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An Assessment of the Publicly Disseminated Evidence of Safety Used in Decisions to Withdraw Medicinal Products from the UK and US Markets

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Abstract

Background: The objective of this study was to assess the publicly disseminated evidence used to support decisions to withdraw medicinal products for safety reasons, and related implications for the conduct of systematic reviews of harm.

Methods: Medicinal products withdrawn from the UK and US markets for safety reasons were identified from websites of the UK Medicines Control Agency (now known as the Medicines and Healthcare products Regulatory Agency) and the US FDA. Related scientific evidence was identified from communications made to the public and healthcare professionals at the time of each product withdrawal. Evidence for each product withdrawal decision was classified according to study design and outcome.

Results: Eleven products were withdrawn during 1999–2001. Randomised trial evidence was cited for two products (18%) and comparative observational studies for two products (18%). Evidence from spontaneous reports supported the withdrawal of eight products (73%), with four products (36%) apparently withdrawn on the basis of spontaneous reports alone. Only two products (18%) were withdrawn on evidence for a patient relevant outcome from comparative studies.

Conclusions: It is rare that evidence other than spontaneous reports is cited in support of drug withdrawals. The serious implications of product withdrawal mandate the elevation of the level of evidence that supports such public health decisions. Once suspicions of important safety hazards have emerged, prospective studies may be unfeasible and may be seen as unethical. Prospective studies can strengthen the evidence base and should be planned to commence when every drug is first marketed. Systematic reviews are unlikely to elicit evidence of harm associated with a drug unless they include spontaneous reports and surrogate outcomes.

Background

Randomised clinical trials (RCTs) provide the highest level of evidence in assessing therapeutic efficacy in drug development, but have limitations in their ability to assess the safety of new drugs.[1] Their small sample sizes, restrictive eligibility criteria and short duration of exposure to the therapeutic agent prevent the full safety profile of products being understood in detail. Postmarketing studies, where a large heterogeneous population is exposed to the drug, play a very important role in monitoring drug safety, although some of their methodologies are relatively new and are yet to gain widespread acceptance.[2]

Product withdrawals due to safety concerns are not common. Of 583 new active substances approved for the British market between 1972 and 1994 only 22 (4%) were withdrawn during that period because of safety concerns.[3] More were withdrawn for commercial reasons (6%) and only one because of efficacy concerns. However, withdrawing a product because of a safety concern may have major public health implications that impact on patient and professional confidence in the licensing and monitoring systems. Moreover, product withdrawals have significant economic implications for drug manufacturers.

Systematic reviews of therapeutic agents rarely search for non-randomised studies or surrogate outcomes and therefore may often miss evidence of adverse effects only assessed in observational studies and case series.[4] Nearly 64% of withdrawal decisions in Spain between 1990 and 1999 were based solely on evidence from individual case reports or case series; nearly 23% reported comparative observational studies, while in only 18% evidence from RCTs was available.[5]

This study aims to assess the publicly disseminated evidence used to support decisions leading to the withdrawal of products for safety reasons, both in terms of study designs and the outcomes assessed. Data are considered from the UK and/or the US markets, two countries considered to have highly developed regulatory systems. We also consider how methods of conducting systematic reviews would need to be changed in order to capture evidence of harm for these products.

Materials and Methods

Medicinal products withdrawn from the UK and/or US markets for safety reasons (either due to a regulatory decision or voluntarily by the manufacturer) during the period 1999–2001 were identified from a list published on the website for the US

Table I. Study designs used in assessments of drug safety

Type of study	Description
Animal study	*In vivo* or *in vitro* studies on whole animals or using animal tissue
Spontaneous report	Suspected adverse drug reactions reported by healthcare professionals to national pharmacovigilance centres, regulatory authorities or the marketing authorisation holders
Published case report	A report of a single patient with a suspected adverse drug reaction
Published case series	A report of a series of patients with the same suspected adverse drug reaction
Cross-sectional study	A study that involves the observation of a defined population at a single point in time or time interval, where the exposure and the outcome are defined simultaneously
Case-control study	A study that involves identifying patients who have had the suspected adverse drug reaction (cases) and control patients without this reaction, and looking to see if they have had the same exposure to the suspected causative agent. Case-control studies are usually retrospective
Cohort study	A study that involves the identification of either one group of patients who received the drug of interest or two groups of patients, one group having received the drug of interest and one group having not, and determination as to whether any developed the adverse reaction of interest. Cohort studies can be either prospective or retrospective. Prescription-event monitoring is an example of a prospective cohort study
Non-randomised study	An experimental study in which patients are not randomly assigned to an intervention group. Groups are followed up for the outcome of interest
Randomised controlled trial	An experimental study in which patients are randomly assigned to either an intervention group or a control group. Both groups are followed up for the variables/outcomes of interest

Table II. Products withdrawn from the UK and US markets for safety reasons during 1999–2001

Drug name	Drug class or use	Country (year withdrawn)	Adverse reaction
Astemizole	Antihistamine	US (1999)	Cardiac arrhythmias
Grepafloxcin	Fluoroquinolone antibacterial	UK (1999), US (1999)	Cardiac arrhythmias QTc interval prolongation Torsades de pointes
Alosetron[a]	5-HT_3 antagonist for the treatment of irritable bowel disease	US (2000)	Ischaemic colitis Severe constipation
Cisapride	Prokinetic agent	UK (2000), US (2000)	Cardiac arrhythmias QTc interval prolongation Ventricular arrhythmias Sudden unexplained death
Pumactant	Lung surfactant	UK (2000)	Increased mortality
Phenylpropanolamine	Nasal decongestant and weight control product	US (2000)	Haemorrhagic stroke
Troglitazone	Antidiabetic for the treatment of type II diabetes	US (2000)	Hepatotoxicity
Cerivastatin	Lipid-lowering agent	UK (2001), US (2001)	Rhabdomyolysis
Droperidol	Neuroleptic agent	UK (2001)	QTc interval prolongation Ventricular arrhythmias Sudden death
Levacetylmethadol	Long-acting opiate for treatment of opioid dependence	UK (2001)	Ventricular rhythm disorders
Rapacuronium bromide	Muscle relaxant for use during anaesthesia	US (2001)	Bronchospasm

a Alosetron has now been reintroduced to the US market.

QTc interval = corrected QT interval.

FDA[6] and through the website of the UK Medicines Control Agency (MCA).[7] The UK list was verified with the Post-licensing Division of the MCA (now known as the Medicines and Healthcare products Regulatory Agency or MHRA).

Both prescription-only and over-the-counter products were included. Veterinary products, herbal drugs, medical devices, diagnostic agents, radiopharmaceuticals, excipients, preservatives, vaccines and biologics were excluded, as were products where withdrawal was for only one of several licensed dose forms, due to manufacturing problems or bioinequivalence or for reasons other than safety.

The anorectic agents amfepramone and phentermine, withdrawn from the market during the study period, were excluded as there was conflicting information about whether withdrawal was due to safety reasons or an unfavourable benefit-risk balance because of a lack of therapeutic efficacy. Marketing authorisations for these products have subsequently been reinstated.

The scientific evidence leading to the withdrawal decision was identified from documents and other communications made available to the public and healthcare professionals at the time of product withdrawal, searches of the websites of the major regulatory authorities of the UK, Europe and the US,[7-9] and by contacting the marketing authorisation holder for each product.

Data collected from these sources were compiled and reviewed. Any evidence or studies that were cited in these sources as support for the decision to withdraw each product from their respective markets were classified according to study design as outlined in table I. Outcomes were classified either as patient-relevant outcomes or as surrogate outcomes, which are potential precursors to adverse events (e.g. prolonged corrected QT [QTc] interval). Information was classified independently by two reviewers (AC and JD). A third reviewer (SAS) settled any differences of opinion.

Results

Eleven products were withdrawn from the UK or US markets during the study period, with three products (grepafloxacin, cisapride and cerivastatin) being withdrawn from both markets (table II).

Cardiovascular system adverse effects prompted withdrawal of 6 of 11 (55%) products (QTc interval prolongation, cardiac arrhythmias or sudden death). Hepatic, musculoskeletal, gastrointestinal and respiratory adverse events and increased mortality were cited as prompting one product withdrawal each.

Study Designs Used in Withdrawal Decisions

One product, pumactant, was withdrawn on the basis of evidence of increased mortality from a single RCT. Droperidol was withdrawn on evidence from a randomised study of a surrogate outcome supported by observational studies, spontaneous reports and animal studies (table III).

Two product withdrawals were supported by evidence from observational studies. A case-control study of phenylpropanolamine provided evidence of increased risk of haemorrhagic stroke, while a cross-sectional study of droperidol provided evidence of increased QTc intervals. Two further product withdrawals (cisapride and levacetylmethadol) cited evidence from non-randomised studies of increased QTc intervals.

Eight products (73%) included spontaneous reports as evidence to support their withdrawal. For four products, withdrawal appeared to be based on this evidence alone, or the combinations of spontaneous reports and premarketing data.

For two products (astemizole and troglitazone), the evidence used to support their withdrawal could not be found in any of the identified documents.

Outcomes Used in Withdrawal Decisions

Harmful effects were presented for patient relevant outcomes for only two of the six randomised or observational studies identified, while the other four reported increases in QTc intervals (a possible pre-

Table III. Presence or absence of evidence (study designs and assessed outcomes) used to support individual product withdrawals from the UK and/or US during 1999–2001

Study design	Outcome type	DRO	CIS	LEV	PHE	PUM	ALO	CER	RAP	GRE	AST	TRO
Animal studies	Surrogate	✓	✓	✓	×	×	×	×	×	×	×	×
Spontaneous reports	Patient relevant	✓	✓	✓	✓	×	✓	✓	✓	✓	×	×
Published case reports		×	×	×	×	×	×	×	×	×	×	×
Published case series		×	×	×	×	×	×	×	×	×	×	×
Cross-sectional study	Surrogate	✓	×	×	×	×	×	×	×	×	×	×
Case-control study	Patient relevant	×	×	×	✓	×	×	×	×	×	×	×
Cohort study		×	×	×	×	×	×	×	×	×	×	×
Non-randomised study	Surrogate	×	✓	✓	×	×	×	×	×	×	×	×
Randomised clinical trials	Surrogate	✓	×	×	×	×	×	×	×	×	×	×
Randomised clinical trials	Patient relevant	×	×	×	×	✓	×	×	×	×	×	×
Other[a]		×	×	×	×	×	✓	×	✓	×	×	×

a Evidence for alosetron and rapacuronium bromide withdrawals described in publicly disseminated documents as 'clinical studies prior to approval' and 'premarketing clinical trials'. Assignment to one of the above study design categories was not possible because of a lack of information

ALO = alosetron; **AST** = astemizole; **CER** = cerivastatin; **CIS** = cisapride; **DRO** = droperidol; **GRE** = grepafloxacin; **LEV** = levacetylmethadol; **PHE** = phenylpropanolamine; **PUM** = pumactant; **RAP** = rapacuronium bromide; **TRO** = troglitazone.

cursor to cardiac conditions). In contrast, spontaneous reports almost always reported patient relevant outcomes.

Discussion

The withdrawal of a product from the market is a multifactorial decision. Safety concerns may arise after licensing, either due to an increased prevalence of known hazards initially considered to be acceptable or from reports of entirely new hazards. In addition to considering evidence of harm, benefit-risk evaluation considers the severity and prognosis of the underlying disease, effectiveness of the product, and the availability, effectiveness and the safety profiles of alternative therapeutic agents. Commercial issues may also contribute to the decision.

Product withdrawal, especially for products that are widely prescribed, can lead to a chain of events that are often difficult to predict and may be undesirable. For example, the discontinuation of zomepirac (a NSAID) in 1985 resulted in the substitute use of alternative analgesics, some of which carried a risk of habituation and other adverse effects.[10]

Strength of Evidence

Because the impact of market withdrawal of a drug is so far reaching, affecting patients, healthcare professionals, regulators and manufacturers, it is imperative that any decisions regarding product withdrawal are based on the most robust evidence available.

Grading of healthcare recommendations typically place evidence from randomised controlled trials and systematic reviews of trials as top level evidence.[11] Although RCTs are considered the gold standard of clinical study design to assess the effects of interventions as they reduce bias and confounding, they are sometimes impractical for studying rare adverse events because of small sample sizes and a short follow-up. They may exclude patients with higher risks of experiencing adverse effects (such as the elderly, women of childbearing age, children and people with complex medical problems or those taking concomitant medications). In addition, levels of compliance may differ between the closely monitored trial setting and general clinical use. Commencing RCTs once strong evidence exists of a beneficial treatment effect also presents an ethical dilemma in the appropriateness of withholding treatment of known benefit, but uncertain harm.

Cohort and case-control designs provide practical techniques to study adverse events too rare to be detected in RCTs. Cohort studies such as prescription-event monitoring (PEM)[12] allow estimation of the incidence of adverse events, and case-control studies can examine events with a long latency period. Although these study designs have their own limitations and weaknesses (such as confounding, under-reporting and misclassification), they have been increasingly used in the last three decades to study the safety of medicines.

Further evaluation is needed to determine the value of RCTs and observational studies that assess surrogate safety outcomes that are possible precursors to adverse events.

From our evaluation, spontaneous reports currently appear to be the cornerstone of postmarketing surveillance and regulatory decision making in the UK and US, as was previously noted for Spain. Spontaneous reports are a hypothesis-generating method that does not necessarily support causality between a drug and an adverse event. They lack information on denominators preventing estimation of the incidence of an adverse effect and under-reporting is common.[13,14] Moreover, the number of adverse event reports is dependent on factors such as the length of time the product has been on the market and the publicity surrounding a drug or an outcome.[15] Other limitations are described elsewhere.[16] However, spontaneous reports typically report patient-relevant outcomes rather than possible precursors of adverse effects.

There are a number of possible explanations as to why almost half of the withdrawals were based on spontaneous reports alone. Firstly, although there is evidence that postmarketing safety studies improve the understanding of the safety profiles of medicines,[17] it is disappointing that such studies are not conducted for many newly introduced

medicines. Secondly, with regard to rare adverse reactions, spontaneous reporting is the only method currently available to detect such reactions.

If a particular product is of limited clinical use and has effective alternatives, it might be argued that spontaneous reports of a potential adverse drug reaction are enough evidence to change (or at least make uncertain) the benefit-risk profile of a product enough to warrant withdrawal. However, in the absence of studies with more robust designs (i.e. when postmarketing safety information is derived only from spontaneous reporting), uncertainty remains about the causality and incidence of adverse effects for these products and the true benefit-risk balance may never be clearly defined.

Inclusion of Harmful Effects in Systematic Reviews

Based on the study designs located in this small study, if systematic reviews of the 11 products withdrawn from market were undertaken, restricting the inclusion criteria to RCTs of patient relevant outcomes, evidence of harm would be detected for only 1 of 11 products (9%, 95% CI 2%, 41%). Inclusion of comparative observational studies would only include evidence for one further product, although evidence of harm for three additional products would be detected if surrogate outcomes of safety were also included (45%, 95% CI 17%, 77%). It would be necessary to include spontaneous reports to locate evidence of harm for the majority of products. The resources that are required, difficulties in locating spontaneous reports and uncertainty about their interpretation means that it is unlikely that the current processes involved in conducting systematic reviews will capture this information.

Limitations of Our Study

The focus of our review has been the information made public or cited at the time of product withdrawal by either the regulatory authority or the marketing authorisation holder (e.g. 'Dear Doctor' letters). We have assumed that all evidence (or at least the strongest evidence) that played a significant role in the decision process would have been cited in the information communicated to the public and/or healthcare professionals at the time of product withdrawal. It is possible that other evidence exists but was not mentioned in the product withdrawal notification. Notably, for astemizole and troglitazone no evidence to support the decision could be found in the identified publicly disseminated documents.

This study focused on examining the publicly disseminated evidence for safety. We did not evaluate the efficacy of the products withdrawn, which is an important part of the benefit-risk evaluation for product withdrawals.

Conclusions

The risk to public health from the availability of products with unacceptable benefit-risk balance for longer than necessary and the serious implications of product withdrawal mandate the elevation of the level of evidence that supports such public health decisions.

Once suspicions of potential adverse drug reactions have emerged, prospective studies may be unfeasible and be seen as unethical, which means that important public health decisions have to be based on limited or grossly incomplete data. To improve evidence on safety, prospective studies must, therefore, be planned to commence when every drug is first marketed. With increasing availability of methods to systematically prospectively monitor the safety of newly introduced medicines, such as PEM[12,18] and the large number of recent linkage databases in some countries, it is mandatory that the level of evidence should be as high as possible in studying drug safety hazards.

Without including spontaneous reports and surrogate outcomes in systematic reviews, evidence of harm associated with a drug currently is unlikely to be elicited.

The focus of our study was publicly disseminated documents informing healthcare professionals about product withdrawals. It would be of interest to compare the evidence cited in these with evidence located in full systematic reviews for each of the products.

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