster than the total number of outpatient prescriptions [17].

Complicating under-reporting are documented incidents where drug companies have disguised the nature of the reactions that they have reported to DRAs. Primary pulmonary hypertension was a recognized problem with dexfenfluramine and therefore reports about this condition were expected, whereas heart valve damage was unknown and reports about this side effect were unexpected [18]. An analysis of adverse drug event reports from the pharmaceutical company involved showed that many reports listed primary pulmonary hypertension first and heart valve damage second possibly in order to downplay the discovery of this new and significant problem [18].

### **The role of regulatory agencies in handling adverse drug reactions**

Many DRAs prioritize the drug approval process over drug safety. Within one agency, over three times the money and three times the number of personnel are devoted to the former as opposed to the latter [19]. In another agency, the hierarchical relationship between the office that approves new drugs and the one that monitors postmarket safety elevates the opinions of officials in the former above those of the epidemiologists, drug safety specialists, and risk communications officers who evaluate safety [20].

Once adverse drug reactions are recognized, they may still not be communicated appropriately and in a timely manner. For example, the FDA wanted to add a warning to the rofecoxib label about cardiovascular risks in light of the findings from the VIGOR trial, but there were objections from the pharmaceutical industry. The resulting negotiations took over a year to ultimately lead to a change and rather than going into the “warning” section of the label, it ended up in the less prominent “precautions” section and was said to be of unknown clinical significance [8].

### **Conclusions**

What is improving and what is not in this complex interplay of factors? The bottom line is that we have not collected the data to assess this. The first step in decreasing the number of people who die from drugs is to understand which issues to focus on. To that end, the first steps involve better resourcing of the postmarket surveillance system, placing drug safety on a par with drug approvals, and increasing the transparency of information from both pharmaceutical companies and DRAs.

**Abbreviations**

DRA: Drug regulatory authority; FDA: United States Food and Drug Administration.

**Competing interests**

From 2011 to 2014 Joel Lexchin was the chair of the Health Action International – Europe Association Board.

**Author's information**

Joel Lexchin received his MD from the University of Toronto in 1977. He is currently a Professor in the School of Health Policy and Management at York University in Toronto, Canada, where he teaches health policy. In addition, he works in the emergency department at the University Health Network also in Toronto. He is the author or co-author of over 145 peer-reviewed articles on a wide variety of topics concerned with Canadian and international pharmaceutical policy.

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