

Is It Ever Too Late to Discover the True Toxicity of a Drug?

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The drug approval process is continuously evolving. Advances in technology, computerized submissions of new drug applications, recent legislation, and regulatory changes have accelerated the process and resulted in an increase in the rate of annual drug approvals in the United States.¹ Patients and practitioners now have more therapeutic options, and can choose among multiple new medications to treat diseases such as AIDS, cancer, epilepsy, and diabetes. However, in this new pharmaceutically friendly era, it appears to be more common for a new medication to be withdrawn from the market because of unforeseen adverse events (see Table I). When this happens, patients and prescribers scramble for answers and alternatives. In examining the spectrum of recent market withdrawals, this article will focus on the theories, possible contributing factors, and implications for clinical practice.

Table I: Summary of Recent Market Withdrawals²⁻⁷

Year of Market Withdrawal	Drug Name (Trade Name)	Year Marketed	Type of Drug and Indication	Reason for Withdrawal
2000	Alosetron (Lotronex [®])	2000	Serotonin antagonist for irritable bowel syndrome	Constipation, Ischemic colitis
	Cisapride* (Propulsid [®])	1993	Pro-kinetic agent for GERD	Cardiac arrhythmias
	Phenylpropanolamine	pre-1990	Sympathomimetic diet aid and decongestant	Hemorrhagic stroke
	Troglitazone (Rezulin [®])	1997	Thiazolidinedione for type 2 diabetes	Liver toxicity
1999	Astemizole (Hismanal [®])	1988	Antihistamine for allergic rhinitis	Cardiac arrhythmias
	Grepafloxacin (Raxa [®])	1997	Fluoroquinolone antibiotic	QT wave prolongation
	Trovafloxacin* (Trovan [®])	1998	Fluoroquinolone antibiotic	Liver toxicity
1998	Bromfenac (Duract [®])	1997	NSAID for acute pain	Liver toxicity
	Mibefradil (Posicor [®])	1997	Calcium channel blocker for hypertension and angina	Drug-drug interactions
	Terfenadine (Seldane [®])	1985	Antihistamine for allergic rhinitis	Cardiac arrhythmias
1997	Dexfenfluramine (Redux [®])	1996	Serotonin agonist for weight loss	Cardiac valve disease
	Fenfluramine (Pondimin [®])	1973	Serotonin agonist/reuptake inhibitor for weight loss	Cardiac valve disease
1983	Zomepirac (Zomax [®])	1980	NSAID for pain	Anaphylactic reactions

* Available via manufacturer's restricted-access program.

Historically, the U.S. Food and Drug Administration (FDA) has been criticized for being too slow to approve drugs that could significantly benefit patients. In 1992, the FDA, under the Prescription Drug User Fee Act (PDUFA), began to collect fees from manufacturers to offset the costs and expedite the drug approval process.¹ From 1992 to 1997, the FDA collected \$329 million in fees from the pharmaceutical industry and dedicated 696 additional employees to the drug approval process. The FDA Modernization Act of 1997 further accelerated the review of "important" new medications and shortened the drug review process from an average of 30 months to an average of 15 months.⁸

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Limitations of Pre-marketing Clinical Trials^{11,12}

- **Too few** — Rare adverse events may not be detectable (< 4,000 subjects)
- **Too short** — Effects that develop with chronic use may not be detectable
- **Too median aged** — Does not include subpopulations, i.e. children, elderly
- **Too narrow** — Pre-marketing study inclusion criteria limit experience
- **Too simple** — Primary objective of pre-marketing studies are to prove efficacy

The main groups of patients that traditionally have been under-represented in clinical trials include women, children, the elderly, HIV/AIDS patients, and cancer patients.

The key to minimizing drug misadventures is rapid association of adverse drug consequences in the immediate post-marketing period. To date, the dissemination of timely warnings and updated information to practitioners has been inadequate.

To rapidly disseminate information about emerging adverse drug reaction trends, UWAMC prescribers receive biweekly UWMC/HMC Safety-Related Drug Alerts! via email.

Various theories have been proposed in an attempt to explain the rate of recent market withdrawals; however, none has emerged as dominant. One theory blames the FDA and the aforementioned legislation, which allows drugs to be approved for marketing in a shorter time period. Critics claim that this condensed testing period does not allow for thorough scrutiny, which in turn may lead to substandard new drug application reviews. It has also been suggested that the “law of averages” may be accountable for the phenomenon.⁹ The number of drugs approved annually by the FDA has more than doubled since the 1990s, to about 40 new drugs each year. The “law of averages” theory suggests that a proportional increase in the number of withdrawals is to be expected as the number of new drug approvals increases. However, the authors of a recent JAMA article¹ counter that there is no historical correlation between market withdrawals, the rate of FDA new drug approvals, or the average length of the review process.

Regardless of the theories, pre-marketing clinical trials have always had inherent design limitations that preclude the detection of certain types of adverse events (see sidebar this page). Pre-clinical trials are typically designed to limit confounding variables in order to unequivocally demonstrate efficacy and safety in a defined set of patients. By design, these studies fail to account for all possible conditions of use and fail to test all segments of the population that the medication may theoretically benefit. For example, prior to marketing, terfenadine (Seldane[®]) was tested in approximately 5,000 patients. After 12 years on the market and experience in 7.5 million patients, the popular drug was withdrawn from the market.¹⁰ In this example, the test population was not large enough nor inclusive enough to detect the problem of cardiac arrhythmias in predisposed patients. While it is nearly impossible to perform a clinical trial that will include all possible uses of a drug prior to its marketing, the shortcomings of such trials are often partially offset by FDA-mandated post-marketing surveillance or by vigilant reporting of serious, emergent adverse drug effects by clinical practitioners. Post-marketing attention to drug safety serves to supplement pre-marketing discoveries and to quickly identify emerging problems and minimize drug misadventures once a new adverse reaction has surfaced in practice.

The key to minimizing drug misadventures is rapid association of adverse drug consequences in the immediate post-marketing period. To date, despite sometimes heroic efforts, the dissemination of timely warnings and updated information to practitioners has been inadequate. As a case in point, in June 1998 Janssen Pharmaceuticals, the makers of cisapride (Propulsid[®]), issued a “black-box” warning in their revised package insert and sent “Dear Doctor” letters to prescribers to alert them to the types of patients who were most at risk for cardiac arrhythmias from cisapride use. A one-year follow-up study analyzed the impact of these warnings on the cisapride prescribing habits of practitioners in three separate medical settings.¹³ The analysis found only a minimal (2%) reduction in the average number of contraindicated cisapride prescriptions (from 38% at baseline to 36% after the warnings). The authors concluded that the methods used to alert health care providers to the change in cisapride prescribing recommendations were ineffective and that new modalities were needed.

In order to assure the safe use of medicines, the pharmaceutical industry, health care professionals, and the FDA must work in unison. It would be pointless to blame the market withdrawals on one specific group or theory. The withdrawals may be a result of a combination of these variables, or perhaps a yet unidentified factor. Regardless, when the next market withdrawal occurs, patients may be less accepting of the risks and less tolerant of unknowledgeable health care practitioners. A recent editorial proposed the assembly of an “independent drug safety board,” which would have no affiliation to the pharmaceutical companies nor to the FDA.¹⁷ Such a board could independently

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Practitioners must remember that all drugs (even receptor-specific drugs) have more than one pharmacodynamic effect in the body and therefore the potential for unintended effects. The true side-effect profile of a medication may be revealed only after much clinical experience and/or long-term use.

Strict attention to post-marketing drug safety serves to supplement pre-marketing discoveries, quickly identify emerging problems, and minimize drug misadventures once a new adverse reaction has surfaced in practice.

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References available upon request.

monitor drug safety, investigate emerging adverse event trends, and recommend interventions to assure safe prescribing. Such a group might also perform comparative studies to determine the relative safety and efficacy between similar drugs in the same or different classes. Many of the recent withdrawals listed in Table I were “me-too” drugs that had well-established alternatives, i.e., mibefradil versus other calcium channel blockers, or bromfenac versus other NSAIDs. Independent comparisons between similar products could aid practitioners by judging the relative importance to clinical practice of newly marketed “me-too” drugs.

Market withdrawals will continue to be a periodic occurrence in our society. When prescribing any medication, practitioners must remember that all drugs have more than one pharmacodynamic effect in the body and therefore the potential for unintended effects. The true side-effect profile of a medication may be revealed only after much clinical experience and/or long-term use. The adverse event profiles of newly marketed drugs may be detected earlier if manufacturers communicate post-marketing surveillance discoveries and if practitioners diligently report adverse drug reactions (ADRs). The Prescription Drug User Fee Act generated more money to speed the FDA approval process, but it did not set aside money to enhance the post-marketing surveillance system.¹⁴ Encouraging broader inclusion criteria, under the FDA Modernization Act, if a manufacturer performs pediatric studies, they can claim “pediatric exclusivity” and prolong the drug’s patent for an additional 6 months.¹⁵ In light of recent media reports suggesting a disproportionate number of women are experiencing adverse drug reactions,² more such incentives are needed to extend drug testing to other under-studied patient groups.

Market withdrawals have the potential to cause significant hardships to both the patient and the prescriber. Prescribers should continue to resist pressure to preferentially prescribe newer, less familiar agents. Increasingly, such pressure comes from patients learning about newly marketed medications via the Internet or through direct-to-consumer advertising. As medical information goes, these sources are typically brief in nature and often lack key information that serves to balance potential benefits against potential risks.¹⁸ It is essential that prescribers take an active role in assisting patients with the interpretation of incomplete or biased medical information sources and by directing motivated patients to better sources such as the National Library of Medicine’s MedlinePlus web site (www.medlineplus.com). Prescribers should be aware that there are inherent limitations in the drug review process that thwart the detection of a complete adverse effect profile of new drugs prior to their marketing. Adverse effect profiles for newly marketed drugs will be fully understood only after thorough post-marketing surveillance, vigilant reporting of adverse events, and the effective dissemination of updated information. Practitioners are a vital link in this process and are urged to report ADRs that arise in clinical practice.

Reporting Adverse Drug Reactions

A.D.R. Phone Lines
HMC: 731-3802
SE Lake Union: 288-6336
UWMC: 598-6837

Adverse drug reactions are unintended, undesired, and unavoidable noxious effects of agents administered to patients for diagnostic, prophylactic, or therapeutic indications. Adverse drug reactions that are reportable are those that are considered serious enough to require a change in therapy (i.e., drug discontinuation, dosage modification, or additional therapeutic intervention).

A.D.R. reporting is crucial to preventing inadvertent patient rechallenges.

If you have a patient you feel is experiencing an Adverse Drug Reaction, in addition to placing the appropriate documentation in the patient’s chart, report it to a clinical pharmacist or call the appropriate A.D.R. Phone Line and leave a message in the voice mail box.

Pharmacy & Therapeutics Committee Actions

Formulary Additions	Dosage Form(s), Strength(s), & Cost [‡]	Therapeutic Classification	Use	Usual Adult Starting Dose*
Eptifibatide (Integrilin)	Injection: 2mg/mL (10mL - \$54.01, 100mL - \$450.01)	Glycoprotein IIb/IIIa inhibitor	Acute coronary syndrome; Percutaneous coronary intervention	Individualized
Fluticasone/salmeterol (Advair)	Inhalation device: 100/50mcg (# 60) - \$72.38; 250/50mcg (# 60) - \$90.77; 500/50mcg (# 60) - \$120.70	Corticosteroid/sympathomimetic combination respiratory inhalant	Treatment of chronic asthma	Individualized
Formulary Deletions	Dosage Form(s) & Strength(s)	Therapeutic Classification	Use	Comment
Tirofiban (Aggrastat)	All dosage forms and strengths	Glycoprotein IIb/IIIa inhibitor	Acute coronary syndrome	Replaced by eptifibatide (Integrilin)

* Refer to product labeling for full prescribing information. ‡ Costs represent UWMC/HMC outpatient acquisition costs and do not include pharmacy dispensing fees.

UW Safety-Related Drug Alerts!

Questions about UW Safety-Related Drug Alerts! should be addressed to the Drug Information Center (druginfo@u.washington.edu or 598-6612).

Together with the UWMC Medical Director's office the Drug Information Center assists in the timely dissemination of safety-related drug alerts. Once every two weeks, brief summaries of the drug alerts judged to be most relevant to the care of UWAMC patients are forwarded via email to the UWMC, HMC, and UWPB Medical Directors for further dissemination to clinical practitioners.

"Safety-Related Drug Alerts!" encompass formulary and non-formulary prescription and non-prescription drugs, products regulated as food supplements, and medical devices that may be prescribed by UWAMC practitioners or used by UWAMC patients. "Safety-Related Drug Alerts!" may originate from the FDA, pharmaceutical manufacturers, or other sources deemed reliable. Alerts are archived on the Internet at <http://uw.pnrx.org/drugSub.asp?Id=2>

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