Timing of New Black Box Warnings and Withdrawals for Prescription Medications

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Context Recently approved drugs may be more likely to have unrecognized adverse drug reactions (ADRs) than established drugs, but no recent studies have examined how frequently postmarketing surveillance identifies important ADRs.

Objective To determine the frequency and timing of discovery of new ADRs described in black box warnings or necessitating withdrawal of the drug from the market.

Design and Setting Examination of the *Physicians' Desk Reference* for all new chemical entities approved by the US Food and Drug Administration between 1975 and 1999, and all drugs withdrawn from the market between 1975 and 2000 (with or without a prior black box warning).

Main Outcome Measures Frequency of and time to a new black box warning or drug withdrawal.

Results A total of 548 new chemical entities were approved in 1975-1999; 56 (10.2%) acquired a new black box warning or were withdrawn. Forty-five drugs (8.2%) acquired 1 or more black box warnings and 16 (2.9%) were withdrawn from the market. In Kaplan-Meier analyses, the estimated probability of acquiring a new black box warning or being withdrawn from the market over 25 years was 20%. Eighty-one major changes to drug labeling in the *Physicians' Desk Reference* occurred including the addition of 1 or more black box warnings per drug, or drug withdrawal. In Kaplan-Meier analyses, half of these changes occurred within 7 years of drug introduction; half of the withdrawals occurred within 2 years.

Conclusions Serious ADRs commonly emerge after Food and Drug Administration approval. The safety of new agents cannot be known with certainty until a drug has been on the market for many years.

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ADVERSE DRUG REACTIONS (ADRs) are believed to be a leading cause of death in the United States.[1] Prior to approval, drugs are studied in selected populations[2,3] for limited periods, possibly contributing to an increased risk of ADRs after approval. Pharmaceutical companies frequently market new drugs heavily to both patients and clinicians before the full range of ADRs is ascertained. Inadequate clinician reporting may delay detection of postmarketing ADRs; less than 10% of all ADRs are estimated to be reported to MEDWATCH,[4] the Food and Drug Administration's (FDA's) voluntary postmarketing reporting system.

Patient exposure to new drugs with unknown toxic effects may be extensive. Nearly 20 million patients in the United States took at least 1 of the 5 drugs withdrawn from the market between September 1997 and September 1998.[5] Three of these 5 drugs were new, having been on the market for less than 2 years. Seven drugs approved since 1993 and subsequently withdrawn from the market have been reported as possibly contributing to 1002 deaths.[6] For example, cisapride was approved for the treatment of a benign condition, nocturnal gastroesophageal reflux in adults. After its introduction, many pediatricians prescribed the drug to infants with gastric reflux, 24 of whom were reported to have died.[6]

For editorial comment see p 2273.

Should clinicians hesitate to prescribe newly approved drugs? Few data are available on how frequently serious ADRs are discovered after drug introduction. Previous studies examining drug labeling changes have found high rates of undetected postapproval risks[7] with low rates of subsequent drug withdrawal.[8,9] However, no study has analyzed changes in the *Physicians' Desk Reference*,[10-35] the most commonly used source of labeling information.[36] We analyzed the incidence of new black box warnings in the *Physicians' Desk Reference* from 1975 to 2000, a marker of the most serious ADRs, and used survival analyses to determine the course of their discovery. We also calculated the frequency and timing of drug withdrawals over this period.

METHODS

Data Sources and Definitions

We chose the study period 1975-2000 because it corresponds with the FDA's

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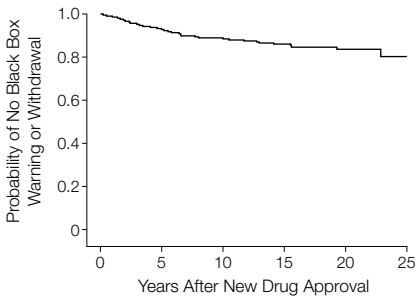
Figure. Kaplan-Meier Estimate of New Drug Survival Without a New Black Box Warning or Withdrawal (*Physicians' Desk Reference* Changes)



modern era of drug surveillance.[37,38] We obtained a list of drugs approved from 1975-1999 from the Tufts Center for the Study of Drug Development.[39] (Drugs approved in 2000 were excluded because none appear in the other data source for the study, the year 2000 *Physicians' Desk Reference*,[34] which was released in November 1999.) We used the drug approval date to approximate the date the drug was first marketed. We compiled a list of drugs withdrawn for safety reasons from a *Federal Register* notice[40] published in 1998 and from information on the FDA Web site about drug withdrawals between 1998 and 2000.[41-43] We defined a drug as "withdrawn for safety reasons" if the drug removal was initiated by the FDA for safety reasons or if the manufacturer voluntarily withdrew it from the market following the identification of life-threatening ADRs.

We included all drugs that the FDA defined as new molecular entities (ie, an active ingredient that had never been marketed in the United States).[44] We excluded over-the-counter medications, diagnostic agents, and biologics (defined as any drug approved through the FDA's Center for Biologics Evaluation and Research[45]). We included drugs initially available by prescription that subsequently became available over-the-counter (eg, cimetidine).

We identified black box warnings through a manual search of all 26 annual volumes of the *Physicians' Desk Reference* between 1975 and 2000.[10-35] The *Physicians' Desk Reference*, an annual compendium of the FDA-approved professional product labeling for selected drugs, is released in November of the year before its cover date. Black box warnings are prominently displayed in the *Physicians' Desk Reference* to alert practitioners to serious risks.[46] According to the *Federal Register*,

> Special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data.[47]

We excluded black box warnings that were present when a drug first appeared in the *Physicians' Desk Reference*. We also excluded black box warnings that a drug should be administered by a qualified physician, as this warning may not indicate a new ADR. We defined a *Physicians' Desk Reference* change as either the addition of 1 or more black box warnings per drug or the withdrawal of a drug.

Analysis

For drugs that had a black box warning in the 2000 *Physicians' Desk Reference*, we examined earlier editions of the *Physicians' Desk Reference* to determine when the black box warning first appeared. If a drug did not have a black box warning in the *Physicians' Desk Reference* in which it first appeared, we measured the time (rounded to the nearest month) that elapsed between the approval date and the year of the first *Physicians' Desk Reference* in which a black box warning appeared. We approximated the exact date of the *Physicians' Desk Reference* year as January 1 of its cover year. We similarly measured the time from approval to withdrawal for drugs withdrawn for safety reasons.

We calculated the proportion of all new drugs that acquired a new black box warning or withdrawal from the market for safety reasons. For drugs that acquired multiple black box warnings, we counted each warning as a separate event. For withdrawn drugs that had a black box warning prior to withdrawal, we counted 2 separate events in the analysis of *Physicians' Desk Reference* changes, and counted only the withdrawal date in the analysis of time until withdrawal. We calculated the time that elapsed before 50% of eventual drug withdrawals took place, and the time that elapsed before 50% of all *Physicians' Desk Reference* changes were made. We also analyzed the content of the black box warnings and the reasons for withdrawal according to the type of toxicity.

Statistical Methods

We used the SAS statistical package (Version 8; SAS Institute, Cary, NC) for frequency analysis, and the Lifetest procedure to calculate Kaplan-Meier survival curves for censored failure-time data. We used Kaplan-Meier survival curves to estimate a drug's "survival" (without reaching the end point of a new black box warning and/or withdrawal from the market) over the study period, taking into account the fact that drugs are on the market for varying periods (some briefly). We censored those drugs that had not reached the end point in question at the time of the analysis.

RESULTS

Five hundred forty-eight new chemical entities were approved from 1975-1999. Of these, 56 (10.2%) drugs acquired a new black box warning or were withdrawn from the market. In Kaplan-Meier analyses, the estimated probability of a new drug acquiring black box warnings or being withdrawn from the market over 25 years was 20% (FIGURE).

Forty-five drugs (8.2%) acquired 1 or more black box warnings that were not present when the drug was approved (TABLE 1). Sixteen drugs (2.9%) approved between 1975 and 2000 were withdrawn from the market between 1975 and 2000; 5 had acquired a black box warning prior to withdrawal (TABLE 2). In Kaplan-Meier analyses, new drugs had a 4% probability of being withdrawn from the market over the study period. Half of withdrawals occurred within 2 years following the drug's introduction. There were 81 changes in the *Physicians' Desk Refer-*

Table 1. Drugs With a New Black Box Warning, 1975-2000*

Drug Name	Food and Drug Administration Class	Drug Approval Date	Warning	Time to First *Physicians' Desk Reference* Black Box Warning in Years
Pemoline	Central nervous system stimulant	January 27, 1975	Hepatic toxicity	22.9
Dacarbazine†	Antineoplastic	May 27, 1975	Hepatic toxicity	4.6
Danazol	Infertility	June 21, 1976	Unsafe during pregnancy	15.5
			Pseudotumor cerebri	15.5
			Peliosis hepatis	15.5
			Thrombotic events and strokes	15.5
Lomustine	Antineoplastic	August 4, 1976	Bone marrow toxicity	1.4
Carmustine†	Antineoplastic	March 3, 1977	Pulmonary fibrosis	4.8
Disopyramide phosphate	Antiarrhythmic	August 31, 1977	Increased mortality with class IC antiarrhythmics	19.3
Valproate sodium	Anticonvulsant	February 28, 1978	Hepatic toxicity	3.8
Metoprolol	Antianginal, antihypertensive β-blocker	August 7, 1978	Exacerbation of coronary artery disease when drug discontinued	6.4
Captopril	Antihypertensive ACE inhibitor	April 6, 1981	Unsafe during pregnancy	11.7
Ketoconazole	Antifungal	June 12, 1981	Hepatic toxicity	12.6
			Cardiotoxic if used with terfenadine	2.6
			Cardiotoxic if used with astemizole	15.6
			Cardiotoxic if used with cisapride	11.6
Atenolol	Antianginal, antihypertensive β-blocker	August 19, 1981	Exacerbation of coronary artery disease when drug discontinued	5.4
Isotretinoin	Dermatologic (acne)	May 27, 1982	Unsafe during pregnancy	2.6
			Pseudotumor cerebri	2.6
			Conditions need to be met for use‡	6.6
Cyclosporine	Immunomodulator	November 14, 1983	Immunosuppression	1.2
			Hypertension (Neoral)	14.2
			Nephrotoxicity (Neoral)	14.2
Tocainide hydrochloride	Antiarrhythmic	November 9, 1984	Pulmonary fibrosis	4.2
			Bone marrow toxicity	5.2
Terfenadine§	Antihistamine	May 8, 1985	Drug interactions causing cardiotoxicity	8.7
Mexiletine hydrochloride	Antiarrhythmic	May 16, 1985	Increased mortality with class IC antiarrhythmics	13.0
Flecainide acetate	Antiarrhythmic	October 31, 1985	Increased mortality in patients with asymptomatic ventricular arrhythmias	3.2
Midazolam hydrochloride	Adjunct to anesthesia	December 20, 1985	Respiratory depression	3.0
Enalapril maleate	Antihypertensive ACE inhibitor	December 24, 1985	Unsafe during pregnancy	7.0
Ribavirin†	Antiviral	December 31, 1985	Increase in pulmonary artery pressures	8.0
Encainide hydrochloride§	Antiarrhythmic	December 24, 1986	Increased mortality in patients with asymptomatic ventricular arrhythmias	3.0
Zidovudine†	Antiviral	March 19, 1987	Hepatomegaly	7.8
			Lactic acidosis	7.8
			Myopathy	7.8
Mitoxantrone hydrochloride	Antineoplastic	December 23, 1987	Bone marrow toxicity	10.0
Lisinopril	Antihypertensive ACE inhibitor	December 29, 1987	Unsafe during pregnancy	5.0
Astemizole§	Antihistamine	December 29, 1988	Drug interactions causing cardiotoxicity	4.0
Ganciclovir†	Antiviral	June 23, 1989	Oral form not as effective as intravenous	6.5
Clozapine†	Antipsychotic, antimanic	September 26, 1989	Hypotension	3.2
Propafenone hydrochloride	Antiarrhythmic	November 1, 1989	Increased mortality with class IC antiarrhythmics	9.2
Ketorolac tromethamine	Analgesic, nonsteroidal anti-inflammatory	November 30, 1989	Gastrointestinal tract bleeding	6.1
			Adjust dose in renal failure	6.1
			Hypersensitivity	6.1
			Not for intrathecal/epidural use	6.1
			Unsafe during pregnancy	6.1
			Adjust dose for age	6.1

(continued)

Table 1. Drugs With a New Black Box Warning, 1975-2000* (cont)

Drug Name	Food and Drug Administration Class	Drug Approval Date	Warning	Time to First *Physicians' Desk Reference* Black Box Warning in Years
Bepridil hydrochloride	Antiarrhythmic	December 28, 1990	Increased mortality with class IC antiarrhythmics	2.0
Moricizine	Antiarrhythmic	June 19, 1990	Increased mortality with class IC antiarrhythmics	5.5
Ramipril	Antihypertensive ACE inhibitor	January 28, 1991	Unsafe during pregnancy	1.9
Fludarabine phosphate†	Antineoplastic	April 19, 1991	Hemolytic anemia	4.7
Fosinopril sodium	Antihypertensive ACE inhibitor	May 16, 1991	Unsafe during pregnancy	1.6
Benazepril hydrochloride	Antihypertensive ACE inhibitor	June 25, 1991	Unsafe during pregnancy	1.5
Zalcitabine†	Antiviral	June 19, 1992	Hepatic toxicity	2.5
			Lactic acidosis	3.5
Enoxaparin sodium	Anticoagulant	March 1, 1993	Spinal hematoma	5.8
Felbamate	Anticonvulsant	July 29, 1993	Bone marrow toxicity	2.4
			Hepatic toxicity	3.0
Cisapride§	Acid/peptic agent	July 29, 1993	Drug interactions causing cardiotoxicity	3.4
Dalteparin sodium	Anticoagulant	December 1, 1994	Spinal hematoma	4.1
Lamotrigine	Anticonvulsant	December 24, 1994	Severe rash	3.0
Danaparoid sodium	Anticoagulant	January 1, 1997	Spinal hematoma	2.0
Troglitazone§	Blood glucose regulator	January 29, 1997	Hepatic failure	1.9
Trovafloxacin mesylate	Fluoroquinolone antibiotic	December 18, 1997	Hepatic toxicity	2.0
Tolcapone	Extrapyramidal movement disorders	January 28, 1998	Hepatic toxicity	1.9

*Drugs found in the 2000 *Physicians' Desk Reference*, which were introduced after 1975, did not have a black box warning in the first *Physicians' Desk Reference* in which they appeared, and subsequently acquired a *Physicians' Desk Reference* black box warning. ACE indicates angiotensin-converting enzyme.
†Had other *Physicians' Desk Reference* black box warnings when first approved.
‡Patient must have severe disfiguring nodular acne recalcitrant to standard therapies, must be reliable in understanding and following instructions, can comply with mandatory contraception, must receive oral and written warnings regarding fetal toxicity, must use 2 contraceptive methods, must have a pregnancy test, and must start therapy during menses.
§Drug subsequently withdrawn from the market for safety reasons. Drug not in 2000 *Physicians' Desk Reference*.

ence during the study period. In Kaplan-Meier analyses, 50% of these changes occurred within 7 years following drug introduction. *Physicians' Desk Reference* changes were most commonly made for hepatic toxicity (n=15 [19%]), hematologic toxicity (n=13 [16%]), cardiovascular toxicity (n=17 [21%]), and risk in pregnancy (n=9 [11%]).

We noted several inconsistencies among *Physicians' Desk Reference* safety warnings. The *Physicians' Desk Reference* entries for the β-blockers timolol maleate, atenolol, and metoprolol contained black box warnings indicating that abrupt discontinuation of the drug could exacerbate coronary artery disease. However, the entries for the β-blockers carteolol hydrochloride, penbutolol sulfate, and bisoprolol fumarate had no such warning. We also observed asynchronous appearances of black box warnings among drugs of the same class. Timolol obtained a black box warning in 1983, while metoprolol and atenolol obtained the same warning in 1985 and 1987, respectively. Similarly, the combination drug triamterene-hydrochlorothiazide obtained a black box warning for hyperkalemia in 1989, while triamterene obtained this warning in 1991. Finally, ketoconazole obtained a black box warning for a life-threatening drug interaction with terfenadine in the 1993 *Physicians' Desk Reference*, while terfenadine did not have a comparable warning until 1994.

COMMENT

Many serious ADRs are discovered only after a drug has been on the market for years. Only half of newly discovered serious ADRs are detected and documented in the *Physicians' Desk Reference* within 7 years after drug approval. Our definition of a serious ADR was conservative, since it was limited to *Physicians' Desk Reference* black box warnings. We did not consider other labeling changes such as bolded warnings without boxes, "Dear Health Care Professional" letters, or case reports in the medical literature. Our finding that half of all drug withdrawals occurred within 2 years is consistent with previous research,[9] as is our documentation of potentially dangerous inconsistencies in the *Physicians' Desk Reference*.[48-50]

Why are so many ADRs brought to light only after drug approval? Premarketing drug trials are often underpowered to detect ADRs,[2,51] and have limited follow-up. In some cases, drugs are

approved despite identification of serious ADRs in premarketing trials.[52] For instance, alosetron hydrochloride was reported to be associated with ischemic colitis prior to its approval, and grepafloxacin hydrochloride was approved despite reports of QT prolongation and 2 possible deaths.[6] Both were subsequently withdrawn from the market because of these adverse events. Some drugs represent a significant advance over existing drugs in the reduction of morbidity and mortality and warrant use despite limited experience. However, the drugs that do not represent a significant advance should be considered second-line drugs until their safety profile is better known.

Despite limited knowledge about the safety of new drugs, their market uptake and sales volume may be explosive. The pharmaceutical industry promotes the early use of new drugs, and influences physicians' adoption of such drugs.[53-55] Direct-to-consumer drug advertising also generates a high volume of new drug prescriptions.[56] Drug firms may rush new drugs to market because of concerns about patent life, a desire to mold prescribing habits prior to the market entry of competitors, and hopes for a fast "ramp-up" in sales that will encourage investors and increase stock prices.[57-59] New drug safety may be further compromised by the apparent failure by drug companies to conduct postmarketing (phase 4) studies, which are required by the FDA when a safety question arises during the preapproval period.[6,60]

Given the frequent introduction of drugs for which new serious adverse events are discovered, the FDA should consider raising its threshold for approving new drugs when safe, effective therapies already exist, or when the new drug treats a benign condition. Postmarketing surveillance should be completed, analyzed, and disseminated to physicians. The date of drug approval should be prominently included in drug labeling, and changes in labeling should be highlighted and dated. Furthermore, when a serious ADR is discovered, labeling of all drugs in the same class should be reviewed if a class effect is suspected.

Based on our results and those of others,[7] clinicians should avoid using new drugs when older, similarly efficacious agents are available. Patients who must use new drugs should be informed of the drug's limited experience and safety record, and be observed for possible he-

Table 2. Drugs Withdrawn From the Market for Safety Reasons, 1975-2000*

Drug Name	Food and Drug Administration Class	Drug Approval Date	Warning	Time to Withdrawal in Years
Azaribine	Dermatologic (psoriasis)	January 1, 1975	Thromboembolism	2.4
Ticrynafen	Antihypertensive	May 2, 1979	Hepatic toxicity	0.7
Zomepirac sodium	Analgesic, nonsteroidal anti-inflammatory	October 28, 1980	Anaphylaxis	2.3
Benoxaprofen	Analgesic, nonsteroidal anti-inflammatory	April 19, 1982	Jaundice	0.3
Suprofen	Analgesic, nonsteroidal anti-inflammatory	December 24, 1984	Flank pain syndrome	1.3
Nomifensine maleate	Antidepressant	December 31, 1984	Hemolytic anemia	1.4
Terfenadine†	Antihistamine	May 8, 1985	Drug interactions causing cardiotoxicity	12.8
Encainide hydrochloride†	Antiarrhythmic	December 24, 1986	Increased mortality in patients with asymptomatic ventricular arrhythmias	5.0
Astemizole†	Antihistamine	December 29, 1988	Drug interactions	10.5
Temafloxacin hydrochloride	Fluoroquinolone antibiotic	January 30, 1992	Hemolytic anemia	0.3
			Hypoglycemia in elderly patients	0.3
			Renal failure	0.3
			Abnormal liver test results	0.3
			Coagulopathy	0.3
Flosequinan	Congestive heart failure	December 30, 1992	Increased mortality	0.5
Cisapride†	Acid/peptic disorders	July 29, 1993	Drug interactions causing cardiotoxicity	6.6
Troglitazone†	Blood glucose regulator	January 29, 1997	Hepatic failure	3.1
Mibefradil dihydrochloride	Antihypertensive calcium-channel blocker	June 20, 1997	Drug interactions	1.0
Bromfenac sodium	Analgesic, nonsteroidal anti-inflammatory	July 15, 1997	Hepatic failure	1.0
Grepafloxacin hydrochloride	Fluoroquinolone antibiotic	November 6, 1997	Cardiovascular events	2.0

*All drugs were approved between 1975 and 1999.
†Drug had a *Physicians' Desk Reference* black box warning prior to withdrawal.

patic, hematologic, or cardiac toxicity. Clinicians should report ADRs to MEDWATCH, the voluntary reporting system. Given the inadequacy of clinician reporting of ADRs, other reporting methods such as patient-initiated reporting should be explored. Innovative new therapies are important, but when safe and effective therapies already exist, any new drug should be considered a black box.

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