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 5519 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 9181 in 2005. The increase was influenced by relatively few drugs: 298 of the 1489 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.[1] Among hospital inpatients, serious ADEs have been reported to occur at a rate of 1.9 per 100 admissions.[2] 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.[3] 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.[1]

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.[4,5] 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.[6] 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.

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Table 1. Reported Serious Drug Adverse Events Over Time by Health Outcome, 1998-2005

Year	All Serious Outcomes	Death	Disability	Other Serious Outcomes
1998	34 966	5519	2851	26 596
1999	39 908	5369	3210	31 329
2000	40 690	6129	2764	31 797
2001	46 181	7940	3414	34 827
2002	59 809	10 855	4635	44 319
2003	71 670	15 192	4881	51 597
2004	84 743	14 769	5472	64 502
2005	89 842	15 107	5695	69 040
Total No. (%)	**467 809** (100)	**80 880** (17.3)	**32 922** (7.0)	**354 007** (75.7)

METHODS

DATA SELECTION

The FDA publishes for research use quarterly extracts of all AERS reports after removing personal identifiers and narrative text.[7] The data are in 7 linked files that include fields describing the report itself, patient characteristics, the health outcome of the event, and details about the drugs administered.

The data for this analysis consist of excerpts of reports of serious ADEs in the United States that were received by the FDA from January 1998 through December 2005 for prescription drugs, biological products (except vaccines), and over-the-counter drugs. The voluntary reports are submitted either directly to the FDA through the MedWatch program or to drug manufacturers. The manufacturers, in turn, are required by federal regulation to forward to the FDA reports of new, serious, and unexpected adverse events within 15 days and other serious events on a quarterly basis.[8] A serious event, in the FDA's regulatory definition, means an adverse event that resulted in a health outcome of death, a birth defect, disability, hospitalization, or was life threatening or required intervention to prevent harm.[8] In the event that multiple reports about the same adverse event were identified in the FDA system by a common case number, only the safety report with the most recent date was used.

We excluded cases specifically identified as occurring in drug manufacturers' clinical studies, both before and after approval. These reports differ from spontaneous reports in that clinical investigators are required to report all serious events that occur whether or not a connection with the drug was suspected.[9] In addition, reports for thalidomide were excluded because, as a condition of approval, the manufacturer agreed to maintain a 100% patient registry and therefore would learn of events through active surveillance without regard to whether drug involvement was suspected.[10] Reports for events occurring in foreign countries were also excluded. This was not only to focus this analysis on events in the United States but also to exclude additional variation caused by different FDA requirements for foreign reporting and different national systems for postmarket surveillance.

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 (eg, 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.

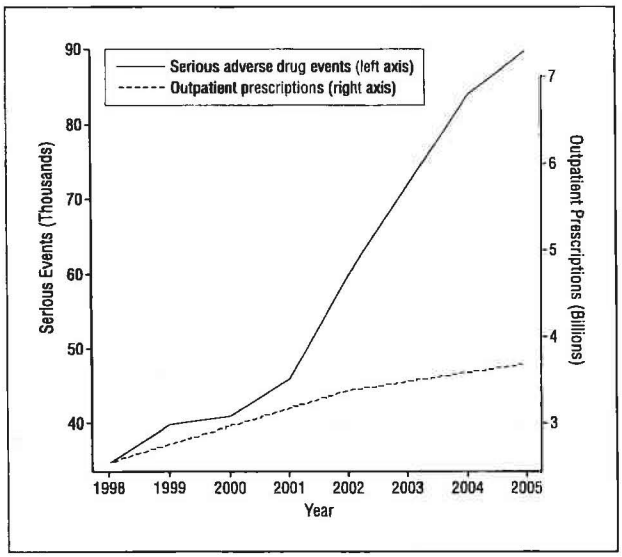

Figure 1. Reported serious events vs outpatient prescriptions, 1998-2005.

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.

Table 2. Report Type and Source by Health Outcome, 1998-2005[a]

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

Abbreviations: FDA, Food and Drug Administration; Mfr, manufacturer.
[a] Data are given as number (percentage) of reports.
[b] Excludes reports not indicating a source.
[c] Includes distributor, company representative, and user facility.

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.[11] 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.[12] Total outpatient prescription volume was based on published estimates for all US outpatient prescriptions for the years 1998 to 2005.[13,14]

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 5519 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 3. Age Burden of Serious Adverse Events, 1998-2005

Age Group, y	Serious Events, %	Total Population, %[a]	Expected Cases, %[b]
<18	7.4	25.8	13.8
18-44	25.3	39.4	31.2
45-64	33.7	22.2	31.4
≥65	33.6	12.6	23.6

[a] Age group percentage of total from standard 2000 US population.
[b] Percentage of population total, adjusted for likelihood of medication use.

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

Table 4. Most Frequent Suspect Drugs in Death and Serious Nonfatal Outcomes, 1998-2005

Drug Name	Rank/Deaths	Drug Class
Death outcome		
Oxycodone	1/5548	Opioid analgesic
Fentanyl	2/3545	Opioid analgesic
Clozapine	3/3277	Antipsychotic
Morphine	4/1616	Opioid analgesic
Acetaminophen	5/1393	Analgesic
Methadone	6/1258	Opioid analgesic
Infliximab	7/1228	DMARD
Interferon beta	8/1178	Immunomodulator
Risperidone	9/1093	Antipsychotic
Etanercept	10/1034	DMARD
Paclitaxel	11/1033	Antineoplastic
Acetaminophen-hydrocodone	12/1032	Combination analgesic
Olanzapine	13/1005	Antipsychotic
Rofecoxib	14/932	NSAID
Paroxetine	15/850	Antidepressant
Disability or other serious outcome		
Estrogens	1/11 514	Hormone
Insulin	2/9597	Hormone
Infliximab	3/8754	DMARD
Interferon beta	4/8320	Immunomodulator
Paroxetine	5/8095	Antidepressant
Rofecoxib	6/7766	NSAID
Warfarin	7/6250	Anticoagulant
Atorvastatin	8/6022	HMG-CoA reductase inhibitor
Etanercept	9/5586	DMARD
Celecoxib	10/4822	NSAID
Phentermine	11/4607	Antiobesity
Clozapine	12/4388	Antipsychotic
Interferon alfa	13/4162	Immunomodulator
Simvastatin	14/3885	HMG-CoA reductase inhibitor
Venlafaxine	15/3688	Antidepressant

Abbreviations: DMARD, Disease modifying antirheumatism drug; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; NSAID, nonsteroidal anti-inflammatory drug.

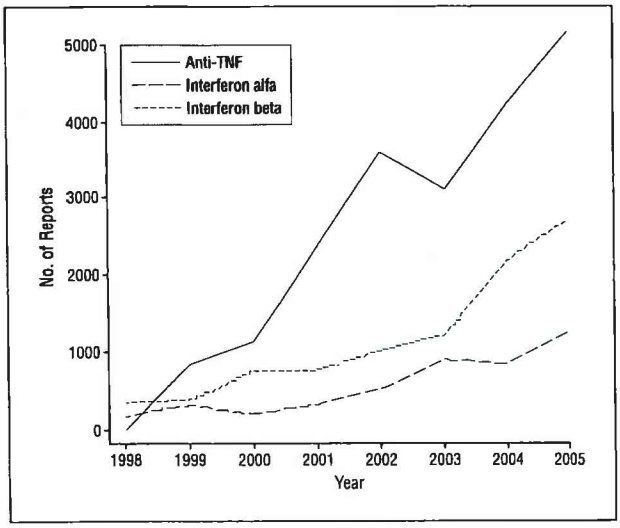

Figure 2. Reported serious events for 15 biological products, 1998-2005. Anti-TNF indicates anti–tumor necrosis factor.

Table 5. Drugs With 500 or More Reported Serious Adverse Drug Events in Any Year

Drug Name	Year of Action	Total	1998	1999	2000	2001	2002	2003	2004	2005
Drugs related to safety withdrawals										
Rofecoxib	2004	**8698**	0	317	1427	1297	1551	1792	2314	0
Phentermine[a]	1997	**4811**	2018	2531	156	19	29	19	11	28
Cerivastatin	2001	**1573**	50	314	673	506	28	2	0	0
Troglitazone	2000	**1348**	665	517	140	17	1	0	0	0
Brompheniramine; phenylpropanolamine[b]	2000	**1210**	0	1	8	71	321	654	143	12
Trovafloxacin[c]	1999	**1185**	403	652	58	48	9	10	5	0
Chlorphenamine; phenylpropanolamine[b]	2000	**1151**	1	3	17	209	723	182	7	9
Total No. (%)	...	**19 986** (9.8)	**3137** (24.3)	**4335** (26.4)	**2479** (15.4)	**2167** (11.3)	**2662** (10.3)	**2659** (8.4)	**2480** (6.2)	**49** (0.1)
Drugs newly approved since 1998	**Year of Approval**									
Infliximab	1998	**9982**	18	233	449	831	1870	1565	2337	2679
Etanercept	1998	**6620**	4	405	493	1413	1583	1181	590	951
Celecoxib	1999	**5357**	0	977	724	415	299	396	658	1888
Rosiglitazone	1999	**2810**	0	55	393	569	344	624	464	361
Teriparatide	2002	**2554**	0	0	0	0	1	329	923	1301
Adalimumab	2002	**2389**	0	0	0	0	0	190	927	1272
Zoledronic acid	2001	**1867**	0	0	0	1	119	201	348	1198
Imatinib	2001	**1571**	0	0	0	72	159	370	525	445
Atomoxetine	2002	**1332**	0	0	0	0	0	309	407	616
Duloxetine	2004	**1053**	0	0	0	0	0	0	143	910
Rosuvastatin	2003	**1812**	0	0	0	0	0	14	535	463
Cetuximab	2004	**981**	0	0	0	0	0	0	328	653
Bosentan	2001	**898**	0	0	0	0	208	512	98	80
Total No. (%)	...	**38 426** (18.8)	**22** (0.2)	**1670** (10.2)	**2059** (12.8)	**3301** (17.2)	**4583** (17.8)	**5691** (18.0)	**8283** (20.7)	**12 817** (30.5)
Drugs available for entire period (1998-2005)										
Estrogens	...	11 973	754	738	630	617	743	949	3996	3546
Insulin	...	10 444	438	575	1343	1246	1513	1762	1767	1800
Interferon beta	...	9498	349	392	769	777	1032	1240	2210	2729
Paroxetine	...	8945	696	649	672	854	1113	1794	1591	1576
Clozapine	...	7665	673	702	770	698	1447	969	1315	1091
Oxycodone	...	7440	14	34	41	443	1311	2414	2176	1007
Warfarin	...	6961	829	909	779	941	819	874	843	967
Fentanyl	...	6373	92	217	423	561	1034	1275	1526	1245
Atorvastatin	...	6361	355	542	543	1164	959	776	867	1155
Interferon alfa	...	4625	202	315	214	334	538	914	849	1259
Paclitaxel	...	4357	370	382	365	459	886	744	606	545
Amfebutamone	...	4244	361	320	217	366	618	627	927	808
Simvastatin	...	4144	212	227	267	365	625	769	925	754
Olanzapine	...	4110	487	291	356	455	437	479	607	998
Venlafaxine	...	4049	122	246	408	461	582	797	799	644
Sertraline	...	3781	442	507	546	348	411	467	526	533
Isotretinoin	...	3774	271	268	408	572	415	588	561	691
Phenytoin	...	3435	333	461	343	390	583	445	449	431
Alendronate	...	3365	292	206	174	240	460	653	657	683
Gabapentin	...	3215	123	151	196	277	411	429	576	1052
Sildenafil	...	3194	665	584	386	241	285	216	196	621
Risperidone	...	3035	227	234	299	300	396	414	656	509
Morphine	...	2846	82	102	116	299	283	594	726	644
Docetaxel	...	2743	201	177	254	277	234	516	604	480
Clopidogrel	...	2539	128	286	313	278	322	309	389	514
Acetaminophen	...	2494	292	225	227	235	263	269	416	567
Lamotrigine	...	2317	84	81	76	128	252	384	588	724
Valproic acid	...	2158	231	196	197	196	239	247	327	525
Cyclosporine	...	2023	256	152	56	72	81	305	711	390
Carbamazepine	...	1944	178	206	148	130	113	289	530	350
Methadone	...	1511	8	21	23	36	75	771	248	329
Total No. (%)	...	**145 563** (71.4)	**9767** (75.6)	**10 396** (63.4)	**11 559** (71.8)	**13 751** (71.5)	**18 480** (71.8)	**23 279** (73.6)	**29 164** (73.0)	**29 167** (69.4)
Overall Total	...	**203 957**	**12 926**	**16 461**	**16 097**	**19 219**	**25 725**	**31 629**	**39 927**	**42 033**

[a] Phentermine was not withdrawn but coadministered with fenfluramine and dexfenfluramine, withdrawn in September 1997.
[b] The Food and Drug Administration proposed withdrawal of phenylpropanolamine as an over-the-counter ingredient in 2000.
[c] Trovafloxacin was restricted in 1999 and was later discontinued.

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%

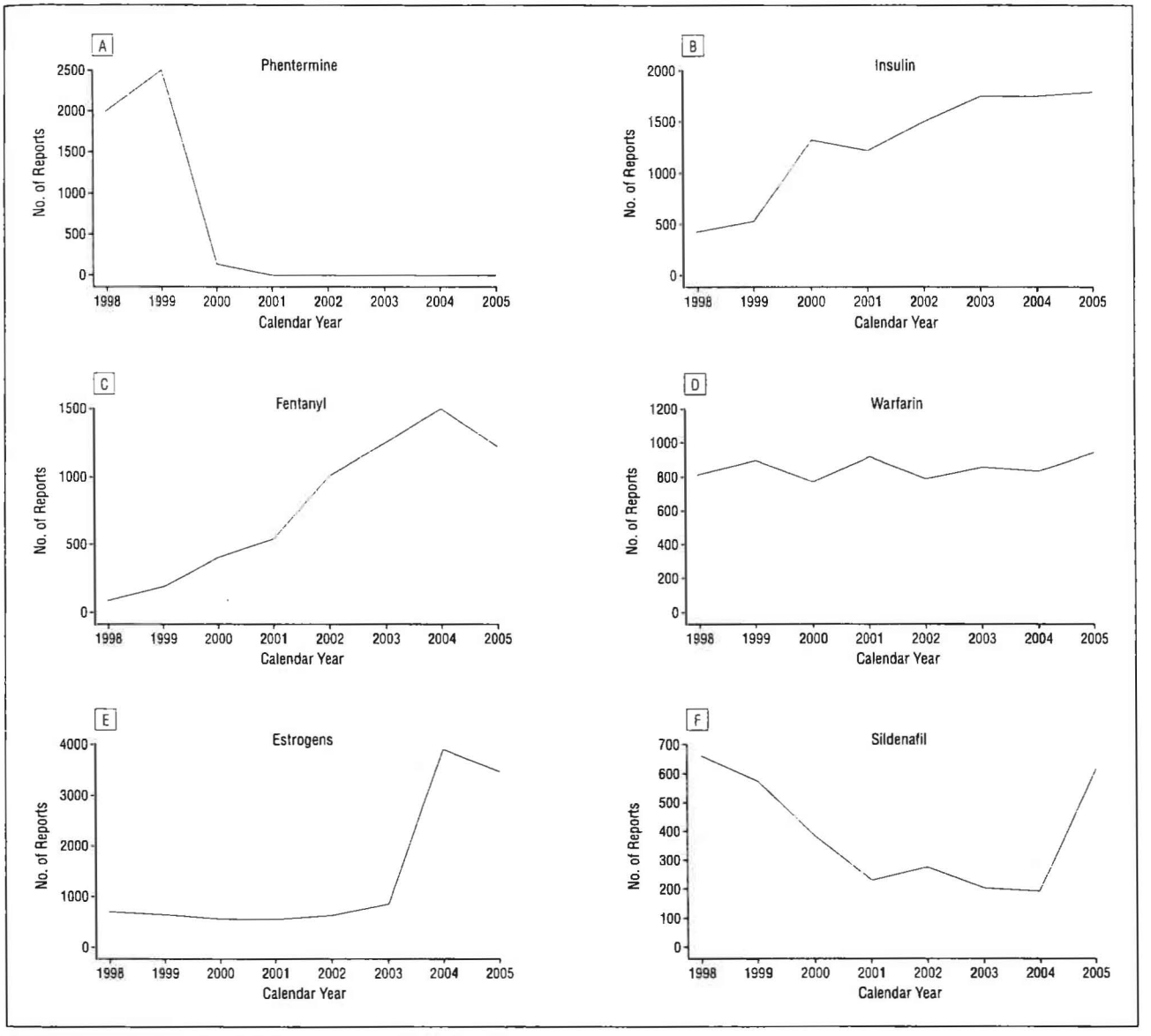

Figure 3. Long-term trends in selected drug products, 1998-2005. A, Phentermine; B, insulin; C, fentanyl; D, warfarin; E, estrogens; F, sildenafil.

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,

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.[15] Estimates of what fraction of serious events were reported to the AERS vary between 0.3% and 33%,[4,16] 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,[17] estrogen therapy and breast cancer and thrombotic cardiovascular events,[18] and atypical antipsychotics and the risk of hyperglycemia and diabetes.[19] 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.[20] 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.[18] 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.[21] 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.[22,23]

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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.
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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.

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