Serious Adverse Drug Events Reported to the Food and Drug Administration, 1998-2005

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Background: The US Food and Drug Administration has operated the Adverse Event Reporting System since 1998. It collects all voluntary reports of adverse drug events submitted directly to the agency or through drug manufacturers.

Methods: Using extracts published for research use, we analyzed all serious adverse drug events and medication errors in the United States reported to the Food and Drug Administration from 1998 through 2005.

Results: From 1998 through 2005, reported serious adverse drug events increased 2.6-fold from 34,966 to 89,842, and fatal adverse drug events increased 2.7-fold from 5,519 to 15,107. Reported serious events increased 4 times faster than the total number of outpatient prescriptions during the period. In a subset of drugs with 500 or more cases reported in any year, drugs related to safety withdrawals accounted for 26% of reported events in that group in 1999, declining to less than 1% in 2005. For 13 new biotechnology products, reported serious events grew 15.8-fold, from 580 reported in 1998 to 9,181 in 2005. The increase was influenced by relatively few drugs: 298 of the 1,489 drugs identified (20%) accounted for 407,394 of the 467,809 events (87%).

Conclusions: These data show a marked increase in reported deaths and serious injuries associated with drug therapy over the study period. The results highlight the importance of this public health problem and illustrate the need for improved systems to manage the risks of prescription drugs.

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SERIOUS ADVERSE DRUG EVENTS (ADEs) are an important public health problem whose dimensions have been imprecisely defined. Serious ADEs have been estimated to account for 3.1% to 6.2% of admissions to hospitals studied. Among hospital inpatients, serious ADEs have been reported to occur at a rate of 1.9 per 100 admissions. In hospital emergency departments, ADEs of all levels of severity were estimated to account for 2.5% of all visits for unintentional injury in 2005-2006, of which 16.7% were severe enough to require hospitalization. A meta-analysis of inpatient hospital and hospital admission studies conducted over several decades estimated that ADEs were associated with 106,000 deaths in 1994.

Most of these studies had methodological limitations that were substantial enough that 2 federal government reviews concluded that insufficient data existed to estimate reliably deaths or serious events associated with drug therapy at any point or over time. Among the problems identified were making population estimates from studies of 1 or 2 hospitals, differing definitions of ADEs, and varied protocols, study periods, and source information. Even less certain are trends over time.

The Adverse Event Reporting System (AERS) of the US Food and Drug Administration (FDA) is the world’s largest database of voluntary, spontaneous reports of adverse drug reactions and medication errors. It has been in operation since 1998 under the same database system, with consistent regulatory requirements for drug manufacturers. Adverse drug events reported to this system are better known to health professionals as “MedWatch” reports, named after the FDA’s promotional program to provide safety information to health professionals and encourage reporting of adverse events for drugs and other medical products. The objectives of this study were to measure any changes in the annual number of reported serious ADEs since 1998, identify drugs frequently implicated, and explore potential reasons for the changes observed.
Table 1. Reported Serious Drug Adverse Events Over Time by Health Outcome, 1998-2005

<table>
<thead>
<tr>
<th>Year</th>
<th>All Serious Outcomes</th>
<th>Death</th>
<th>Disability</th>
<th>Other Serious Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>34,966</td>
<td>5,519</td>
<td>2,851</td>
<td>26,596</td>
</tr>
<tr>
<td>1999</td>
<td>39,908</td>
<td>5,369</td>
<td>3,210</td>
<td>31,329</td>
</tr>
<tr>
<td>2000</td>
<td>40,690</td>
<td>6,129</td>
<td>2,764</td>
<td>31,797</td>
</tr>
<tr>
<td>2001</td>
<td>46,181</td>
<td>7,940</td>
<td>3,414</td>
<td>34,827</td>
</tr>
<tr>
<td>2002</td>
<td>59,809</td>
<td>10,655</td>
<td>4,635</td>
<td>44,319</td>
</tr>
<tr>
<td>2003</td>
<td>71,670</td>
<td>15,192</td>
<td>4,881</td>
<td>51,597</td>
</tr>
<tr>
<td>2004</td>
<td>84,743</td>
<td>14,769</td>
<td>5,472</td>
<td>64,502</td>
</tr>
<tr>
<td>2005</td>
<td>89,842</td>
<td>15,107</td>
<td>5,695</td>
<td>69,040</td>
</tr>
<tr>
<td>Total No. (%)</td>
<td>467,809 (100)</td>
<td>80,880 (17.3)</td>
<td>32,922 (7.0)</td>
<td>354,007 (75.7)</td>
</tr>
</tbody>
</table>

DRUG IDENTIFICATION

In the original data, suspect drugs were identified variously by brand name, ingredient name, or chemical name without standardization. For this study, suspect drug names were recoded according to the following rules: FDA Orange Book, National Drug Code Directory, or World Health Organization ingredient names were used, except that drug products that differed only by salt or ester were grouped together (e.g., amoxicillin trihydrate and amoxicillin sodium), as were certain other closely related compounds. We excluded reports that identified medical devices, vaccines, dietary supplements, or illegal drugs such as heroin as the primary suspect as well as reports that were vague. The drug identification did not distinguish between dosage forms or routes of administration. While wholly illegal drugs were excluded, these data include drugs that are abused as well as cases reported as accidental or intentional overdoses. The FDA MedWatch Forms 3500 and 3500A allow identification of a primary suspect drug, a secondary suspect drug, and additional drugs used in concomitant therapy. In this study, only the principal suspect drug was used.

To minimize the effect of reports connected to legal claims, we excluded cases in which the report was received by the FDA more than 14 days after a drug was withdrawn for safety reasons. We did not exclude reports for phenylpropanolamine as an ingredient in over-the-counter drugs because it was impossible to determine when various manufacturers chose to remove the ingredient or for trovafloxacin, which was initially restricted and then later discontinued.

FDA REPORT TYPES

The FDA classifies serious reports into the following 3 types: (1) direct reports submitted to the FDA rather than through a manufacturer, (2) expedited reports from manufacturers that describe a serious and unexpected ADE that is not in the product labeling, and (3) periodic reports from manufacturers that involve a serious ADE that is already described in the product labeling.
HEALTH OUTCOMES

The FDA permits the individual observing the event to identify several different serious health outcomes on the same case report. To prevent double counting, the health outcome was recoded into the following mutually exclusive categories in the following order of priority: death, disability (disability or congenital anomaly), and all other serious outcomes (hospitalization, required intervention, or life-threatening or other serious outcomes). Reports without serious outcomes were excluded.

AGE CATEGORIES AND PRESCRIPTION VOLUME

The reported age, which can be described in days, weeks, years, or even decades on the FDA MedWatch Form 3500, was recoded into 4 categories and compared with the standard year 2000 US population. Medication use for the age groups was measured as the proportion reporting prescription drug use in the previous month for the years 1999 to 2002. Total outpatient prescription volume was based on published estimates for all US outpatient prescriptions for the years 1998 to 2005.

BIOTECHNOLOGY PRODUCTS

One feature of the study period was the introduction or increased use of biotechnology products, notably immunomodulators created through genetic engineering. To measure the impact of this change, we examined the reports associated with 13 biotechnology products of 3 types: anti–tumor necrosis factor immunomodulators, interferon alfa products, and interferon beta products.

SUBSET OF IMPORTANT DRUGS

We created a subset of all drugs that accounted for 500 or more cases in any calendar year. The subset was further divided into the following categories: drugs associated with a safety withdrawal or restriction or discontinuation, new drugs first approved in 1998 or later, and drugs available throughout the study period.

STATISTICAL ANALYSIS

We analyzed these data as a population, which permits direct comparison between categories without calculation of confidence intervals or other estimates of sampling error. The excerpts of FDA data were maintained in a Microsoft Access relational database (Microsoft Corp, Redmond, Washington) in accord with agency documentation. The data were analyzed with R language and environment for statistical computing software (version 2.3.1, http://www.r-project.org).

RESULTS

In the 8-year period, 467,809 serious events met the study criteria for inclusion in this analysis. Serious ADEs reported to the FDA increased from 34,966 in 1998 to 89,842 in 2005, a 2.6-fold increase (Table 1). Reported deaths increased 2.7-fold, from 5,519 in 1998 to 15,107 in 2005. The overall relative increase was 4 times faster than the growth in total US outpatient prescriptions, which grew in the same period from 2.7 billion to 3.8 billion (Figure 1).

REPORT TYPES

A total of 89,312 reports (19.1%) were submitted directly to the FDA; 314,145 (67.2%) were expedited reports from manufacturers about new, serious adverse events not already included in the product labeling, and 64,352 (13.8%) were periodic reports from manufacturers about serious adverse events already reflected in the product label (Table 2). The increase over time was largely explained by increases in just 1 type of report—expedited reports from manufacturers of new, serious events not on the product label. Of the increase of 54,876 additional events in 2005 compared with 1998, expedited reports accounted for 48,080 (87.6%) of these events.

Health professionals were predominantly the original source of the report (whether sent directly to the FDA or through manufacturers). Health professional accounted for 70.4% of all serious reports, including 82% of reported deaths (Table 2).

ADVERSE EVENT HEALTH OUTCOME

In total, 80,880 cases (17.3%) reported a death outcome; 32,922 (7%) indicated permanent disability or birth defect; and the remainder (354,007 [75.7%]) had 1 or more of the other serious outcomes (Table 1). The proportion

<table>
<thead>
<tr>
<th>Category</th>
<th>All Serious</th>
<th>Death</th>
<th>Disability</th>
<th>Other Serious Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Report type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct to FDA</td>
<td>89,312 (19.1)</td>
<td>9120 (11.3)</td>
<td>7340 (22.3)</td>
<td>72,852 (20.6)</td>
</tr>
<tr>
<td>Mfr expedited</td>
<td>314,145 (67.2)</td>
<td>61,700 (76.3)</td>
<td>20,793 (63.2)</td>
<td>231,652 (65.4)</td>
</tr>
<tr>
<td>Mfr periodic</td>
<td>64,352 (13.8)</td>
<td>10,060 (12.4)</td>
<td>4789 (14.5)</td>
<td>49,503 (14.0)</td>
</tr>
<tr>
<td>Report sourceb</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consumer</td>
<td>76,289 (25.9)</td>
<td>8510 (14.5)</td>
<td>6096 (31.8)</td>
<td>61,683 (28.4)</td>
</tr>
<tr>
<td>Health professional</td>
<td>207,760 (70.4)</td>
<td>48,077 (82.0)</td>
<td>11,340 (59.2)</td>
<td>148,343 (68.3)</td>
</tr>
<tr>
<td>Otherc</td>
<td>10,945 (3.7)</td>
<td>2009 (3.4)</td>
<td>1718 (9.0)</td>
<td>7218 (3.3)</td>
</tr>
</tbody>
</table>

Abbreviations: FDA, Food and Drug Administration; Mfr, manufacturer.

Data are given as number (percentage) of reports.

Excludes reports not indicating a source.

Includes distributor, company representative, and user facility.
of serious events with a death outcome was relatively consistent over time, accounting for 15.8% of events in 1998 and 16.8% in 2005. The disability category included 3385 cases of a reported birth defect (0.7% of all cases).

**AGE AND SEX**

The patients were more frequently female (55.5%) than male (45.5%), and the sex imbalance was stable over time. A disproportionate share of adverse events occurred among elderly patients, while fewer than expected were reported among children younger than 18 years (Table 3). Children younger than 18 years accounted for 25.8% of the total US population but accounted for 7.4% of the reported serious adverse events. After adjusting for a lower likelihood of taking prescription drugs, the 7.4% of events reported in children remained lower than the 13.8% expected, based on the population size adjusted for medication use. Among the persons 65 years and older, the opposite occurred. This age group constituted 12.6% of the total US population but accounted for 33.6% of the reported serious adverse events. After adjustment for more intensive medication use, the 33.6% of reported cases still exceeded the 23.6% expected.

**DRUGS IDENTIFIED AS SUSPECT**

While a total of 1489 drug products were identified as principal suspects, relatively few accounted for most of the events. The 298 drugs (20%) with the highest event totals accounted for 407 394 of all reported study events (87.1%). On the other extreme, the 298 drugs (20%) with the lowest event totals accounted for 1459 of the reported events (<0.01%). The 15 drugs most frequently identified in fatal and nonfatal serious events are listed in Table 4.

Among the 15 drugs most frequently named in fatal events, 7 were pain medications and 4 had primary effects on the immune system. Among nonfatal serious events, the most frequently identified drugs were of more varied classes. The number of serious adverse events associated with 13 prominent biotechnology products grew 15.8-fold during the period, from 580 in 1998 to 9181 in 2005 (Figure 2).

**SUBSET OF IMPORTANT DRUGS**

Fifty-one drugs were identified through the criteria of having accounted for 500 or more reports in any study year (Table 5). Together, this subset accounted for 203 957 cases (43.6% of the study total). As Figure 3 illustrates, there were markedly different patterns among selected agents, suggesting that the long-term trend was
not apparently a result of a single common factor but rather a combination of many different upward and downward changes. However, 2 general changes over time could be identified in this subset. Drugs that were related to safety withdrawals or restrictions played a declining role in this subset during the period, accounting for 26.4% of the total number of reported adverse drug events. Drugs newly approved since 1998 also showed a notable decline in the number of reported adverse events, with 18.8% of the total number of events occurring in the first year of approval. Overall, the total number of reported adverse drug events for the period 1998-2005 was 42,033, with a significant decrease in the number of events reported in recent years.
of all reported events in 1999 and declining steadily to less than 1% in 2005. Overall, drugs related to safety withdrawal accounted for 9.8% of the events in this subset total. In addition, reports identifying drugs available for the entire period increased from 9767 in 1998 to 29,164 in 2005, a 3-fold increase.

COMMENT

These data show that a nearly 3-fold increase has occurred in reported serious injuries, disability, and death associated with drug therapy in the 8-year study period. The change and overall risks can be primarily attributed to a minority of important drugs—an example of the quality assurance rule of thumb that holds that 80% of the consequences spring from 20% of the causes. We estimate that increasing population and more intensive use of drug therapy—as measured by prescription volume—might account for 25% of the observed increase, as illustrated in Figure 1. An additional 15% of the increase is accounted for by 13 prominent new biotechnology products shown in Figure 2. Contrary to our expectations, drugs related to safety withdrawals were a modest share of all reported events and declined in importance over time. Among the most frequently reported drugs associated with fatal events, we observed a disproportionate contribution of pain medications and drugs that modify the immune system.

LIMITATIONS OF THE DATA

While the AERS data are the primary data source for monitoring the postmarket safety of approved drug products, it has many known limitations. It is a collection of voluntary reports rather than the systematic observation of any defined patient group. The submission of an adverse event report does not establish causality—only that the reporters suspected a relationship might exist. Also,
In this analysis focused on only the primary suspect drug even though a median of 2 drugs per case were named and one quarter of the cases identified 5 or more drugs. Reported events include adverse drug reactions, medication errors, accidental and intentional overdoses, and product problems. The reporting rate for adverse events may vary among drugs and for the same drug over time. Estimates of what fraction of serious events were reported to the AERS vary between 0.3% and 33%, depending on event, period, and drug. However, the reporting requirements, definitions of serious events, and other fundamentals of the system were unchanged throughout the study period.

ALTERNATIVE EXPLANATIONS

We also explored whether the results were influenced by external factors such as highly publicized scientific discoveries, safety withdrawals, or legal claims. Our 8-year study period featured several such episodes. Examples include cyclooxygenase 2 inhibitors and thrombotic cardiovascular events, estrogen therapy and breast cancer and thrombotic cardiovascular events, and atypical antipsychotics and the risk of hyperglycemia and diabetes. It seemed possible that increased reporting could have been stimulated through media publicity and lawyers seeking injured clients through radio, television, and Internet advertising. We limited the impact of this phenomenon by excluding reports received more than 14 days after a drug was withdrawn for safety reasons. Even if all cases associated with withdrawn drugs involved legal claims, the subset data showed that such claims accounted for less than 10% of all events and declined since 1999. Nevertheless, the influence of publicity and legal claims can be seen in specific drugs listed in Table 5. Phentermine was administered in combination with fenfluramine and dexfenfluramine, which were withdrawn in September 1997. We speculate that the initial upsurge and then decline in phentermine reports was related to the diet drug litigation that focused primarily on the fenfluramines. Similarly, reports for estrogen increased sharply after the Women's Health Initiative Trial documented increased risks of cancer and thrombotic cardiovascular events for hormone therapy. However, overall, the increased reporting effect from these events was partially adjusted for, was limited to relatively few drugs, and may have declined over time.

An additional question was whether all or part of the increase could be explained by some broad-based increase in adverse event reporting rate in the medical community, perhaps spurred by expert panel proceedings such as the 1999 report on medication error by the Institute of Medicine. However, as illustrated in Figure 3, the data showed markedly different patterns among specific drugs, with numerous increases and decreases observed. Also, if some broad increase had occurred in the propensity to report ADEs, then one would expect to observe an equal or greater increase in the volume of direct reports to the FDA rather than through manufacturers. This did not occur. While insufficient data exist to either rule in or rule out this possibility, we concluded that such a broad change in spontaneous reporting was unlikely.

IMPLICATIONS

This study shows that substantially growing numbers of patients are experiencing serious injuries from drug therapy, although the exact magnitude of the population increase cannot be estimated from these data. Future initiatives to improve drug safety require more accurate and capable systems to monitor postmarketing ADEs. This growing toll of serious injury shows that the existing system is not adequately protecting patients and underscores the importance of recent reports urging far-reaching legislative, policy, and institutional changes.

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Author Contributions: Mr Moore had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Moore, Cohen, and Furberg. Acquisition of data: Moore. Analysis and interpretation of data: Moore, Cohen, and Furberg. Drafting of the manuscript: Moore. Critical revision of the manuscript for important intellectual content: Moore, Cohen, and Furberg. Statistical analysis: Moore. Administrative, technical, and material support: Cohen. Study supervision: Cohen.

Financial Disclosure: None reported.

Additional Information: The FDA encourages health professionals and consumers to report serious adverse events and product problems using the secure online form at: https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm. Actual and potential medication errors may be reported to the USP-ISMP Medication Errors Reporting Program at https://www.ismp.org/orderForms/reporterrortoISMP.asp.

REFERENCES

9. IND safety reports. 21 CFR §312.32. 2006.