

**An evidence-based approach to the post-marketing withdrawal of
medicinal products because of adverse reactions**

Igho Jovwoke Onakpoya

Kellogg College

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Nuffield Department of Primary Care Health Sciences
University of Oxford



Abstract

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Igho J. Onakpoya

Nuffield Department of Primary Care Health Sciences, Kellogg College, Oxford
University

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Background: The aim of this thesis was to develop an evidence-based approach to the post-marketing withdrawal of medicinal products when harms are attributed to their use.

Methods: Electronic and non-electronic searches were conducted to identify medicinal products withdrawn from the market because of adverse reactions. Data relating to the time periods between launch, first adverse reaction reports and withdrawals, the mechanism through which the adverse reactions occurred, and the countries of withdrawal were extracted. Standard criteria were used to document the levels of evidence used by drug regulators to make the withdrawal decisions; scatter plots and two-by-two tables used to explore the trends over time. A previously published algorithm was used to examine the justification for withdrawals. To examine the benefits and harms of medicinal products before regulatory approval, searches were conducted on drug regulatory websites and scientific databases. The Cochrane criterion was used to examine the risk of bias, Review Manager Software for meta-analysis, and GRADE criterion to rate the quality of evidence.

Results: Improvements in pharmacovigilance over the past six decades have resulted in quicker detection of harms caused by approved medicinal products; however, there have not been corresponding improvements in how quickly harmful products are withdrawn from the market following the reports of harms. Harmful drugs are significantly less likely to be withdrawn in low resource settings. The quality of evidence in drug trials for which regulatory approval decisions are based is on the whole, poor. There is a lack of consistency in the methods used by drug regulators to assess the harms of medicinal products before granting marketing licences.

Conclusions: Universally accepted guidelines for deciding when to withdraw approved medicinal products from the market should be developed. Pharmacovigilance systems in low-resource settings should be strengthened. The methods used to assess harms in clinical trials require improvement.

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DPhil-related impacts

Chapter-related journal publications

Onakpoya IJ, Heneghan CJ, Aronson JK. Post-marketing withdrawal of 462 medicinal products because of adverse drug reactions: a systematic review of the world literature. BMC Med. 2016 Feb 4;14:10. (**Chapter 2**)

Onakpoya IJ, Heneghan CJ, Aronson JK. Delays in the post-marketing withdrawal of drugs to which deaths have been attributed: a systematic investigation and analysis. BMC Med. 2015 Feb 5;13:26. (**Chapter 3**)

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LIST OF ABBREVIATIONS

Abbreviation	Meaning
95% CI	95% confidence interval
ADR	Adverse drug reaction
CAAOMP	Centrally-acting anti-obesity medicinal product
CDSCO	Indian Central Drugs Standard Control Organization
CJH	Carl J. Heneghan
COX	Cyclooxygenase
CTA	Clinical trial application
DHPC	Direct Health-care Professional Communication
DJC	Dylan J. Collins
DPD	Health Canada Drug Product Database
DRA	Drug regulatory authority
EMA	European Medicines Agency
EU	European Union
FAERS	FDA Adverse Event Reporting System
FDA	United States Food and Drug Administration
GRADE	Grading of Recommendation, Assessment, Development, and Evaluation
IARC	International Agency for Research on Cancer
IJO	Igho J. Onakpoya
IND	Investigational new drug
INNs	International Non-proprietary Names
IQR	Interquartile range
ITT	Intention to treat
JKA	Jeffrey K. Aronson
MAA	Marketing authorization application
MAH	Marketing authorization holder
MCC	South Africa Medicines Control Council
MD	Mean difference
MedDRA	Medical dictionary for regulatory activities
MHRA	UK Medicines and Healthcare products Regulatory Agency
NAFDAC	Nigeria National Agency for Food and Drug Administration and Control
N-B	Naltrexone-bupropion
NDA	New drug application
NJHB	Niklas J.H. Bobrovitz
NNTB	Number needed to treat to benefit
NNTD	number need to treat to discontinue treatment
NNTH	Number needed to treat to harm
NSAIDs	Non-steroidal anti-inflammatory drugs
OCEBM	Oxford Centre for Evidence-based Medicine
OTC	Over-the-counter
PASS	Post-Authorization Safety Study
PMS	Post-marketing surveillance
P-T	Phentermine-topiramate
PV	Pharmacovigilance
SAEs	Serious adverse events
SmPC	Summaries of Product Characteristics
SoF	Summary of findings
SUSARs	Serious unexpected suspected adverse reactions
TGA	Therapeutic Goods Administration
WHO	World Health Organization

LIST OF DEFINITIONS

Term	Definition
Adverse drug reaction	An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product ¹
Adverse event	Any undesirable experience associated with the use of a medical product in a patient ²
PASS	A study conducted after a medicinal product has been authorised to obtain further information the product's safety, or to measure the effectiveness of risk-management measures ³
Pharmacovigilance	The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem ³
PMS	A study required of or agreed to by a sponsor that is conducted after marketing approval to gather additional information about a product's safety, efficacy, or optimal use. ⁵
PV system	A system used by the marketing licence holder and drug regulatory authorities to fulfil tasks and responsibilities designed to monitor the safety of approved medicinal products and to detect any changes in the benefit-harm profile ⁶
SAE	An adverse event that results in one of the following: (i) life-threatening event; (ii) requires hospitalisation or prolongation of existing hospitalisation; (iii) persistent or significant disability or incapacity; or (i) death ⁷
Signal	Information that arises from one or multiple sources (including observation and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, which would command regulatory, societal or clinical attention, and is judged to be of sufficient likelihood to justify verificatory and, when necessary, remedial actions ⁸
SmPC	A legal document that forms the basis for information on how to use an approved medicinal product safely and effectively ⁹
SUSAR	A serious adverse reaction that is inconsistent with the product information in the SmPC ¹⁰

¹Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet. 2000 Oct 7;356(9237):1255-9.

²<https://www.fda.gov/safety/medwatch/howtoreport/ucm053087.htm> [Last accessed 12/10/2017]

³http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000377.jsp&mid=WC0b01ac058066e979 [Last accessed 12/10/2017]

⁴http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/ [Last accessed 12/10/2017]

⁵<https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Post-MarketActivities/Phase4Trials/default.htm> [Last accessed 12/10/2017]

⁶http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129132.pdf [Last accessed 12/10/2017]

⁷<https://www.fda.gov/ohrms/dockets/ac/00/slides/3602s1g/tsld008.htm> [Last accessed 12/10/2017]

⁸Hauben M, Aronson JK. Defining 'signal' and its subtypes in pharmacovigilance based on a systematic review of previous definitions. Drug Saf. 2009;32(2):99-110.

⁹http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2012/05/WC500127919.pdf [Last accessed 12/10/2017]

¹⁰http://www.dcn.ed.ac.uk/ist3/Web_docs_110310/SUSARS/SUSARs%20What%20to%20do%20for%20Trial%20manual%20Version%203%2001022010.pdf [Last accessed 12/10/2017]

Chapter 1 Background

1.1 PROLOGUE

After I arrived at the University of Oxford in 2011 to take up the position of Research Assistant in Pharmacovigilance, I came across a list of medicines withdrawn from the market because of adverse drug reactions [1] being compiled Dr. Jeffrey Aronson. On studying the list, I discovered that some medicines we were taught to prescribe to patients during my undergraduate and internship medical training in Nigeria had been banned years earlier either in Europe or the US because of serious adverse reactions. This left me puzzled as to why we were still prescribing these medicines in Nigeria – and thereby exposing patients who have placed their trust in us to unnecessary harms. Upon discussion of this issue with Dr Aronson and Professor Carl Heneghan, we thought that a logical way to address the problem was first to examine the trends in the post-marketing withdrawal of medicines. This DPhil thesis is the result of these discussions.

1.2 A BRIEF OVERVIEW OF DRUG DEVELOPMENT AND APPROVAL

After a new chemical entity is discovered, and preclinical testing for drug pharmacokinetics, pharmacodynamics and toxicology successfully conducted in animals [2,3], drug sponsors usually file applications to a drug regulatory authority (DRA) to conduct human testing of the chemical compound [4] (Figure 1). In Europe, this could be in the form of a clinical trial application (CTA) [5], and in the USA an investigational new drug (IND) application [6]. If the pre-marketing trials are successful, the sponsors file a marketing authorization application (MAA) with the European Medicines Agency (EMA) if the trial was conducted in Europe [5], or a new drug application (NDA) with the United States Food and Drug Administration (FDA) if the trial was registered in the USA [6].

The interval between discovery of a new compound and subsequent approval by a DRA varies between eight and 12 years [7]; and for every 5,000 to 10,000 new chemical entities that undergo preclinical testing, only one receives marketing licences from DRAs [8,9]. Because the benefit-harm profile of a medicinal product changes with time [10], adverse event monitoring occurs both in the pre-licensing and post-licensing phases [11].

1.3 HARMS MONITORING DURING THE LIFE CYCLE OF A MEDICINAL PRODUCT

1.3.1 Adverse event monitoring in the pre-marketing phase

In premarketing studies of a new medicinal product, harms are assessed through preclinical testing in animals, and phase I, II and III (pivotal) studies in humans [12]. During these periods of testing, common adverse events, serious adverse events (SAEs), and serious unexpected suspected adverse reactions (SUSARs) are documented; these may be reported in scientific journal publications (Figure 1). If studies of the new medicinal product show favourable benefit-to-harm profile and there are no major safety concerns (i.e. is safe, effective, and of good quality), the product is granted a marketing authorization, which allows the manufacturer (who becomes the marketing authorization holder (MAH)) to market the product within the geographical jurisdiction of the DRA.

1.3.2 Adverse event monitoring in the post-marketing phase

The full adverse events profile of a medicinal product is rarely known at the time the marketing licence is granted [13]. Consequently, monitoring for harms of medicinal products continues in the form of post-marketing surveillance (PMS) after regulatory approval – this aims to monitor trends in the frequencies of adverse events in real life settings and to detect any new adverse events that were not previously observed in the pre-

marketing phase [14]. PMS is an important part of pharmacovigilance (PV), which is “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem” [15]. Many countries have national PV systems that use spontaneous reporting methods (e.g., the European Union Drug Regulating Authorities Pharmacovigilance (EudraVigilance) or the FDA Adverse Event Reporting System (FAERS) to monitor and assess reports of suspected adverse drug reactions attributed to use of medicinal products (Figure 1) [16]. Through the use of spontaneous reporting systems, individual case reports and/or observational studies, data on adverse events may accumulate over time. Many spontaneous reporting systems use statistical methods, e.g. proportional reporting ratio (PRR) or reporting odds ratio (ROR), to explore drug-adverse event associations.

The PRR is the proportion of spontaneous reports for a given medicinal product that are related to a specific adverse event, divided by the corresponding proportion for all other medicinal products (or products in the same class) [17]. The ROR is defined as the ratio of the odds of reporting one specific AE versus all other events for a given medicinal product divided by the reporting odds for all other products [18]. When the number of spontaneous reports exceeds a threshold, a signal that links a specific product with an adverse event can be generated [19,20] (Figure 1). The threshold for a signal varies and is determined by a number of factors including the seriousness of the reports; a WHO preferred term that suggests presence of a serious disease and requires follow-up; a previously unknown adverse reaction; and the strength of the disproportionate association (e.g. $PRR > 2$) [21]. The generated signals can be used to issue safety alerts about suspected harm(s) associated with the use of the specific product. Spontaneous reporting systems are well developed for

use in high-income countries; however, many low-and middle-income countries do not have fully functional reporting systems [22].

Although PPR and ROR are quick and inexpensive tools for investigating drug-adverse event associations, their reliability at detecting drug-adverse event association is undermined by the possibility of biased reporting, sampling errors, and multiple reports of same case or same patient [23,24]. Other strategies used to complement these traditional statistical methods include prescription event monitoring [25]; collaboration between PV databases [26]; the use of case-control networks and electronic health records [27]; observational phase IV trials [28]; systematic reviews [29]; and web-based tools that collect primary information from patients [30].

1.4 FLAWS IN THE MONITORING AND ASSESSMENT OF HARMS

1.4.1 Flaws in pre-marketing monitoring and reporting of adverse events

- I. ***Lack of statistical power:*** Clinical trials evaluating the effectiveness of drug interventions are usually underpowered to detect harms, either because low-risk populations are recruited into the trials [31], or the sample sizes are too small to detect differences in harms between groups [32]. The recruitment of “ideal” populations result in the trial results not being representative of the population for which the product is intended [33], and small sample sizes can result in false positive conclusions because of Type I errors [34].
- II. ***Misclassification of adverse events:*** This occurs especially when adverse events data are collected through spontaneous reports from trial participants instead of systematic monitoring [31]. Current evidence suggests that the classification of adverse events is

unreliable and non-reproducible, and can distort the interpretation of harms in clinical trials [35].

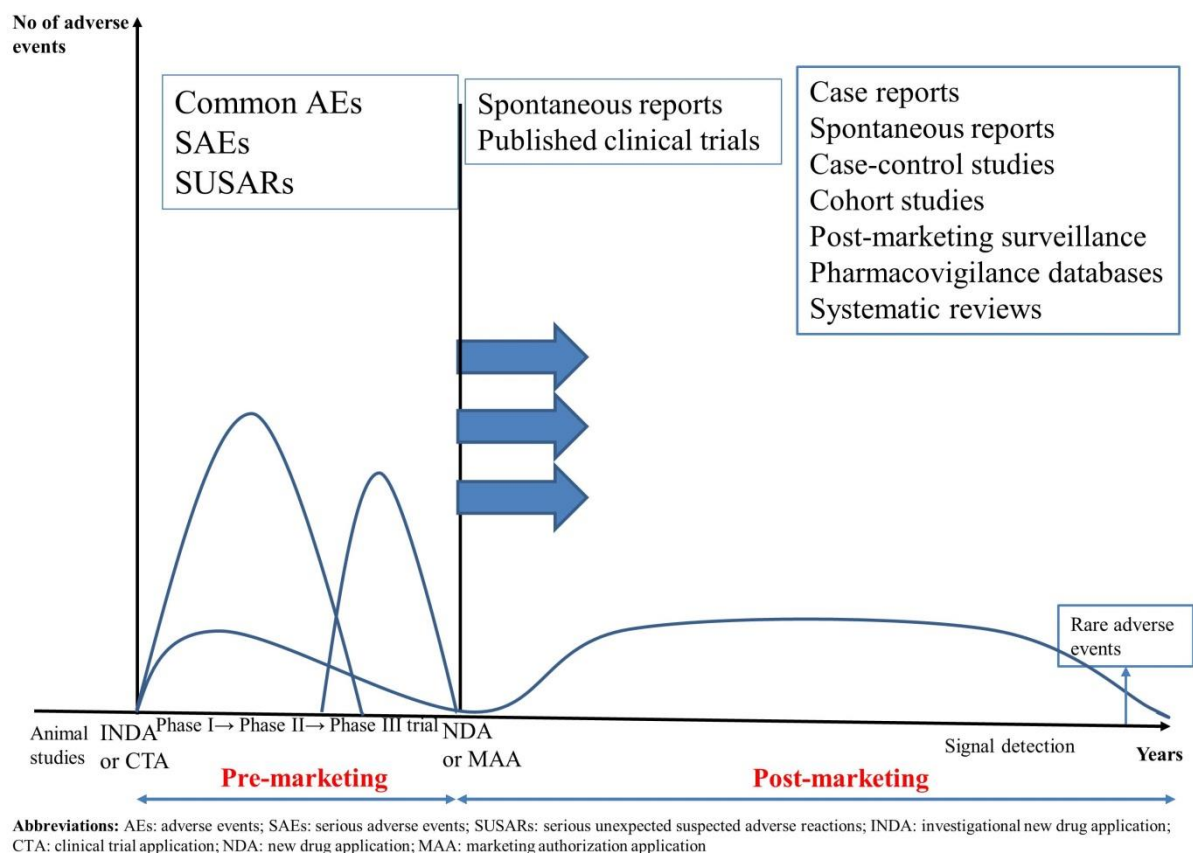
III. ***Potential bias in the interpretation of adverse events data:*** Investigators of published trials funded by drug manufacturers tend to downplay the risk of adverse events attributed to medicinal products, even when there are statistically increased risks of such events [36]. Drug regulators are also suspected of prioritizing industry interests over objective benefit-harm assessments [37].

1.4.2 Flaws in the post-marketing monitoring and reporting of adverse events

- I. ***Under-reporting:*** Spontaneous reporting detects only about 5% of adverse events [38], and has a propensity to miss serious adverse drug reactions [39]. This is accentuated when we consider that most low-to-middle income economies have no strong PV systems for reporting suspected adverse drug reactions. Evidence also suggests that harms in post-marketing studies are underreported because of small sample sizes and conflicts of interest among trial physicians [40].
- II. ***Possibility of false causality attribution:*** Although attempts have been made to improve methods for establishing causality, through complementing the methods used in traditional spontaneous reporting systems [16,41], there is no universally acceptable method for determining whether a signal detected through the use of spontaneous reporting represents a true risk [31]. This results in inconsistencies in decision-making processes across regulatory authorities when harms are attributed to medicinal products. Because a vast majority of the evidence in spontaneous reporting systems is based on case reports, there is the chance of wrongly attributing specific suspected adverse drug reactions [42].

III. **Failure to verify important clinical details:** Data from spontaneous reports and electronic databases are characterized by a dearth of important clinical details that may help in determining whether an observed adverse event is due to a specific medicinal product [43].

Figure 1: Trends in the frequency of adverse events during the life cycle of a medicinal product



The limitations in benefit-harm assessments cause controversy when new medicinal products are approved [44,45], and when approved products are withdrawn from the market because of adverse reactions [46]: this can result in mistrust between pharmaceutical companies and DRAs; between physicians and DRAs; between physicians and pharmaceutical companies; and between physicians and patients and/or the general public [47].

Previous research has shown evidence of selective reporting of harms outcomes in clinical trials [48,49]. Research evidence also suggests that acceleration of regulatory review has led to the granting of marketing licences to products with unfavourable benefit-to-harm balance [50], and that post-marketing withdrawals have ramifications that can affect both patients and the medical community [51].

Because of flaws in the monitoring and reporting of harms, there is a need to develop evidence-based approaches that (i) more reliably determine the benefit-to-harm balance of new medicinal products in the premarketing phase (ii) determine drug-adverse event causality associations after medicinal products have been granted regulatory approval and; (iii) assist drug regulatory agencies with timely regulatory courses of action when adverse reactions are attributed to approved medicinal products.

1.5 THESIS AIMS

Based on this preliminary background work there is a clear problem with the current regulation of approved medicinal products; this means that too many people are exposed to harmful products and are being let down by the current system. The deficiency in the literature that this thesis aimed to address is the current lack of an evidence-based approach to the post marketing withdrawal of medicines when harms have been attributed to their use. To address these evidence-based deficiencies the specific aims were to:

- a. Identify medicinal products that have been withdrawn from the market after approval because of suspected adverse drug reactions, and determine the evidence used to make the decisions;

- b. Compute the time lapse between the approval of a product and the emergence of evidence of adverse reactions, and the time lapse between the emergence of evidence of adverse drug reactions and withdrawal of products from the market;
- c. Determine the trends in the patterns of post-marketing withdrawal of medicinal products because of adverse drug reactions;
- d. Explore trends in regulatory actions across geographical regions when adverse drug reactions are attributed to product use;
- e. Determine the extent to which confirmatory studies are used to investigate drug-adverse event relationships when medicinal products are withdrawn;
- f. Analyse how well we investigate drug-adverse event associations when medicinal products are withdrawn because of serious adverse drug reactions; and
- g. Understand the extent to which adverse events and discontinuation rates influence the benefit-to-harm balance of medicinal products.

1.7 THESIS STRUCTURE

Chapter 2 is a systematic review of the post-marketing withdrawal of medicinal products from the market because of adverse drug reactions.

Chapter 3 is a systematic review of medicinal products withdrawn from the market because of drug-attributed deaths.

Chapter 4 is a systematic review of medicinal products withdrawn worldwide because of adverse drug reactions.

Chapter 5 is a systematic review of medicinal products withdrawn from the market because of adverse reactions in animals.

Chapter 6 is a systematic review of analgesic medicinal products withdrawn from the market because of adverse drug reactions.

Chapter 7 is a systematic review of anti-obesity medicinal products withdrawn from the market because of adverse drug reactions.

Chapter 8 determines whether the withdrawals of medicinal products from the market because of drug-attributed deaths were justified, and explores whether confirmatory studies were used to explore drug-adverse event relationships.

Chapter 9 is a systematic review and meta-analysis of benefits and harms in pivotal trials used for gaining regulatory approval of medicinal products using the centrally-acting anti-obesity medicinal products as a case study.

Chapter 10 is a summary of the overall results of the thesis, and concludes with a list of recommendations to improve pharmacovigilance.

1.8 Chapter Summary

- Pre- and post-marketing monitoring for adverse events helps with detection of harms attributed to medicinal products
- There is a dearth of information on the evidence used by regulatory authorities to make withdrawal decisions when adverse reactions are attributed to medicinal products
- We do not know how consistent regulatory actions are across geographical regions when serious adverse reactions are attributed to medicinal products
- There are flaws in how the harms attributed to medicinal products are assessed and interpreted in pre-marketing trials, and after regulatory approval
- There is a need for an evidence-based approach that improves the effectiveness of methods used to determine whether approved medicinal products should be withdrawn from the market when suspected adverse reactions are attributed to their use

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Chapter 2 Post-marketing withdrawal of medicinal products because of adverse drug reactions: a systematic review of the world literature

2.1 INTRODUCTION

When drug regulatory authorities consider that a medicinal product has a favourable benefit to harm balance, they award a licence and the product becomes available [1].

However, some adverse reactions are discovered only after approval and marketing [2,3], when regulators have several possible courses of action, depending on the risk and seriousness of the adverse reaction. They can:

- require the reaction to be added to the label (§4.8, “Undesirable effects”, in the EU Summaries of Product Characteristics (SmPC));
- require the addition of a warning (§4.4, “Special warnings and precautions for use”);
- require the addition of a contraindication (§4.3), if applicable;
- allow the patient, informed by the prescriber, to decide whether to use the drug;
- require an amendment to any Post-Authorization Safety Study (PASS) that is being performed as a condition of the licence;
- require a revision of specific risk minimization measures mentioned in the product's Risk Management Plan;
- require the marketing authorization holder (MAH) to issue a Direct Health-care Professional Communication (DHPC);
- in the USA require the use of a Black Box warning, which confirms that the drug carries a significant risk of a serious adverse reaction.

Post-marketing withdrawal of medicinal products because of adverse drug reactions can be triggered by evidence obtained from various sources—anecdotal reports, observational studies, clinical trials, systematic reviews, or animal data. The removal of previously approved products from the market can result in loss of confidence in medicines by the public, loss of effective compounds (i.e. effective for treating the specific indication, but for which the benefit to harm balance was considered unfavourable), and loss of revenue for drug manufacturers. When there is no concrete evidence linking drug use with a suspected adverse reaction, such withdrawals can be contentious.

To date, there has been no comprehensive and systematic review of medicinal products that have been withdrawn because of adverse drug reactions in general. In addition, there is a paucity of data about the evidence on which such withdrawal decisions are based.

Furthermore, the pattern of post-marketing withdrawals across geographical regions worldwide has never been examined. Therefore, this systematic review was conducted:

- to identify medicinal products that have been withdrawn after approval because of any kinds of adverse drug reactions;
- to assess the types of evidence on which the withdrawal decisions were based;
- to identify the types of attributed adverse drug reactions responsible;
- to examine the patterns of withdrawal across geographical regions;
- to examine the intervals between launch dates and (a) the times of the first reports of adverse reactions and (b) the first dates of withdrawal;
- to examine the intervals between the first reports of adverse drug reactions and the first withdrawals.

2.2 METHODS

2.2.1 Search strategy

The first reviewer (IJO) searched for medicinal products withdrawn from the market because of adverse drug reactions from 1950 onwards from the following sources:

- the World Health Organization's (WHO's) database of Consolidated List of Products whose consumption and/or sale have been banned, withdrawn, severely restricted, or not approved by governments (Issues 6, 8, 12, and 14, and the updated version of issue 14);
- the WHO's Drug Information (Volumes 1–28);
- the WHO's Pharmaceuticals Newsletter (1997–2014);
- *Meyler's Side Effects of Drugs: The International Encyclopaedia of Adverse Drug Reactions and Interactions*, volumes 1–8 and editions 9–15, and the *Side Effects of Drugs Annuals* 1–36;
- *Stephens' Detection of New Adverse Drug Reactions*, 5th edition [4];
- the website of the UK Medicines and Healthcare products Regulatory Agency (MHRA);
- the website of the US Food and Drug Administration (FDA);
- the database of withdrawn drugs of the European Medicines Agency (EMA);
- Health Canada Drug Product Database (DPD)
- the website of Indian Central Drugs Standard Control Organization (CDSCO);
- the website of the Australian Therapeutic Goods Administration (TGA);
- the website of the Nigeria National Agency for Food and Drug Administration and Control (NAFDAC);
- the website of Ghana Food and Drugs Authority (FDA);

- the website of the South Africa Medicines Control Council (MCC);
- PubMed;
- Medline;
- Google Scholar.

[See appendix 1 for full list of drug regulatory websites and sources accessed].

For each medicinal product withdrawn, the following databases were then searched for the first reported adverse drug reaction:

- PubMed;
- Medline;
- Google Scholar;
- the database of withdrawn drugs of the European Medicines Agency (EMA);
- the website of the UK Medicines and Healthcare products Regulatory Agency (MHRA);
- the website of the US Food and Drug Administration (FDA).

Search terms used included “drug withdrawal”, “fatal*”, “death(s)”, “side effect”, “adverse effect”, “adverse reaction”, “adverse event”, “poison”, “toxicity”, “voluntary recall”, “suspension”, “prohibition”, “banned”, “remov*”, “revoke*”, “discontinued”. [See appendix 1]. If information on a medicinal product using its chemical name for searches could not be found, the trade name or code name was used to conduct searches. The references of retrieved full texts were searched for any earlier dates of reports of suspected adverse reactions. If an article had evidence of an earlier reported date, that date was chosen as the first adverse reaction date. If a drug was withdrawn because of two or more adverse reactions, the first reported date of any such reactions was used.

To determine the accuracy of launch dates, the information on the WHO database of Consolidated List of Products was compared with the information on the Merck index [5], the Pharmaceutical Manufacturing Manual [6], and a newly developed database for withdrawn and discontinued products [7]. The WHO data was cross-checked with the database for withdrawn products to determine the dates of first withdrawal and countries of withdrawal; if the information was not found in that database, the dates from the results of searches in PubMed and Google Scholar were compared.

2.2.2 Inclusion/exclusion criteria

A medicinal product was defined as “Any substance or combination of substances which may be used in, or administered to, human beings, either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis” [8]. For the purpose of this review, such applications could be via oral, intravenous, intramuscular, sublingual, inhalational, subcutaneous, anal, or topical routes. To be included in the review, a product must have been withdrawn from the market because of reports of a suspected adverse reaction or reactions, or problems related to hazards or harms. Medicinal products that had previously been withdrawn (by regulatory authorities and/or drug manufacturers) because of adverse reactions but had been re-introduced or made available in other, safer, formulations were included. When only one formulation of a product was withdrawn, the product was included in the list, and the formulation was noted; however, if all formulations of the product were subsequently withdrawn, the earliest date was used, irrespective of formulation, as the year of first withdrawal. Products were not excluded based on routes of administration. Medicines were excluded for which there was documented regulatory evidence that they had been voluntarily withdrawn by marketing

authorization holders (MAHs) solely for “commercial reasons”, or withdrawn based on contamination of the active ingredient by other agents (such as organisms and active or toxic compounds). Herbal products, non-human medicines, and non-prescription medicines were also excluded.

2.2.3 Assessing the types of evidence

The highest level of available evidence before the year of first withdrawal of products were documented based on the Oxford Centre for Evidence-based Medicine (OCEBM) criteria [9] rating the levels of evidence of harms as follows: Level 1: systematic reviews (highest); Level 2: randomized clinical trials; Level 3: non-randomized, cohort, or follow-up studies; Level 4: case-series or case-control studies; and Level 5: mechanism-based reasoning (lowest). The first reviewer (IJO) documented levels of evidence and these were independently verified by a second reviewer (JKA). Discrepancies were resolved through discussion.

2.2.4 Data extraction

For each withdrawn product, data was extracted on: the date of marketing authorization, the launch date, or the date of first recorded use; the drug class, and therapeutic indication [10]; the year in which an adverse drug reaction related to the reason for withdrawal was first reported; the year of first withdrawal; the country or countries of withdrawal; and the reported organ or system that was affected by the drug. When the exact launch date of a product was not available (16 cases), the first date of reported use in humans was used by cross-checking references on PubMed with Medline. If two or more adverse reactions were reported as reasons for withdrawal, the date of the first reported reaction was used.

The first reviewer (IJO) extracted all the data and these were independently verified by a second reviewer (JKA). When there were discrepancies, both reviewers re-checked the information together and arrived at a consensus through discussion.

2.2.5 Statistical analysis

Summary tables were used to document the intervals between launch year and the year of first reports of adverse drug reactions, the interval between launch year and the year of first withdrawal, and the interval between the first report of an adverse drug reaction and the year of first withdrawal. Because these intervals were skewed, we used medians and interquartile ranges (IQR) as measures of central tendency and spread.

Scatter plots were used to explore the relationships between launch dates and times to first reports of adverse drug reactions and withdrawals. Because modern drug regulations began to take shape from the 1950s after the WHO's initiation of the use of International Non-proprietary Names (INNs) for active pharmaceutical ingredients [11], sub-analyses of the patterns of reports and withdrawals of medicinal products launched from 1950 onwards were also conducted.

Because drug regulatory systems in most African countries are not well developed [12,13,14], withdrawal rates in Africa were compared with five other continents—this was based on the assumption that if a product was withdrawn in one country, similar action ought to have been taken by drug regulatory authorities in countries in the same continent. Data on the relative rates (RR) and 95% confidence intervals (CI) of withdrawals per country in Africa *versus* the other five continents were computed. A P value < 0.05 was

considered statistically significant; Bonferroni correction was used to address the issue of multiple comparisons.

2.3 RESULTS

Figure 2.1 shows that 644 withdrawn medicinal products were identified: 96 were excluded because they were marketed as herbal or over-the-counter preparations, another 75 because they were withdrawn for “commercial reasons”, one (ergometrine) because of instability in tropical conditions, and five because they had no pharmacological actions (e.g. colourings and artificial sweeteners). Three products were excluded because the reason for withdrawal was contamination, one because there was no information on adverse reactions, and one because it was not licensed through conventional drug approval procedures. This left 462 products for inclusion – 354 (77%) of which were launched after 1950. The withdrawals occurred between 1953 and 2013 (except for dinitrophenol which was first withdrawn in 1938 in the USA, and prohibited for use in humans again by the FDA in 1986). [The details of the withdrawn products are available in Table 2.1].

Figure 2.1: Flow chart showing the process for inclusion of medicinal products withdrawn after regulatory approval because of adverse drug reactions

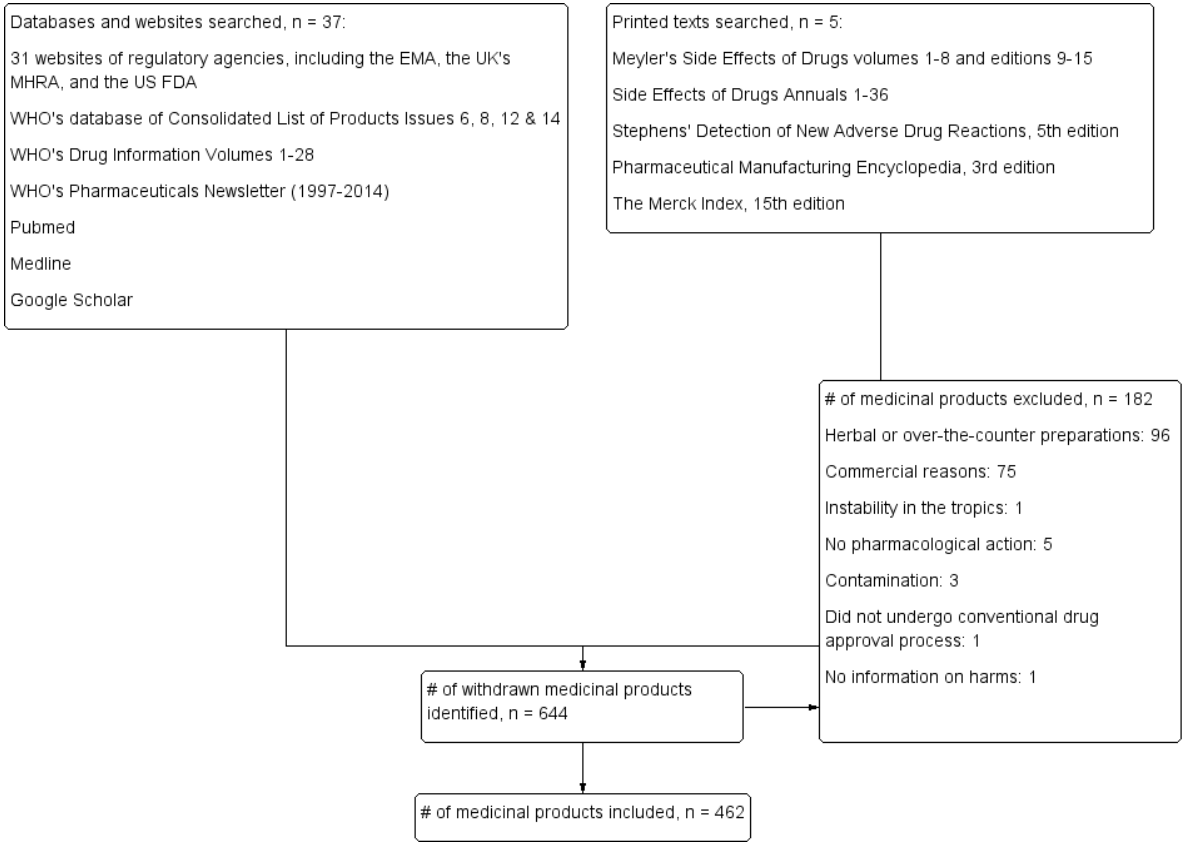


Table 2.1: List of medicinal products withdrawn from the market because of adverse drug reactions

Medicinal product	Class	Mechanism of action	Launch date	Year of 1st ADR report	Year first withdrawn	Countries withdrawn	Reason for withdrawal
Acetanilide	Analgesic	Metabolised to paracetamol	1886	1940	1971	Japan	Aplastic anaemia
Acetarsol	Antimicrobial	Unknown	1921	1941	1982	Mauritius	Haematologic
Acetylfuratrizine	Antimicrobial	Damages ribosomal proteins	1962	1977	1977	Japan, Saudi Arabia, Venezuela	Superseded by safer products: carcinogenic
Acitretin	Retinoid	Binds to the retinoic acid receptor (RAR)	1989	1989	1990	Netherlands, France	Teratogenicity
Acridine derivatives	Antimicrobial		1922	1975	1979	Denmark, Venezuela	Mutagenic
Adenosine phosphate	Antiarrhythmic	Direct nodal inhibition	1930	1957	1973	USA	Cardiovascular
Alatrofloxacin	Antimicrobial	Inhibit DNA gyrase	1997	1998	2000	Armenia, Singapore, Europe	Liver
Alclofenac	Analgesic	Inhibit COX-1 & COX-2	1972	1974	1977	Ireland, Cyprus, Italy, Germany, UK, New Zealand, Egypt, Greece, Denmark, Indonesia, India, Jordan, Morocco	Immunologic, liver, skin, urinary tract
Aliskiren	Anti-hypertensive	Direct renin inhibitor	2007	2011	2011	Europe	Angioedema
Alosetron‡	Antispasmodic	5HT3 receptor antagonist	2000	2000	2000	USA	Gastrointestinal
Alphacetyl-methadol	Analgesic	OP1 receptor agonist	1993	2001	2003	USA	Cardiovascular
Alpidem	Anxiolytic	GABA-A receptor antagonist	1991	1994	1994	France	Liver
Althesin (alphadolone/alphaxolone)	Sedative-hypnotic	Potential of the GABA-A chloride channel	1972	1973	1984	UK, Germany, France	Immunologic
Amfepramone	Centrally-acting anti-obesity product	Norepinephrine releasing agent	1957	1974	1975	Turkey, Sweden, Oman, UAE, Norway, Venezuela, EU, France, UK	Cardiotoxicity
Amfetamine	Psychostimulant	TAAR1 agonist	1939	1957	1973	USA, UAE, Turkey, Oman, Malaysia, Nigeria	Drug dependence
Amineptine	Antidepressant	Dopamine receptor antagonist	1960	1984	1999	France, Thailand, UAE, Bangladesh, Morocco, Vietnam	Drug dependence, liver, skin
Amino-glutethimide	Anxiolytic	Steroid synthesis inhibitor	1960	1966	1966	US, Saudi Arabia, Norway	Endocrine
Amino-phenazone (aminopyrine)	Analgesic	Inhibit COX-1 & COX-2	1887	1936	1965	10 European, 14 Asian, & 4 African countries; Australia; USA; Canada; Chile; Brazil; Venezuela	Haematologic, carcinogenic
Aminophylline	Xanthines	Nonselective phosphodiesterase inhibitor	1908	1955	1992	Netherlands	Immune-mediated reactions
Aminorex fumarate	Psychostimulant	Catecholamine release	1962	1967	1967	Germany, Venezuela	Respiratory
Amobarbital	Barbiturate	GABA-A receptor agonist	1961	1979	1985	Sweden, New Zealand	Respiratory depression
Amoproxan	Antianginal	Nonselective β -blocker	1969	1970	1970	France	Sensory systems, skin
Anabolic steroids	Hormones	Androgen-receptor modulation	1952	1966	1989	Thailand, India	Androgenic effects
Anagestone	Hormones	Inhibition of	1968	1969	1969	Worldwide	Tumorigenicity

acetate		ovulation					
Anti-D immunoglobulin	Immune prophylaxis	Binds to the erythrocyte D antigen	1968	2000	2009	Europe	Safety concerns: haemo-globinemia
Anti-histamine (topical)	Phenothiazine derivatives	H1-antagonism	1942	1947	1986	Malaysia, Sri Lanka	Immune-mediated reactions
Antrafenine	Analgesic	COX-1 & COX-2 inhibition	1977	1979	1984	France	Urinary tract
Aprobarbital	Barbiturate	GABA-A receptor modulation	1920	1966	1985	Sweden	Respiratory depression
Aprotinin	Antifibrinolytic	Pancreatic trypsin inhibitor	1959	1964	2007	Worldwide	Anaphylaxis
Arsenate	Chemotherapeutic agent	Oncoprotein expression	1951	1973	1988	Austria, Spain, Italy, France, Philippines	Drug abuse, carcinogenic
Aspirin (acetylsalicylic acid)	Analgesic	COX-1 & COX-2 inhibition	1899	1970	1986	UK, US, Hong Kong, Nigeria, Spain	Liver
Astemizole	Antihistamine	H1-receptor antagonist	1977	1986	1987	Norway, New Zealand, Philippines, USA, Canada, South Africa, UAE, Mauritius, Brunei, Tanzania, Armenia, Brazil, Spain, Argentina, Singapore, India, Chile	Cardiovascular, drug interactions
Azaribine	Antipsoriatic	Inhibition of orotidine-5'-monophosphate decarboxylase	1975	1976	1976	USA; Thailand; Mauritius; Saudi Arabia; Venezuela	Haematologic, psychiatric
Barbital	Barbiturate	GABA-A receptor modulation	1903	1913	1971	Italy	Respiratory depression
Beclobrate	Antilipemic	Activates PPAR	1985	1990	1990	Switzerland	Hepatotoxicity
Bendazac	Analgesic	COX-1 & COX-2 inhibition	1983	1987	1993	Spain	Liver
Benfluorex	Hypoglycaemic	Fenfluramine analogue	1976	2003	2009	Europe	Cardiotoxicity
Benoxaprofen	Analgesic	COX-1 & COX-2 inhibition	1980	1982	1982	Worldwide	Liver, skin, urinary tract
Benzarone‡	Thrombolytic	Antagonistic on mediators of muscle contraction, direct action on smooth muscle cells	1964	1987	1992	Germany, Portugal, France	Liver
Benzbromarone	Uricosuric agent	Xanthine oxidase inhibitor	1976	1994	2003	Portugal, France	Liver
Benziodarone	Uricosuric agent	Inhibits hURAT1	1962	1964	1964	UK, France, Spain	Liver
Benzydamine (Difflam)	Analgesic	COX-1 & COX-2 inhibition	1967	1980	1995	Germany	Skin, psychiatric, sensory
Benzyl alcohol	Antimicrobial	Alteration of bacterial membrane permeability	1972	1981	1982	Israel, USA, Oman, Iraq	Metabolic acidosis
Benzylpenicillin sodium (topical preparations)	Antimicrobial	Inhibits cell wall biosynthesis	1944	1953	1972	USA, Italy, Philippines, Ethiopia, Bangladesh, India, Chile, Cyprus, Spain, Thailand, Venezuela	Skin, immune
Bepidil	Antiarrhythmic	Calcium channel blockers	1981	1982	2004	USA	Cardiovascular
Beta-ethoxy-acetanilide	Analgesic	Metabolized to paracetamol?	1886	1978	1986	Germany	Tumorigenicity, urinary tract
Bezitamide	Analgesic	Unknown	1961	1983	2004	Netherlands	Overdose
Bicalutamide	Anti-androgen	Androgen receptor modulation	1995	2001	2003	Canada, UK	Accelerated deaths

Bismuth salts‡	Intestinal adsorbent	Unclear. Forms insoluble complexes	1875	1930	1978	France; Egypt; Japan; Greece; Austria; Bangladesh; Turkey; Mauritius; Oman; Cuba; India	Nervous, cardiovascular
Bithionol	Antihelmintic	Exact mechanism unclear	1958	1960	1967	USA, Canada, Japan	Skin
Boric acid and borates	Antimicrobial	Destruction or inhibition of growth of pathogenic organisms	1875	1945	1990	Ireland, Malaysia, Korea, Philippines, Thailand, Germany, Japan, Costa Rica, UK, India, Peru, USA	Neurotoxicity
Bovine tissue-derived medicines	Various: heparin, glucagon, insulin, blood factors	Various	1982	1986	1989	Ireland, Switzerland, France	Neurotoxicity
Bromfenac	Analgesic	COX-1 & COX-2 inhibition	1997	1998	1998	USA, Saudi Arabia	Liver
Bromisoval	Sedative-hypnotic	Similar to barbiturates	1909	1930	1987	Netherlands	Drug dependence
Bromocriptine mesylate	Prolactin inhibitor	D2 and D3 agonist	1976	1983	1989	USA	Cardiovascular, drug interactions nervous system, pregnancy, psychiatric
Brotizolam	Sedative-hypnotic	GABA-A receptor modulation	1982	1983	1989	UK	Tumorigenicity
Broxyquinoline	Antiprotozoal	Production of free radicals	1960	1968	1970	Japan, UAE, Saudi Arabia	Sensory
Bucetin	Analgesic	Phenacetin analogue	1968	1985	1986	Germany	Urinary tract: Mutagenic, carcinogenic
Budipine	Antiparkinsonian	Muscarinic & NMDA receptor antagonist	1979	2000	2000	Germany	Cardiovascular
Bufexamac	Analgesic	COX-1 & COX-2 inhibition	1973	1973	1990	France	Skin
Buflomedil	Vasodilator	α -adrenergic blockade	1970	1981	2006	France, Europe	Neurotoxicity; cardiotoxicity
Buformin‡	Hypoglycaemic	Reduce gluconeogenesis	1950	1969	1978	Germany, Austria, Belgium, Ireland	Metabolism
Bumadizone injection	Analgesic	COX-1 & COX-2 inhibition	1972	1978	1986	Oman	Haematologic
Bunamiodyl	Radiography	Selective secretion in bile	1958	1962	1964	USA, Sweden, Venezuela	Kidney
Buprenorphine	Analgesic	Agonist-antagonist opioid receptor modulator	1978	1983	1986	Egypt	Fatalities (IV use)
Bupropion	Antidepressant	Norepinephrine-dopamine reuptake inhibitor	1985	1985	1986	USA	Nervous system
Butamben	Anaesthetic	↓ neuronal membrane permeability to sodium ions	1923	1947	1964	UK	Allergic, psychiatric, skin
Cadralazine	Anti-hypertensive	Peripheral arteriolar vasodilator	1989	1991	1992	Norway	Immunologic
Camazepam	Sedative-hypnotic	GABA-A receptor modulation	1978	1984	1984	Netherlands	Immunologic
Canrenone	Anti-hypertensive	Diuresis, aldosterone antagonist	1966	1976	1986	Germany	Tumorigenicity
Carbinoxamine	Antihistamine	Competes with free histamine for binding at HA-receptor sites	1953	1987	2008	Iraq	Neurotoxicity
Carisoprodol	Muscle relaxant	Unknown	1959	2002	2007	Sweden, EU, Indonesia	Abuse
Cartilage + bone marrow	Antiarthritic		1960	1989	1992	Germany	Skin
Catechic extract	Anti-inflammatory	Unclear	1972	1979	1982	France	Haematologic

Cefaloridine	Antimicrobial	Disruption of cell wall synthesis	1964	1969	1989	Spain	Nephrotoxic
Celecoxib (Onsenal)	Analgesic	COX-2 inhibitor	2003	2006	2011	Europe	Increased risk of serious cardiovascular events
Cell preparations‡ Cerivastatin‡	Antiageing		1931	1957	1987	Austria, Germany, Switzerland	Immunologic
	Antilipemic	HMG CoA reductase inhibition	1997	1998	2001	Worldwide	Renal, musculoskeletal
Cheno-deoxycholic acid	Antilipemic	↓ cholesterol saturation of bile	1975	1976	1987	Norway	Tumorigenicity
Chloral hydrate	Sedative-hypnotic	GABA receptor modulation	1869	1986	2001	USA, France, India	Tumorigenicity
Chloramphenicol	Antimicrobial	Disruption of cell wall synthesis	1947	1950	1978	France, Spain, Hungary, India	Haematologic
Chlormadinone acetate	Hormones	Inhibition of ovulation	1965	1970	1972	USA, UK, Italy, Egypt, Venezuela	Tumorigenicity
Chlormezanone	Muscle relaxant	GABA receptor modulation	1960	1983	1996	Worldwide	Skin, drug dependence, liver
Chlornaphazine	Chemotherapeutic agent	Cell hydrolysis	1964	1964	1964	Denmark, Venezuela	Tumorigenicity
Chloroform (trichloromethane)	Anaesthetic	Depression of the respiratory centres	1847	1976	1976	Greece, Turkey, Japan, USA, Panama, Saudi Arabia, Brazil, Italy, Canada, Norway, Philippines, UK, Denmark, NZL, Ethiopia, Zimbabwe, Bangladesh, Dominican Republic, Belgium, Nigeria, Ireland, Oman, Cuba, India	Cardiovascular, liver, urinary tract, tumorigenicity
Chloroquine	Antiprotozoal	Cell lysis	1939	1959	1975	Japan, Guinea Bissau	Eyes
Chlorphentermine	Psychostimulant	TAAR1 agonist	1962	1970§	1969	Germany, Venezuela	Respiratory, cardiovascular
Chorionic gonadotrophin	Hormones	Spermatogenesis	1934	1961	1972	USA	Immunologic
Cianidanol	Antioxidant	Free radical scavenger	1976	1980	1985	Worldwide	Haematologic
Cincophen	Analgesic	Adrenal stimulation	1910	1923	1991	Germany, Italy	Liver
Cinepazide	Vasodilator	Phosphodiesterase inhibition	1974	1985	1988	Egypt, Spain	Haematologic
Cisapride monohydrate	Prokinetic agent	5-HT4 receptor agonist	1993	1993	2000	Philippines, Oman, USA, Germany, UK, Serbia, Mauritius, Canada, Brunei, Turkey, Indonesia, Singapore, Japan, Cuba, Bahrain, Australia, Armenia, India	Cardiovascular, drug interactions
Cliobutinol	Antitussive	Unclear	1961	2004	2007	Europe, Argentina	Cardiovascular
Clioquinol	Antimicrobial	Inhibition of DNA replication	1934	1964	1970	Japan, Norway, Sweden, Denmark, UAE, Nigeria, Bangladesh, Philippines, Italy, Nepal, Dominican Republic, Zimbabwe, Spain, Hong Kong, Ethiopia, Honduras, Oman, Pakistan, Ghana, Libya, Bahrain, Netherlands, Saudi Arabia, Canada	Nervous system

Clobenzorex	Centrally-acting anti-obesity product	Similar to amphetamine	1966	1986	2000	Mauritius, USA	Drug abuse, psychiatric
Clofenotane	Pesticide	Interfere with voltage-gated sodium channel	1945	1969	1972	USA	Carcinogenicity
Clofibrate	Antilipemic	Activates PPAR	1967	1973	1978	Germany, Israel, Norway, Bangladesh	Accelerated deaths
Cloforex	Psychostimulant	Similar to amphetamine	1965	1967	1967	Germany, Sweden, Venezuela	Cardiovascular, drug abuse, psychiatric
Clomacron	Analgesic	COX-1 & COX-2 inhibition	1966	1970	1982	UK	Liver
Clometacin	Analgesic	COX-1 & COX-2 inhibition	1971	1981	1990	France	Liver, skin, urinary tract
Clozapine	Antipsychotic	Unknown	1972	1975	1975	Finland, Singapore, Norway	Cardiovascular, Haematologic
Cobalt	Hematinic	As cobalamin	1951	1954	1967	USA, Kuwait	Cardiovascular, liver
Codeine	Analgesic	G-protein receptor modulation	1832	1951	1985	Bangladesh, Malaysia	Abuse
Co-proxamol (paracetamol + dextro-propoxyphene)	Analgesic	?COX-3 inhibition; agonist at mu opioid receptors	1957	1960	2007	Europe, India, USA, Zimbabwe, New Zealand, Iraq	Overdose; respiratory depression; cardio and hepatotoxicity
Coumarin (synthetic)	Anticoagulant	Vitamin K reductase inhibition	1996	1996	1996	France, Australia	Liver
Cupric bisquinoline	Antiartritic	Antiinflammatory with penicillamine complex	1958	1967	1978	France	Neuromuscular
Cyclandelate	Vasodilator	Direct effect on vascular smooth muscle	1987	1989	1996	USA	Not effective for use
Cyclobarbital	Sedative-hypnotic	GABA-A receptor agonist	1962	1974	1980	Norway, France	Drug dependence, drug overdose
Cyclofenil	Anti-hormone	Oestrogen receptor modulation	1970	1980	1987	France	Liver
Cyclovalone + retinol + tiratricol‡	Choleretic	?	1964	1984	1988	France	Liver
Cyproheptadine	Antihistamine	Antihistamine, anticholinergic	1961	1977	1982	Bangladesh, Malaysia, UK	Drug abuse
Dalkon shield	Hormones	Prevention of fertilization	1971	1974	1974	USA, UK, New Zealand	Septic abortions
Danthron (chrysazin)	Laxative	?	1959	1985	1987	Norway, Germany, Japan, USA, Singapore, Canada	Tumorigenicity
Datura	Analgesic	Muscarinic receptor antagonist (atropine)	1920	1962	1992	France	Drug abuse
Dequalinium chloride	Lozenges	?	1956	1970	1984	Greece	Low efficacy, skin reactions
Desensitizing vaccines	Vaccines	?	1973	1985	1989	UK	Immunologic
Dexamfetamine	Psychostimulant	Adrenergic receptor agonist	1937	1966	1973	USA, Turkey, Oman, Nigeria	Drug abuse and dependence
Dexfenfluramine	Centrally-acting anti-obesity product	Serotonin receptor agonist	1995	1995	1997	USA, Canada, Morocco, Philippines, Lithuania, India	Cardiovascular, respiratory
Diacetoxy-diphenolisatin	Laxative	Phenacetin analogue	1971	1971	1971	Australia	Liver
Diamthazole	Antimicrobial	?	1951	1953	1972	US, France	Nervous system, psychiatric
Dibenzepine hydrochloride	Antidepressant	Norepinephrine reuptake inhibitor	1963	1967	1983	Sweden	Suicides

Dibromsalan	Antimicrobial	?	1962	1966	1975	USA, Japan	Skin
Diclofenac sodium	Analgesic	COX-1 & COX-2 inhibition	1979	1979	1983	Philippines, Norway	Haematologic, tumorigenicity
Dicycloverine	Antispasmodic	Muscarinic anticholinergic	1952	1974	1986	Bangladesh, Norway	Nervous, psychiatric
Dienestrol	Hormones	Oestrogen receptor agonist	1947	1972	1977	Austria, Italy, Kuwait, Saudi Arabia	Carcinogenicity
Diethyl-amino-ethoxyhexestrol	Antianginal	?	1964	1970	1970	Japan	Liver
Diethylstilbestrol	Hormones	Uterine desensitization, local arteriolar constriction	1938	1971	1973	Panama, Austria, Italy Kuwait	Tumorigenicity
Difemerine	Antispasmodic	Muscarinic antagonist	1967	1980	1986	Germany, France, USA	Nervous system
Difenoxin	Antispasmodic	Opioid receptor agonist	1970	1979	1991	Pakistan, Oman, South Korea, Lebanon	Atropism
Difurazone	Antimicrobial	?	1966		1977	Japan, Saudi Arabia, Venezuela	Superseded by safer products
Dihydro-streptomycin	Antimicrobial	Protein synthesis inhibitor	1947	1949	1970	USA, Philippines, Spain, Dominican Republic, Italy, Peru	Nervous system, psychiatric, sensory systems
Dihydroxy-methyl-furatrizine	Antimicrobial	Nitrofur analogue	1975	1975	1977	Japan, Saudi Arabia, Venezuela	Tumorigenic
Diiododiethyltin	Antimicrobial	?	1954	1955	1957	France	Nervous system
Dilevalol	Anti-hypertensive	Nonselective beta blocker; beta-2 receptor agonist	1989	1989	1990	Worldwide	Liver
Dinitrophenol	Organic compound	Uncoupling of oxidative phosphorylation	1933	1933	1938 ^A	USA	Cataracts, agranulocytosis
Dinoprostone	Prostaglandin	Direct vasodilator	1971	1987	1990	UK	Foetal distress; uterine hypertonia
Diphenazine (quietidin)	Analgesic	?	1962	1967	1967	Hungary, Venezuela	Photosensitivity
Diphenoxylate	Antispasmodic	Opioid receptor agonist	1956	1969	1990	Libya, Pakistan, Mexico, Nepal, Philippines, South Korea, Lebanon, Thailand	Nervous system
Dithiazanine iodide	Anthelmintic	Interruption of glucose uptake in cells	1959	1960	1964	USA; France; Chad; Italy; Cuba	Cardiovascular, metabolism
Dofetilide	Antiarrhythmic	Potassium channel blocker	1999	1999	2004	Europe	Cardiovascular
Dolansetron	Propulsive	5-HT ₃ receptor antagonist	1997	2005	2011	Germany	Cardiovascular
Domperidone (injectable) ‡	Propulsive	Dopamine receptor antagonist	1979	1982	1985	Worldwide	Cardiovascular, drug overdose, endocrine, nervous system
Doxycycline (IV)	Antimicrobial	Protein synthesis inhibitor	1959	1984	1989	France, Morocco	Anaphylaxis
Doxylamine/dicyclomine	Antihistamine	H ₁ -receptor blocker	1956	1981	1983	UK, USA	Teratogenicity
Drotrecogin alfa (activated)	Antithrombotic	Unclear	2001	2001	2011	Worldwide	Insufficient evidence; bleeding risk
Droperidol	Antipsychotic	Dopamine 2 receptor antagonist	1970	1991	2001	UK, Indonesia	Cardiovascular
Droxicam	Analgesic	COX-1 & COX-2 inhibition	1990	1992	1994	Europe	Liver
Ebrotidine	Anti-ulcer	H ₂ receptor antagonist	1997	1998	1998	Spain, Peru	Liver

Efalizumab	Monoclonal antibody	Inhibits CD11a	2003	2008	2009	EU, USA, Canada, Mexico	Leukoencephalopathy
Emetin (ipecac syrup)	Emetic	Stimulation of the CTZ, local irritation	1912	1947	1982	Mauritius	Cardiotoxicity
Encainide	Antiarrhythmic	Na channel blocker	1985	1989	1991	UK	Cardiovascular
Epinephrine (topical)	Anaesthetic	Vasoconstriction	1899	1963	2004	Ireland, Venezuela	Cardiovascular, nervous
Erythrityl tetranitrate	Anti-hypertensive	Nitric oxide synthesis	1955	1987	1998	USA	Insufficient evidence: skin
Erythromycin balleul	Antimicrobial	Protein synthesis inhibitor	1955	1975	1995	France	Teratogenic
Erythromycin estolate	Antimicrobial	Protein synthesis inhibitor	1958	1961	1976	Singapore, Greece, Sudan, Mauritius, Bangladesh, Bahrain, Denmark, Sweden	Liver
Ethanol	Antimicrobial	GABA-A receptor modulation, protein coagulation	1850	1946	1985	Chile, Sri Lanka, Brazil, UAE	Neurotoxicity, abuse
Ethchlorvynil	Sedative-hypnotic	Unknown	1955	1959	1978	USA	Drug dependence, respiratory
Ethinyl estradiol	Hormones	?Gonadotropin suppression	1943	1963	2004	Germany, France	Venous thrombosis
Ethyl nitrite (spirit)	Antimicrobial	Increased GFR, nitric oxide synthesis	1850	1977	1980	USA	Methaemoglobinemia
Ethylene dichloride (topical)	Antimicrobial		1794	1977	1978	Germany, Saudi Arabia	Carcinogenic
Ethylestrenol	Hormones	Stimulate anabolism & inhibit catabolism	1964	1965	1982	Bangladesh	Inappropriate use in malnourished children
Etomidate	Anesthetic	GABA-A receptor modulation	1972	1983	1985	UK	Endocrine
Etretinate	Retinoid	Inhibits cell differentiation & hyperkeratinization	1981	1982	1992	Norway, Brazil, France, USA, Canada	Teratogenicity, tumorigenicity
Exifone	Psychostimulant	Free radical scavenger?	1988	1989	1989	France	Liver
Factor IX	Anti-hemophilic	Hydrolysis of disulfide bonds	1952	1986	1986	Sweden	HIV
Factor VIII	Anti-hemophilic	Cofactor for factor IXa	1965	1986	1986	UK	HIV
Febarbamate	Sedative-hypnotic	GABA-A receptor modulation	1967	1991	1997	France	Liver
Felbamate	Anti-epileptic	NMDA receptor antagonist	1993	1993	1994	USA, European Union	Haematologic, liver
Fenbutrazate	Centrally-acting anti-obesity product	Phenmetrazine analogue	1957	1963	1969	Europe	Drug abuse, psychiatric
Fenclofenac	Analgesic	COX-1 & COX-2 inhibition	1978	1984	1984	Worldwide	Skin, urinary tract tumorigenicity
Fenclozic acid	Analgesic	COX-1 & COX-2 inhibition	1969	1970	1970	UK, USA	Liver
Fenetylline	Psychostimulant	Amphetamine + theophylline properties	1961	1962	1991	Oman, Bulgaria	Abuse
Fenfluramine	Centrally-acting anti-obesity product	Serotonin receptor antagonist	1973	1981	1997	Worldwide	Cardiovascular, respiratory
Fenoterol	Beta-2 adrenoreceptor agonist	Beta 2 adrenergic agonist	1971	1987	1990	New Zealand, Australia	Death
Fenproporex	Psychostimulant	Amphetamine analogue	1966	1997	1999	Europe	Drug abuse, psychiatric

Fentanyl hydrochloride	Analgesic	μ -opioid receptor agonist	2006	2006	2009	Europe	Risk of overdose
Feprazone	Analgesic	COX-1 & COX-2 inhibition	1978	1981	1984	UK, Germany, Greece, Egypt	Liver, skin, gastrointestinal, urinary tract
Fipexide‡	Nootropic	TAAR1 receptor modulation?	1973	1990	1991	France	Haematologic, liver
Floctafenine	Analgesic	COX-1 & COX-2 inhibition	1976	1976	1987	Belgium	Dermatologic
Flosequinan‡	Vasodilator	Direct relaxing effects	1992	1992	1993	UK, USA	Death
Flosulide	Analgesic	COX-2 inhibitor	1994	1995	1996	Germany	Kidneys
Flunitrazepam	Sedative-hypnotic	GABA-A receptor modulation	1974	1979	1986	South Africa, Sweden	Drug abuse
Fluproquazone	Analgesic	COX-1 & COX-2 inhibition	1979	1984	1989	USA	Liver
Fluvoxamine	Antidepressant	Selective serotonin re-uptake inhibitor	1984	1987	1987	Iceland	Teratogenicity, renotoxicity
Furazolidone	Antimicrobial	Disruption of bacterial DNA	1954	1965	1977	Japan, Iraq, Malaysia, South Korea, Lebanon, Yemen, India	Skin, Haematologic, nervous, respiratory, sensory
Gadofosveset trisodium	Radiography	Binds to human serum albumin	1988	2006	2010	European Union	Kidney
Gallopamil	Antiarrhythmic	Calcium channel blockers	1983	1985	2001	Turkey	Not specified: Cardiovascular
Ganglioside (bovine)	Glycolipids	Dimerization of neurotrophic factor tyrosine kinases	1975	1985	1989	Germany	Nervous system
Gatifloxacin	Antimicrobial	Inhibition of DNA gyrase	1999	2002	2011	Europe, India	Dysglycemia
Gelatin	Coagulant	?	1915	1978	1978	USA	Haematologic
Gemfibrozil	Anticholesterol	Activates peroxisome proliferator-activated receptor-alpha (PPAR α)	1982	1982	1987	Norway	Negative benefit-to-harm balance
Gemtuzumab ozogamicin	Monoclonal antibody	Binds to the CD33 antigen	2000	2010	2010	USA	Accelerated deaths
Genaconazole	Antimicrobial	Interferes with the fungal synthesis of ergosterol	1970	1992	1992	USA	Hepatocellular cancer
Gentamicin (topical)	Antimicrobial	Interruption of protein synthesis	1966	1976	1994	Netherlands, UAE	Resistance
Glafenine	Analgesic	COX-1 & COX-2 inhibition	1965	1973	1984	Worldwide	Urinary tract
Glucosamine sulphate (injection)	Antiarthritic	Precursor in biochemical synthesis of glycosylated proteins and lipids	1980	1981	1986	Germany, Egypt	Immune: hypersensitivity
Glutethimide	Sedative-hypnotic	Similar to barbiturates	1955	1962	1980	Norway, Zimbabwe, Pakistan, France	Drug abuse, drug dependence, sensory systems
Glycos-aminoglycan	Antiarthritic	?	1975	1982	1982	Germany	Haematologic
Grepafloxacin	Antimicrobial	Inhibition of DNA gyrase	1997	1999	1999	Worldwide	Cardiovascular
Guanethidine	Anti-hypertensive	Sympathetic antagonist	1973	1978	1986	UK	Sensory systems
Guanofuracin	Antimicrobial	Disruption of bacterial DNA	1966		1977	Japan, Venezuela	Safer alternatives
HA-1A (Centoxin)	Monoclonal antibody	Endotoxin lipopolysaccharide	1991	1991	1993	US	Death

Halogenated hydroxyl-quinoline derivatives	Antimicrobial	Production of free radicals	1949	1971	1978	Denmark, Cyprus, India, Philippines, Bangladesh, Ghana, Turkey, Italy, Greece, Oman, UAE,	Nervous
Halogenated salicylanilides	Antimicrobial	Production of free radicals	1954	1964	1975	USA, Japan	Skin, eyes
Heptabarb	Sedative-hypnotic	GABA-A receptor modulation	1956	1984	1984	Sweden	Drug abuse
Herpes simplex vaccines	Vaccines	Herpes simplex antibodies	1964		1984	Germany, Saudi Arabia, Venezuela	Potential hazards
Hexa-chlorophene	Antimicrobial	Production of free radicals	1948	1968	1972	Germany, Japan, Turkey, Europe, USSR, Peru	Encephalopathy, mutagenicity, teratogenicity
Hexestrol	Chemotherapeutic agent	Nonsteroidal oestrogen	1946	1977	1977	Austria, Italy, Kuwait, Armenia, Saudi Arabia, Venezuela	Carcinogenic
Hexestrol bis (beta-diethyl-aminoethyl ether)	Vasodilator	Coronary vasodilatation	1952	1963	1969	Japan	Hepatotoxicity
Hexobarbital‡	Sedative-hypnotic	GABA-A receptor modulation	1945	1962	1984	Sweden	Drug abuse
Human placental extract	Placenta derived tissue	?	1956	1988	1994	Germany, UK, India	Neurotoxicity; Immune; skin
Hydrochlorothiazide + sotalol	Anti-hypertensive	Diuresis plus beta receptor antagonist	1970	1979	1986	France	Cardiovascular, drug interactions
Hydromorphone	Analgesic	Opioid receptor agonist	1926	1985	2005	USA, Switzerland	Overdose potential
Hyoscine methonitrate	Antispasmodic	Muscarinic receptor antagonist	1947	1964	1981	Sweden	Drug abuse
Ibuprofen	Analgesic	COX-1 & COX-2 inhibition	1961	1964	1968	UK	Liver
Indalpine	Antidepressant	SSRI	1983	1985	1985	France	Gastrointestinal, Haematologic
Indometacin (Osmosin)	Analgesic	COX-1 & COX-2 inhibition	1963	1978	1983	UK	Gastrointestinal
Indoprofen	Analgesic	COX-1 & COX-2 inhibition	1976	1982	1983	Worldwide	Carcinogenic
Indoramin	Vasodilator	Alpha-1 adrenoceptor antagonist	1981	1986	2011	UK	Cardiovascular
Influenza virus, split, inactivated (pandremix)	Vaccines	Antibody production	2006	2010	2010	Europe	Narcolepsy
Insulin, inhaled (Exubera)	Hormones	Decreased gluconeogenesis	2006	2008	2008	USA, Europe	Lung cancer
Interferon-gamma-1b	Immuno-modulator	Binds directly to the type II interferon gamma receptor IFNGR1	2002	2007	2007	USA	Accelerated deaths
Iodinated casein	Hormones	Thyroxine analogue	1944	1964	1964	USA	Endocrine, metabolism
Iophendylate	Radiography		1946	1976	1987	UK	Nervous system
Iproniazid	Antidepressant	MAOI	1952	1958	1959	Italy, Canada	Immunologic, liver
Isaxonine phosphate	Neurotrophic	Muscle re-innervation	1981	1983	1984	France, Tunisia	Haematologic, liver
Isocarboxazid	Antidepressant	MAOI	1959	1966	1974	Japan, Cuba, Venezuela	Metabolic
Isoprenaline	Cardiac stimulant	Non-selective beta-adrenergic agonist	1949	1968	1992	Sri Lanka, UK, Australia, New Zealand	Cardiovascular

Isotretinoin	Retinoid	Unknown; apoptosis	1982	1983	1988	Denmark, Austria, Germany, Portugal, Norway,	Teratogenicity
Isoxicam‡	Analgesic	COX-1 & COX-2 inhibition	1983	1985	1985	Worldwide	Skin
Kaolin	Antidiarrhoeal		1954	1968	1991	India, Sri Lanka	Metabolism
Ketoconazole	Antimicrobial	Inhibits the cytochrome P450 14 α -demethylase	1976	1981	2013	EU, Australia	Hepatotoxicity
Ketoprofen (gel)	Analgesic	COX-1 & COX-2 inhibition	1980	1983	2008	Egypt, France	Immunologic
Ketorolac (inj)	Analgesic	COX-1 & COX-2 inhibition	1989	1992	1992	Germany, France, Jamaica	Gastrointestinal, skin
Lapdap (chlorproguanil + dapsone)	Antimalarial	Inhibits dihydrofolate reductase	2003	2008	2008	Worldwide	Haemolytic anaemia
Laropiprant / nicotinic acid	Antilipemic	Prostaglandin receptor blocker	2008	2008	2008	Worldwide	Higher frequency of non-fatal but serious side effects
Lead oxide and lead salts (topical)	Astringent		1892	1977	1980	France, Denmark, Saudi Arabia, Venezuela	Nervous: encephalopathy
Levacetyl-methadol	Antidote	mu-opioid receptor agonist, nicotinic acetylcholine receptor antagonist	1995	2001	2001	Europe, USA	Cardiovascular
Levamphetamine	Psychostimulant	Amphetamine analogue	1944	1954	1973	USA, Oman, UAE	Drug abuse and dependence
Levamisole	Anthelmintic	Neuromuscular depolarizing blockade	1966	1976	1999	US, Canada, Vietnam	Haematologic, nervous system
Levarterenol	Vasopressor	L-norepinephrine analogue	1904	1958	1973	Ireland, Venezuela	Nervous, cardiovascular
Lindane	Insecticide	CNS stimulation	1942	1972	2001	Brazil	Toxicity
Letrozole	Hormone antagonist	Non-steroidal aromatase inhibitor	2001	2005	2011	India	Teratogenic
Loperamide (syrup/ drops) ‡	Antidiarrhoeal	Opioid receptor agonist	1975	1990	1990	Worldwide	Paralytic ileus
Loxoprofen sodium‡	Analgesic	COX-1 & COX-2 inhibition	1983	1993	2000	Singapore	Colonic ulceration
L-Tryptophan	Antidepressant	Converted into serotonin	1963	1989	1989	Worldwide	Eosinophilia-myalgia syndrome (EMS)
Lumiracoxib	Analgesic	COX-2 inhibitor	2006	2007	2007	Australia, USA, Canada, Europe, New Zealand, Brazil, Philippines, Colombia	Liver
Lyme disease vaccine	Vaccines	Immunogenicity	1998	2001	2002	USA	Musculoskeletal (arthralgia)
Lynestrenol	Hormones	Inhibits gonadotropin, suppression of follicle maturation	1962	1970	1980	Australia	Tumorigenicity
Lysine amidotriazolate	Radiography		1975	1981	1995	Germany	Cardiovascular, Haematologic, immunologic, urinary tract (safer alternatives)
Mazindol	Centrally-acting anti-obesity product	Norepinephrine & dopamine reuptake inhibitor	1970	1980	1987	Oman	Drug abuse, psychiatric (interaction with lithium)
Mebanazine	Antidepressant	MAOI	1963	1964	1975	UK	Drug interactions,

							liver
Meclozine (meclizine)	Antihistamine	H1 receptor antagonist	1953	1963	1963	Indonesia	Teratogenic potential
Medifoxamine	Antidepressant	Dopamine reuptake inhibitor; 5HT-receptor agonist	1983	1991	1999	Morocco, France	Liver
Mefenorex	Centrally-acting anti-obesity product	Amphetamine analogue	1966	1995	1999	Europe	Drug abuse, psychiatric
Megestrol acetate	Hormones	Progesterone receptor agonist	1963	1975	1976	Greece, Norway, Germany, New Zealand	Tumorigenicity
Mepacrine (quinacrine)	Antimicrobial	Unclear	1935	1953	1998	India	Carcinogenicity; ectopic pregnancy; political?
Mepazine	Antiepileptic	Unclear	1955	1957	1970	USA	Cardiovascular, gastrointestinal, Haematologic, liver, urinary tract
Mephenesin	Muscle relaxant	Spinal reflex inhibition	1948	1955	1976	Japan, Saudi Arabia	Cardiotoxicity
Meproamate	Muscle relaxant	GABA-A receptor modulation	1955	1957	1981	Sweden, Europe	Drug abuse
Mercuriothiolate (thiomersal)	Antimicrobial	Organomercury analogue	1928	1996	1999	UK, Malaysia, Brazil	Nervous system tumorigenicity, urinary tract
Mercury amide	Antimicrobial	Organomercury analogue	1956	1964	1969	Japan, Brazil, Philippines, France, Nigeria, Ghana, Italy, Canada	Nervous system
Mercurous chloride	Antimicrobial	Organomercury analogue	1796	1949	1953	Worldwide	Nervous system
Mesna	Detoxifying agent	Antioxidation?	1984	1985	1991	Germany	Anaphylaxis
Metamfetamine (desoxyephedrine)	Psychostimulant	TAAR1 receptor agonist	1944	1954	1973	USA, Turkey, Oman, Nigeria	Drug abuse, drug dependence
Metamizole (dipyrone)	Analgesic	COX-1 & COX-2 inhibition	1921	1952	1965	9 European, 11 Asian, and 5 African countries; Australia; USA; Mexico; Canada	Haematologic, immunologic: agranulocytosis
Methapyrilene	Sedative-hypnotic	Histamine and cholinergic receptors' antagonist	1947	1979	1979	Germany, Dominican Republic, UK, Italy, Canada, Singapore, Hong Kong, Australia, Egypt, Panama, Brazil, Philippines, UAE, India, Oman, Chile, New Zealand, USA, Venezuela	Tumorigenicity
Methaqualone	Sedative-hypnotic	GABA receptor agonist	1965	1966	1979	Greece, Turkey, Oman, Zimbabwe, Pakistan, Ghana, UAE, India	Drug abuse
Methiodal sodium	Radiography		1964	1972	1975	Sweden	Muscle
Methyl-androstrenolone	Hormones	Protein synthesis	1960	1982	1982	USA, France, UK, Germany,	Endocrine (masculinization)
Methyl-hexanamine (DMAA)	Nasal decongestant	Norepinephrine & dopamine transporter blockade	1948	1950	1983	Worldwide	Cardiovascular, nervous
Methylphenidate	Psychostimulant	Dopamine-norepinephrine	1956	1961	1982	Turkey, Oman, Nigeria	Drug abuse

		reuptake inhibitor					
Methylrosanilinium chloride	Antimicrobial		1890	1970	1998	Malaysia	Immunologic
Methypyrilone	Sedative-hypnotic	GABA-A receptor modulation	1955	1961	1984	Zimbabwe	Drug abuse
Metipranolol	Anti-hypertensive	Non-selective beta blocker	1986	1991	1991	UK	Sensory systems (uveitis)
Metofoline	Analgesic	Opioid receptor agonist	1962	1965	1965	USA	Sensory systems
Metrizamide	Radiography		1977	1980	1992	UK, Netherlands	Nervous system, sensory systems
Metrodin	Hormones	GnRH agonist	1993	2003	2003	UK	Nervous system
Mianserin	Antidepressant	Norepinephrine & serotonin reuptake inhibitor	1975	1979	1988	Oman	Haematologic: agranulocytosis
Mibefradil	Anti-hypertensive	Calcium channel blockers	1997	1998	1998	USA; UK; Peru; South Africa; Jamaica; Bulgaria; Armenia	Drug interactions, musculoskeletal
Miglustat	Enzyme inhibitor	Glucocerebrosidase	2002	2002	2002	Israel	Unexplained cognitive dysfunction
Minaprine	Antidepressant	Reversible inhibitor of MAO-A	1972	1983	1996	France, Spain, Germany	Drug abuse, nervous system
Minocycline	Antimicrobial	Protein synthesis inhibitor	1967	1974	1989	Norway	Dizziness, vertigo
Molsidomine	Vasodilator	Nitric oxide synthesis	1972	1975	1985	Germany	Tumorigenicity
Moxisylyte (thymoxamine; uroalpha)	Vasodilator	Alpha1-adrenergic antagonist	1989	1991	1993	France	Liver
Mucopolysaccharide polysulfuric acid ester	Antiarthritic	Endogenous hyaluronate synthesis	1962	1987	1988	Switzerland, France, Portugal, Austria	Skin: histochemical study
MMR vaccine (Urabe)	Vaccines	Antibody production	1983	1987	1988	Worldwide	Nervous system, psychiatric
Muzolimine†	Anti-hypertensive	Diuresis	1983	1987	1987	Worldwide	Nervous system
Naftidrofuryl oxalate (IV)	Vasodilator	5HT2 receptor antagonist	1974	1976	1992	France; Germany, Spain	Cardiovascular, immunologic, liver, urinary tract
Nandrolone decanoate (injectable)	Hormones	Stimulate anabolism & inhibit catabolism	1962	1989	1997	France, Bangladesh	Drug abuse
Nandrolone phenylpropionate (injectable)	Hormones	Stimulate anabolism & inhibit catabolism	1959	1972	1982	Bangladesh	Drug abuse
Natalizumab	Monoclonal antibody	Inhibits $\alpha 4$ integrin	2004	2005	2005	USA	Nervous (combination)
Nebacumab	Monoclonal antibody	Endotoxin-specific IgM	1991	1993	1993	Worldwide	Infection risk
Nefazodone	Antidepressant	5HT2 receptor antagonist	1994	1999	2003	European Union; Canada; Singapore	Hepatotoxicity
Neomycin sulfate (inj)	Antimicrobial	Protein synthesis inhibitor	1949	1967	1983	Bangladesh, Philippines, Nigeria, USA; Canada	Drug abuse, sensory systems, urinary tract
Nevirapine	Antimicrobial	Non-nucleoside reverse transcriptase	1996	1997	2007	Brazil	Liver

		inhibitor (NNRTI)					
Nialamide	Antidepressant	MAOI	1959	1969	1974	Japan, India, Cuba, Denmark, Thailand, Venezuela, Canada	Drug interactions, liver
Nifedipine (10mg)	Anti-hypertensive	Calcium channel blockers	1975	1989	1996	Australia	Cardiovascular
Nifuroxazide (nifuroxazine)	Antimicrobial	Janus kinase inhibitor	1966	1997	2008	Belgium	Immunologic, Haematologic
Nikethamide	Respiratory stimulant	Unclear	1922	1953	1988	Worldwide	Nervous system
Nimesulide	Analgesic	COX-2 inhibitor	1986	1998	1999	Portugal, Israel, Spain, Bangladesh, Nigeria, India, Ireland, Ghana, Thailand, Vietnam	Liver
Niperotidine	Anti-ulcer	H2 receptor antagonist	1990	1995	1995	Italy	Hepatotoxicity
Nitrefazole	Anti-addiction	Inhibition of aldehyde dehydrogenase	1982	1984	1984	Germany, Austria	Liver
Nitrofurazone (Nitrofur)	Antimicrobial	Unclear	1946	1974	1977	Japan, USA, Armenia	Mutagenicity
Nitroxoline	Antimicrobial	↓ in the biofilm density of <i>P. aeruginosa</i>	1965	1966	1973	Ireland, Thailand, Venezuela	Eyes
Nomifensine	Antidepressant	Norepinephrine-dopamine reuptake inhibitor	1976	1980	1986	Worldwide	Haematologic, liver, respiratory
Norpseudoephedrine (Phenyl-propanolamine)	Psychostimulant	Adrenoreceptor agonist, D1 receptor agonist	1947	1985	1987	Germany, Brazil, Malaysia, Singapore, USA, Oman, Canada, Cuba, India, Cameroun, Nigeria, Portugal, Temor-Leste, South Korea	Haemorrhagic stroke
Noscapine	Antitussive	σ-receptor agonist	1959	1984	1990	Ireland, UK, Netherlands	Genotoxicity
Novobiocin (cathomycin)	Antimicrobial	Inhibitors of bacterial DNA gyrase	1956	1957	1987	Malaysia	Haematologic
Omeprazole (injectable)	Anti-ulcer	Proton pump inhibitor	1989	1994	1994	Germany	Endocrine, genotoxicity, liver, musculoskeletal, nervous system, sensory systems
Opium in antitussives	Antitussive	Opioid receptor agonist	1812	1842	1982	Bangladesh, Italy	Drug dependence
Orciprenaline (metaprotenerol)	Bronchodilator	Beta2 adrenoceptor agonist	1961	1972	2009	UK	Cardiovascular
Orgotein	Anti-inflammatory	Free radical scavenging	1968	1987	1990	Switzerland, Germany, Portugal	Immunologic
Oxeladin	Antitussive	Unclear	1972	1991	1994	Germany, France, Armenia, Canada	Carcinogenic
Oxolamine	Antitussive	Unclear	1969	1972	1984	Netherlands	Nervous system: hallucination in children
Oxomemazine	Antitussive	Histamine and cholinergic receptors' antagonist	1937	1979	1991	European Union; USA	Respiratory depression in children (SIDS)
Oxyphenbutazone	Analgesic	COX-1 & COX-2 inhibition	1955	1974	1984	Worldwide	Haematologic : Bone marrow suppression
Oxyphenisatin	Laxative	↑d mucosal tissue permeability	1925	1970	1972	Worldwide	Liver

Pangamic acid	“Vitamin”	Transmethylation	1950	1980	1984	Greece	Mutagenic
Paramomycin	Antimicrobial	Protein synthesis inhibitor	1959	1970	1989	Spain	Renal damage, neuromuscular blockage and ototoxicity
Parecoxib	Analgesic	COX-2 inhibitor	2002	2005	2005	USA, European Union	Cardiovascular, respiratory
Pargyline	Anti-hypertensive	Monoamine oxidase inhibitor	1963	1964	1979	Germany	Interaction with tyramine
Pectin	Antidiarrhoeal	↑d viscosity	1936	1974	1991	Libya, India, Sri Lanka	Metabolic
Pemoline	Psychostimulant	Dopamine agonist?	1960	1973	2005	Worldwide	Liver: hepatotoxicity
Pentobarbital	Sedative-hypnotic	GABA-A receptor modulation	1930	1953	1985	Sweden	Drug overdose
Pentosan polysulfate sodium	Anti-thrombotic	Protective coating to the damaged bladder wall?	1965	1985	1994	France, USA	Haematologic : thrombocytopenia
Pentyl-enetetrazol	Circulatory & respiratory stimulant	Unclear	1934	1954	1982	USA	Convulsion
Pergolide Mesylate	Anti-parkinsonian	Dopamine receptor agonist	2002	2002	2007	USA, Canada	Cardiovascular
Perhexiline laurate	Antianginal	Inhibits mitochondrial CPT1	1974	1974	1985	UK, Spain, France	Hypoglycaemia, liver, musculoskeletal, nervous system
Phenacetin	Analgesic	Metabolized to paracetamol	1887	1948	1965	16 European, 14 Asian, 5 African, 4 S. American countries. New Zealand, USA, Canada	Haematologic, liver, tumorigenicity, urinary tract
Phenazone (antipyrine)	Analgesic	COX-1 & COX-2 inhibition	1883	1958	1981	UAE, Malaysia, Bahrain, Germany, Iraq	Haematologic
Phenazopyridine	Analgesic	Unclear	1927	1978	1984	Greece	Carcinogenic
Phendimetrazine	Psychostimulant	Norepinephrine-dopamine releasing agent	1961	1979	1982	Turkey	Drug abuse
Phenformin	Hypoglycaemic	↓d gluconeogenesis	1957	1963	1970	15 European & 6 Asian countries; Canada; New Zealand; Brazil; USA; Ethiopia	Metabolic acidosis
Phenicarbazide (phenyl-semicarbazide)	Analgesic	Unclear	1948	1950	1979	Ireland	Haemolytic anaemia
Phenmetrazine	Psychostimulant	Norepinephrine-dopamine releasing agent	1956	1959	1982	Turkey, Oman, Nigeria	Drug abuse
Phenobarbital	Sedative-hypnotic	GABA-A receptor modulation	1912	1929	1985	Sweden, Mauritius, France	Abuse and intoxication; skin
Phenol (topical)	Antimicrobial	Absorption by bacteria	1867	1973	1983	Dominican Republic, Lithuania	Safer alternatives
Phenolphthalein	Laxative	Direct action on intestinal muscles	1902	1953	1979	Europe, Yemen, Bangladesh, Canada, France, Morocco, Oman, Japan, Saudi Arabia, Bahrain	Skin, metabolic, muscular
Phenoxy-propazine	Antidepressant	MAOI	1961	1964	1966	UK	Drug interactions, liver
Phentermine	Centrally-acting anti-obesity product	TAAR1 agonist	1959	1964	1981	Sweden, UAE, Mauritius, Turkey, Oman, UK, Venezuela	Drug abuse
Phentolamine mesilate	Anti-hypertensive	Alpha-adrenergic antagonist	1998	1998	2000	Singapore	Carcinogenicity

Phenylbutazone	Analgesic	COX-1 & COX-2 inhibition	1949	1953	1985	6 European, 6 Asian & 3 African countries; Chile; Panama	Haematologic, liver, urinary tract
Phenylephrine	Decongestant	α 1-adrenergic receptor agonist	1949	1968	1987	UK	Eyes
Phthalyl-sulfathiazole	Antimicrobial	Inhibits dihydropteroate synthetase	1946	1950	1982	Bangladesh	Granulocytopenia
Pifoxime	Analgesic	COX-1 & COX-2 inhibition	1975	1975	1976	France	Nervous system, psychiatric
Pioglitazone	Hypoglycaemic	PPARs activation	1999	2011	2011	Europe	Risk of bladder CA
Pipamazine	Emetic	Phenothiazine analogue	1959	1960	1969	USA	Lack of efficacy
Pipenzolate	Anti-ulcer	Muscarinic receptor antagonist	1960	1990	1990	Pakistan	Overdose potential
Piperazine	Anthelmintic	GABA receptor inhibition	1949	1957	1983	Malaysia, Armenia	Immunologic, nervous system, tumorigenicity
Pipradrol	Psychostimulant	Norepinephrine-dopamine reuptake inhibitor	1953	1968	1982	USA, Turkey, Denmark, Venezuela	Nervous, cardiovascular
Pirprofen	Analgesic	COX-1 & COX-2 inhibition	1982	1986	1990	Worldwide	Gastrointestinal, liver, urinary tract
Pituitary chorionic gonadotropin (injectable)	Hormones	Ovulation trigger	1930	1958	1972	USA	Immunologic
Podophyllum resin	Laxative	Mitotic spindle poison	1844	1962	1970	Italy, France, Egypt	Teratogenicity
Polidexide	Antilipemic	Anion exchange	1974	1977	1977	UK	Oculomucocutaneous syndrome
Polyoxyethylated castor oil	Adjuvant		1970	1973	1984	Worldwide	Anaphylaxis, hyperlipidemia
Polyvinylpyrrolidone (Polyvidone; povidone)	Adjuvant	Permeability through circulatory system	1957	1967	1983	Germany, Pakistan, Egypt, USA	Metabolic: granulomatous lesions
Potassium arsenate	Tonic	Degradation of the aberrant retinoic acid receptor α fusion protein	1878	1968	1980	USA	Tumorigenicity
Potassium canrenoate	Anti-hypertensive	Aldosterone antagonist	1968	1985	1986	Germany	Carcinogenic
Potassium chloride	Electrolyte	Replenishment of potassium stores	1962	1964	1989	Belgium, France, USA, Canada	Gastrointestinal perforation
Potassium nitrate	Anti-hypertensive	Nitric oxide synthesis	1901	1975	1981	France, Egypt, Venezuela	Tumorigenicity
Practolol	Anti-hypertensive	Beta-blocker	1970	1972	1975	Greece, Turkey, New Zealand, Denmark, Thailand, Singapore, UK, Mauritius, India, Germany, Norway, Venezuela	Gastrointestinal, sensory systems, skin
Pramipexole dihydrochloride monohydrate	Anti-parkinsonian	Dopamine receptor agonist	1997	1999	2006	Europe	Sudden onset of sleep
Prenylamine	Vasodilator	Calcium channel blocker	1960	1973	1989	Worldwide	Cardiovascular: multifocal ventricular tachycardia
Probucol	Antioxidant	Unclear	1980	1989	1989	Germany, France, USA	Cardiovascular: Torsade de pointes

Proglumide	Anti-ulcer	Cholecystokinin antagonist	1970	1984	1989	Japan, Germany	Respiratory
Pronethalol	Anti-hypertensive	Beta-blockade	1963	1963	1965	UK	Tumorigenicity
Propanidid	Anaesthetic	Unclear	1963	1965	1983	UK, Norway, France	Immunologic reactions
Propofol (children)	Anaesthetic	GABA-A receptor agonist, sodium channel blockade	1987	1992	1992	Israel, Norway, UK, Lithuania	Metabolic, hepatic, nervous; deaths
Propyphenazone‡	Analgesic	COX-1 & COX-2 inhibition	1951	1980	1989	Turkey, UAE, Bahrain, Ireland	Haematologic, Immunologic: Lyell's syndrome
Proxibarbal	Sedative-hypnotic	GABA-A receptor modulation	1956	1990	1998	France, Italy, Spain, Portugal and Turkey	Haematologic, immunologic
Pseudoephedrine	Sympatho-mimetic	Direct action on adrenergic receptors	1959	1963	2008	Iraq, Colombia, Thailand	Nervous, GIT, immunologic, cardiovascular, teratogenic
Pumactant‡	Surfactant	Lowers lung surface tension	1992	2000	2000	UK	“Accelerated deaths”
Purified hexavalent vaccine (Hexavac)	Vaccines	Immunogenicity	2000	2005	2005	Europe	Decreased immunogenicity
Pyrithyldione/Diphenhydramine	Sedative-hypnotic	Similar to barbiturates	1940	1949	1997	Spain	Haematologic: agranulocytosis
Pyritinol	Nootropic	Increased cerebrovascular blood flow	1961	1973	1982	Bangladesh	Insufficient therapeutic value and risk of misuse
Pyrovalerone	Psychostimulant	Norepinephrine-dopamine reuptake inhibitor	1974	1975	1979	France	Drug abuse
Pyrrolizidine	Antitussive	Coating effect	1967	1968	1992	Germany, Belgium, UK	Liver
Rapacuronium bromide	Anaesthetic	Non-depolarizing neuromuscular blocker	1999	1999	2001	USA	Respiratory: Bronchospasm
Remoxipride	Antipsychotic	D2 receptor antagonist	1991	1993	1994	Worldwide	Haematologic
Rimonabant	Psychostimulant	Cannabinoid receptor agonist	2006	2006	2007	Europe, India	Psychiatric
Rofecoxib	Analgesic	COX-2 inhibitor	1999	2002	2004	Worldwide	Cardiotoxicity
Rosiglitazone	Hypoglycaemic	↓ gluconeogenesis	1999	2007	2011	UK; New Zealand; South Africa, India	Cardiovascular
Rotavirus vaccine	Vaccines	Immunogenicity	1998	1999	1999	USA, UK	Gastrointestinal: intussusception
Santonin‡	Anthelmintic	Paralysis of nerve impulses	1911	1933	1978	Singapore	Neurotoxicity
Sargramostim	Immuno-stimulator	Granulocyte macrophage colony-stimulating factor (GM-CSF)	1993	1999	2008	USA	Immune-mediated
Secobarbital/quinabarbital	Sedative-hypnotic	GABA-A receptor modulation	1934	1958	1990	France, Norway, Netherlands, Ghana, New Zealand, Oman	Drug abuse
Selegiline	Anti-parkinsonian	MAO-B inhibitor	1982	1991	1997	USA	Drug interaction
Sertindole	Antipsychotic	5HT & D2 receptor antagonist	1996	1996	1998	UK, Bulgaria, Spain	Cardiovascular
Sibutramine	Centrally-acting anti-obesity product	Serotonin-norepinephrine reuptake inhibitor	2001	2002	2002	European Union; 4 Asian countries; Australia; Canada; Mexico; New Zealand; USA	Cardiovascular

Sitaxentan sodium‡	Anti-hypertensive	Endothelin receptor antagonist	2006	2009	2010	Worldwide	Hepatotoxicity
Sodium dibunate (ethyl dibunate)	Antitussive	Unclear	1963	1968	1982	Philippines	Nervous
Sodium hydrogen bicarbonate (pediatric)	Antacid	Counteracts acidity	1966	1983	1997	Nepal	Safety concerns: metabolic
Somatropin (growth hormone)	Hormones	Binds to the human growth hormone receptor	1973	1985	1985	Europe; Egypt; New Zealand; USA; Oman; Thailand	Infection risk: Creutzfeldt-Jakob disease
Soruvudine	Antimicrobial	Inhibits DNA polymerase	1993	1993	1993	Germany; Japan	Drug interactions with 5-fluorouracil
Sparfloxacin	Antimicrobial	Inhibits DNA gyrase	1993	1995	1995	Europe, USA	QTc prolongation, phototoxicity
Sparteine sulphate	Hormone analogue	Prostaglandin stimulation?	1939	1963	1979	USA	Uterine tetany
Strychnine and salts	Aphrodisiac	Acetylcholine receptor antagonist	1753	1882	1979	Canada, Brazil, Bangladesh, Japan, Pakistan, UAE, Philippines	Nervous
Sulfacarbamide (Sulfanilylurea)	Antimicrobial	Inhibits dihydropteroate synthetase	1946	1959	1992	Germany	Haematologic, liver, skin, urinary tract
Sulfadacrimide (sulfacetamide)	Antimicrobial	Inhibits dihydropteroate synthetase	1942	1976	1992	Germany	Negative benefit-to-harm balance: eye, skin, immune
Sulfa-dimethoxine	Antimicrobial	Inhibits dihydropteroate synthetase	1958	1961	1966	USA	Skin
Sulfadimidine	Antimicrobial	Inhibits dihydropteroate synthetase	1942	1954	1992	USA; Germany; Armenia	Haematologic : thrombocytopenia
Sulfaguandine	Antimicrobial	Inhibits dihydropteroate synthetase	1941	1969	1971	Dominican Republic, Iran, Turkey, Pakistan, Nepal, Germany, UAE, Denmark, Venezuela	Haematologic: agranulocytosis
Sulfamerazine sodium	Antimicrobial	Inhibits dihydropteroate synthetase	1943	1955	1992	Germany	Haematologic ; skin
Sulfamethizole	Antimicrobial	Inhibits dihydropteroate synthetase	1953	1963	1984	Sweden	Immunologic
Sulfa-methoxydiazine	Antimicrobial	Inhibits dihydropteroate synthetase	1962	1968	1988	Germany	Skin
Sulfamethoxypropyridazine	Antimicrobial	Inhibits dihydropteroate synthetase	1957	1958	1984	Sweden, Pakistan, UAE, UK, Canada, Argentina, France	Haematologic, skin
Sulfanilamide	Antimicrobial	Inhibits dihydropteroate synthetase	1936	1957	1992	Germany	Sensory, Immunologic
Sulfathiazole	Antimicrobial	Inhibits dihydropteroate synthetase	1941	1954	1970	USA, Philippines, Dominican Republic, France, UAE, India	Haematologic, liver, skin, urinary tract
Sulfisomidine	Antimicrobial	Inhibits dihydropteroate synthetase	1952	1972	1992	Germany	Negative benefit-to-harm balance
Sulfonamides (topical)	Antimicrobial	Inhibits dihydropteroate synthetase	1930	1957	1986	Chile	Immune-mediated
Suloctidil‡	Vasodilator	Calcium channel blockade, inhibits thromboxane B2	1975	1983	1985	Worldwide	Liver: hepatotoxicity

Suprifen with tussilax	Antitussive		1971	1971	1972	France, Germany	Liver: hepatotoxicity
Suprofen	Analgesic	COX-1 & COX-2 inhibition	1983	1986	1986	Worldwide	Urinary tract
Suxibuzone	Analgesic	COX-1 & COX-2 inhibition	1974	1982	1986	Oman, Italy	Carcinogenesis
Technetium (^{99m} Tc) fanolesomab	Radiography	Radioisotope	2004	2005	2005	USA	Cardiovascular
Tegaserod	Antispasmodic	5-HT ₄ receptor agonist	2002	2004	2007	USA, Canada, India, Jordan, Australia, Switzerland, China, Argentina	Cardiovascular
Temafloxacin‡	Antimicrobial	Inhibits DNA gyrase	1991	1992	1992	Worldwide	Haematologic, immunologic, liver, metabolism, urinary tract
Temazepam (gel capsules)	Sedative-hypnotic	GABA-A receptor binding	1969	1981	1999	Australia	Drug abuse
Terconazole	Antimicrobial	Disrupts cell membrane permeability by cytochrome P450 14-alpha-demethylase	1980	1988	1991	Sweden, Germany	Immunologic, skin
Terfenadine	Antihistamine	H ₁ -receptor antagonist	1985	1985	1997	3 European, 2 African, 3 Asian & 3 South American countries; USA, Canada	Cardiovascular, immunologic, liver, skin
Terodiline	Antispasmodic	Calcium channel blockade, blocks cholinergic receptor	1965	1989	1991	Worldwide	Cardiovascular
Testosterone propionate (injectable)	Hormones	Androgen-receptor modulation	1937	1952	1982	Bangladesh	Drug abuse
Tetrabamate	Anxiolytic	Febarbamate, difebarbamate plus phenobarbital	1981	1992	2001	France, Spain	Liver, skin
Tetrachlorosalicylanilide	Antimicrobial	Leakage of cell contents	1949	1961	1975	USA, Japan	Skin
Tetracycline (pediatric)	Antimicrobial	Protein synthesis inhibitor	1948	1959	1975	8 Asian, 2 African, 2 Australasian countries; USA, Italy	Teeth; bone
Tetrazepam	Sedative-hypnotic	Benzodiazepine site agonist	1960	1988	2013	EU	Dermatitis
Thalidomide	Immuno-modulator	? CNS mechanism	1957	1961	1961	Belgium, Finland, Indonesia, Canada, Brazil, Denmark, India, Singapore, Venezuela, UK, Germany	Nervous system, teratogenicity
Thenalidine tartrate	Antihistamine	H ₁ -receptor blocker	1953	1958	1958	USA; UK; Sweden; France; Cyprus; Australia; Finland; Norway, Canada	Haematologic : neutropenia
Thiobutabarbital	Sedative-hypnotic	GABA-A receptor modulation	1939	1981	1993	Germany	Urinary tract
Thioridazine	Antipsychotic	5HT ₂ receptor antagonist	1959	1961	2000	Worldwide	Retinopathy, cardiovascular
Thorium dioxide	Radiography	Radiocontrast	1928	1931	1955	UK	Tumorigenicity
Tick-borne encephalitis vaccine	Vaccines	Immunogenicity	1999	1999	2000	Germany	Hyperpyrexia
Tienilic acid (ticrynafen)	Anti-hypertensive	Loop diuretic	1976	1979	1980	Greece; Philippines; USA; Brazil; Germany; Panama; France; India; Venezuela	Liver, urinary tract

Tilbroquinol	Antiprotozoal	?	1969	1996	1997	France, Morocco, Saudi Arabia, Switzerland	Liver, nervous system
Timonacic acid (thioprolin)	Antioxidant	Cysteine release and restoration of glutathione concentrations	1975	1981	1982	France	Drug overdose (toxicity)
Tocainide	Antiarrhythmic	Sodium channel blockade	1981	1986	1986	USA	Haematologic: agranulocytosis, aplastic anaemia
Tolcapone	Anti-parkinsonian	COMT inhibitor	1998	1998	1998	UK; Australia; Ireland; Spain; Portugal; Lithuania; Bulgaria; Canada	Liver
Tolrestat†	Hypoglycaemic	Aldase reductase inhibitor	1982	1995	1996	Worldwide	Liver
Tranyl-cypromine	Antidepressant	MAOI	1961	1963	1964	Italy, Belgium, Venezuela, Canada	Cardiovascular, drug interactions
Trazodone	Antidepressant	Binds at 5-HT ₂ receptor	1973	1983	1985	Norway	Carcinogenic
Tretinoin	Retinoid	Modulates cell-cycle progression, cellular differentiation, cell survival and apoptosis	1973	1977	1988	Germany	Carcinogenic
Triacetyldiphenolisatin	Laxative	↑d mucosal tissue permeability	1961	1967	1971	Australia, Germany, Italy, Canada, Cyprus, New Zealand, Venezuela	Photosensitivity hepatotoxicity
Triazolam	Sedative-hypnotic	GABA-A receptor binding	1978	1978	1979	Mauritius, Europe, Brazil, Oman	Nervous system, psychiatric
Trimetho-benzamide (suppository)	Antihistamine	?Chemoreceptor trigger zone	1959	1976	2007	USA	Due to new FDA regulation; lack of effectiveness. Teratogenicity
Triparanol	Antilipemic	δ 24-reductase inhibitor	1959	1961	1962	USA, France	Sensory systems, skin
Troglitazone	Hypoglycaemic	PPARs activation	1997	1997	1997	UK; Switzerland; Peru; Jamaica; Chile, USA, Canada	Liver
Trovaflouxacin‡	Antimicrobial	Inhibits DNA gyrase	1997	1997	1999	European Union; Philippines; Syria; Vietnam; Singapore, Canada, USA	Liver
Urethane	Solvent	?Interferes with pyrimidine metabolism	1933	1943	1963	Brazil, Cuba, Denmark, Egypt, Japan, Thailand, USA, Canada, Italy, Greece, Denmark, Venezuela, France	Haematologic, liver, tumorigenicity
Valdecobix	Analgesic	COX-2 inhibitor	2001	2003	2005	USA, Canada, Europe, India	Cardiovascular; skin
Veralipride	Neuroleptic	Selective antagonism of hypothalamic D ₂ receptors	1979	1982	2007	Europe, Brazil (reference to EMA)	Psychiatric
Vigabatrin (gamma-vinyl-GABA)	Antiepileptic	Inhibits GABA transaminase (GABA-T)	1989	1989	1991	Norway	Not medically justified; neurotoxicity
Vinbarbital‡	Sedative-hypnotic	GABA-A receptor modulation	1939	1975	1984	Sweden	Drug abuse
Vincamine	Nootropic	Unclear	1955	1974	1980	Hungary, Germany	Cardiovascular, Haematologic
Vitamin B complex (injectable)	Hematinic	Co-factor for biochemical transformation	1949	1953	2008	Iraq	Immunologic
Vitamin E (injectable)	Antioxidant	Downregulation of ICAM-1 and VCAM-1	1983	1984	1984	USA	Haematologic, liver, urinary tract
Xenazoic acid (xenalamine)	Antimicrobial	? Inhibits intracellular stages viral biological cycle	1960	1965	1965	Belgium, France, Venezuela	Liver

Ximelagatran	Anticoagulant	Direct thrombin inhibitor	2005	2006	2006	Europe, Brazil	Liver
Zimeldine	Antidepressant	5 HT reuptake inhibitor	1982	1982	1983	Worldwide	Liver, nervous system
Zipeprol HCl	Antitussive	Laryngeal nerve stimulation; excitation of tracheo-bronchial receptors	1971	1984	1991	Philippines, Brazil, Spain, Switzerland, Turkey	Drug abuse, drug dependence, nervous system
Zomepirac Na	Analgesic	COX-1 & COX-2 inhibition	1979	1981	1983	Worldwide	Immunologic, urinary tract
Zopiclone	Sedative-hypnotic	GABA-A receptor binding	1985	1985	1986	Israel, Norway	Carcinogenicity

ABBREVIATIONS: ADHD: Attention deficit hyperactivity disorder; ADR: Adverse drug reaction; COMT: Catechol-O-methyl transferase; COX-1: Cyclooxygenase 1; COX-2: Cyclooxygenase 2; CPT1: Carnitine palmitoyltransferase I; CTZ: Chemoreceptor trigger zone; DNA: Deoxyribonucleic acid; D1: Dopamine 1; D2: Dopamine 2; D3: Dopamine 3; DVT: Deep venous thrombosis; GABA: Gamma-aminobutyric acid; HMG CoA: 3-hydroxy-3-methyl-glutaryl-CoA; hURAT1: Human uric acid transporter 1; H1: Histamine 1; ICAM-1: Interleukin Adhesion Molecule 1; MAOI: Monoamine oxidase inhibitor; NMDA: N-methyl-D-aspartate; PCM: Paracetamol; PPAR: Peroxisome proliferator-activated receptors; SSRI: Selective serotonin reuptake inhibitor; TAAR 1: Trace amine-associated receptor 1; VCAM-1: Vascular cell adhesion protein 1; 5 HT: 5-hydroxytryptamine

‡Product was withdrawn because of reports of drug-attributed deaths

^ARe-prohibited again in 1986 following FDA legal action (<http://www.atsdr.cdc.gov/toxprofiles/tp64.pdf>)

§The first reported adverse reaction appeared after first withdrawal from the market

2.3.1 Types of adverse drug reactions

Hepatotoxicity (81 cases; 18%) was the most commonly reported adverse drug reaction that led to withdrawal (Table 2.1). This was followed by immune-related reactions (79 cases; 17%), cardiotoxicity (63 cases; 14%), neurotoxicity (76 cases; 16%), haematological toxicity (53 cases; 11%), carcinogenicity (61 cases; 13%), and drug abuse and dependence (52 cases; 11%).

2.3.2 Levels of evidence used for product withdrawals

The levels of available evidence that triggered drug withdrawal decisions, according to the OCEMB criteria, are shown in Table 2.2. Of the 462 included products, case reports were used as evidence for withdrawals in 330 instances (71%); in 49 cases (11%), withdrawal

decisions were based on the results of animal studies. Of products launched after 1950 (n=354), case reports were used as evidence in 247 instances (70%). The comparable figures for each decade since 1950 are as follows: 1950s 85% (n=68); 1960s 74% (n=88); 1970s 69% (n=77); 1980s 68% (n=50); 1990s 64% (n=45); 2000-8, 35% (n=26).

Table 2.2: Levels of evidence used to justify post-marketing withdrawal of medicinal products

Level of evidence*	Number (%) of withdrawals	
	All marketed drugs (n=462)	Marketed drugs launched since 1950 (n=286)
Level 1: Systematic reviews	6 (1.3%)	6 (2.1%)
Level 2: Randomized studies	27 (5.8%)	25 (8.7%)
Level 3: Non-randomized studies	43 (9.3%)	30 (10.5%)
Level 4: Case reports	330 (71.4%)	189 (66.1%)
Level 5: Mechanism-based reasoning	56 (12.1%)	36 (12.6%)

*Based on the Oxford Centre for Evidence-Based Medicine Levels of Evidence [9]. Level 1: Systematic review of randomized trials, systematic review of nested case-control studies, Level 2: Individual randomized trial or (exceptionally) observational study with dramatic effect; Level 3: Non-randomized controlled cohort/follow-up study (post-marketing surveillance); Level 4: Case-series, case-control, or historically controlled studies; Level 5: Mechanism-based reasoning

2.3.3 Therapeutic indications for which medicinal products were withdrawn

Antimicrobial drugs (15%) and analgesics (13%) were the most common groups of medicinal products withdrawn, followed by hypnotosedatives and psychostimulants (6% each), and antihypertensive drugs and antidepressants (4% each) (Table 2.1).

2.3.4 Patterns of withdrawals

Of the 462 products, 43 (9.3%) were withdrawn worldwide, and 179 (39%) were withdrawn in only one country. The remaining 240 (52%) were withdrawn in two or more countries. In terms of withdrawals by geographical region, 63 products were withdrawn in Africa, 150 in Asia, 32 in Australasia and Oceania, 309 in Europe, 134 in North America, and 65 in South America (Table 2.3). The rate of withdrawals per country was significantly

lower in Africa than in Asia, Australasia, Europe, North America, or South America.

However, there were no significant differences in the relative rates of withdrawals across the five African sub-regions (data not shown).

Table 2.3: Post-marketing withdrawal of medicinal products because of adverse drug reactions in different continents

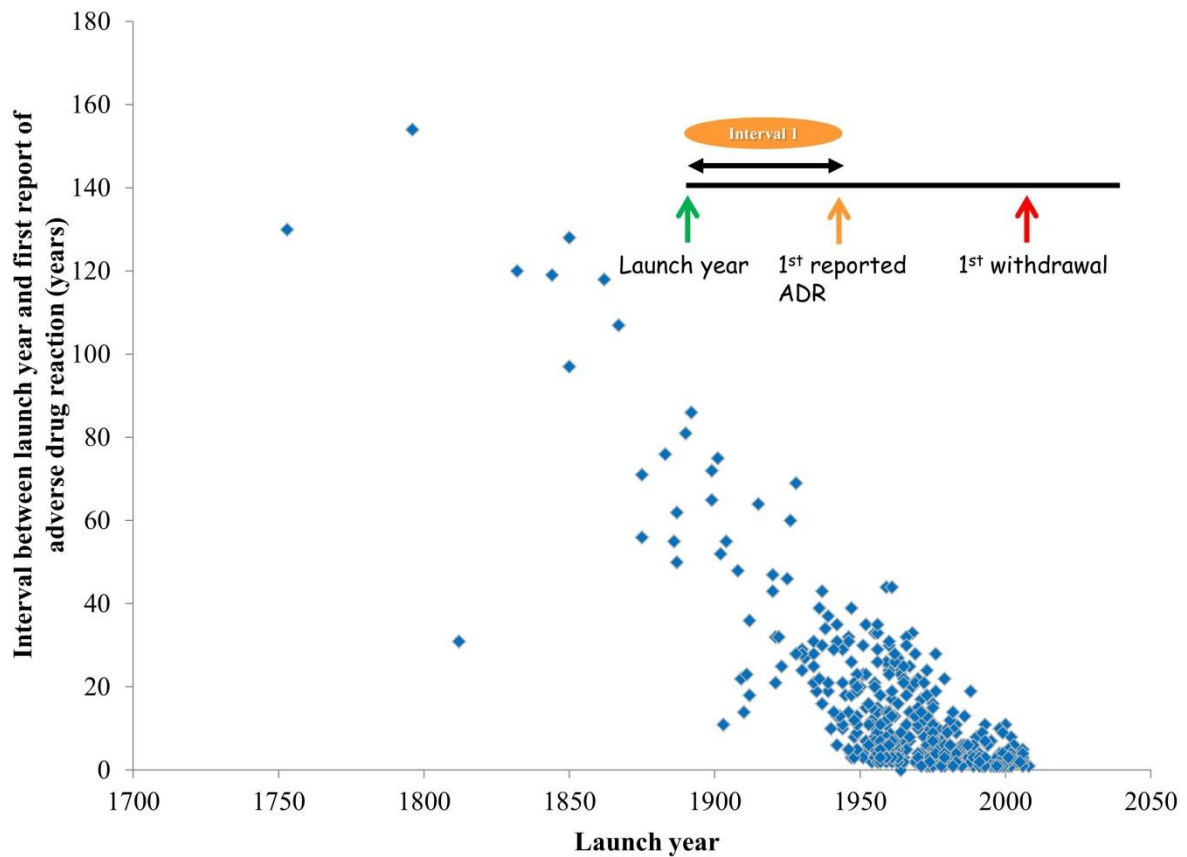
Continent	No. of countries	Total population (millions)	No. of withdrawn products	Rate of withdrawals/million population	Rates of withdrawal per country	*RR of withdrawal per country versus Africa (95% CI)	*P value versus Africa
Africa	54	1111	63	0.06	1.17	-	-
Asia	46	4427	150	0.03	3.26	1.42 [1.18 to 1.71]	0.001
Australasia & Oceania	11	30	32	1.07	2.91	1.38 [1.08 to 1.76]	0.045
Europe	50	742.5	309	0.42	6.18	1.60 [1.34 to 1.90]	< 0.0005
N. America	23	528.7	134	0.25	5.83	1.59 [1.32 to 1.90]	< 0.0005
S. America	12	387.5	65	0.17	5.42	1.57[1.29 to 1.90]	< 0.0005

*The P values have been corrected for multiple tests using the Bonferroni method. The relative rates of withdrawal are calculated based on the assumption that if a medicinal product was withdrawn in one country, it should also have been withdrawn in all countries in that continent. The data for total populations are obtained from the 2013 World Population Data Sheet (http://www.prb.org/pdf13/2013-WPDS-infographic_MED.pdf). This analysis excludes 43 medicinal products that were withdrawn worldwide.

2.3.5 Interval between launch year and first reported adverse drug reaction

The median interval between launch year and the year in which an adverse reaction was first reported was 8 years (IQR = 2 to 20 years) for all the medicinal products and 5 years (IQR = 2 to 11 years) for products launched after 1950. The more recent the launch date of a drug, the quicker a report of an adverse reaction appeared in the literature (Figure 2.2). A similar trend was observed for products launched after 1950. At least 5 years elapsed before the first report of an adverse drug reaction appeared in the literature in 49% of instances.

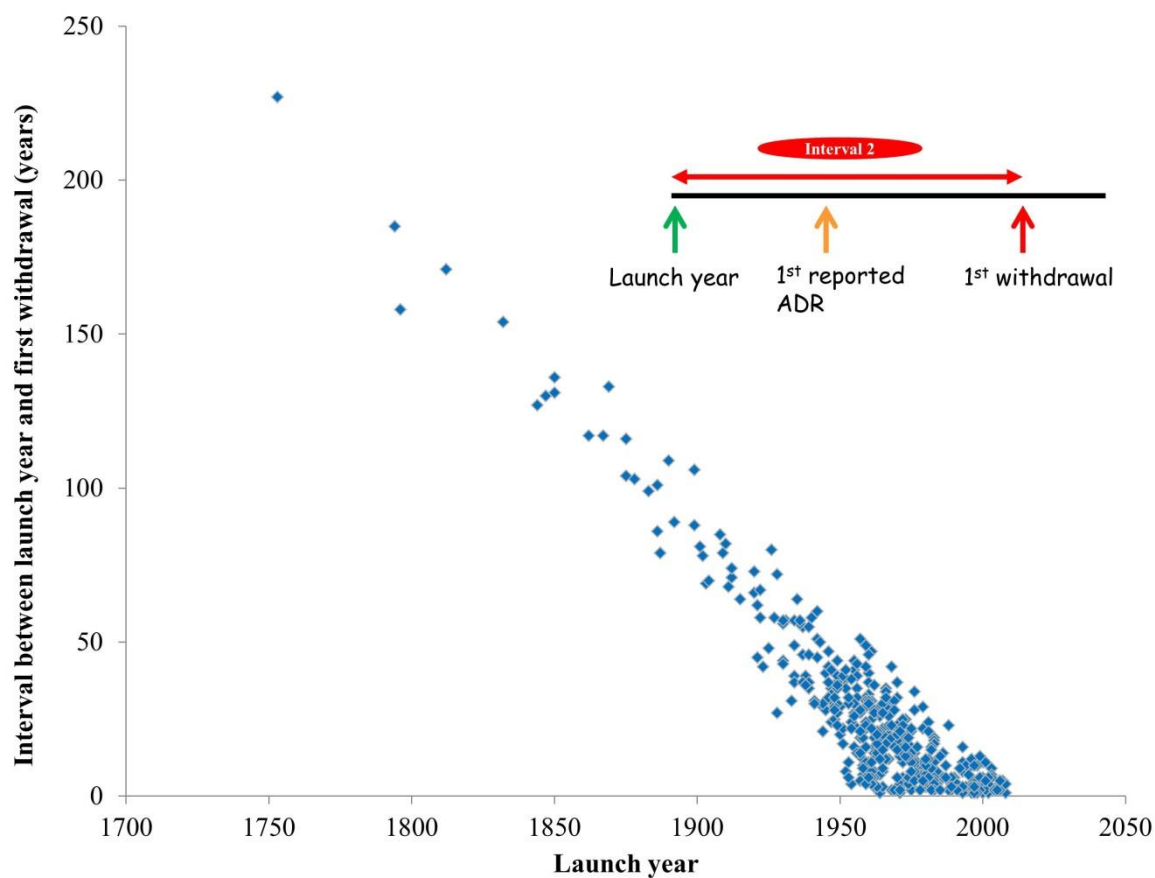
Figure 2.2: Time lapse between launch year and first reported adverse drug reaction (ADR)



2.3.6 Interval between launch year and first withdrawal

The median interval between first launch and first withdrawal was 18 years (IQR = 6 to 34 years) for all the medicinal products and 12 years for products introduced after 1950 (IQR = 5 to 23 years). There were trends towards shorter delays between the year of first launch and the year of first withdrawal for all 462 products and for the 354 products launched after 1950 (Figure 2.3). The interval between launch and withdrawal was over 5 years in 70% of instances.

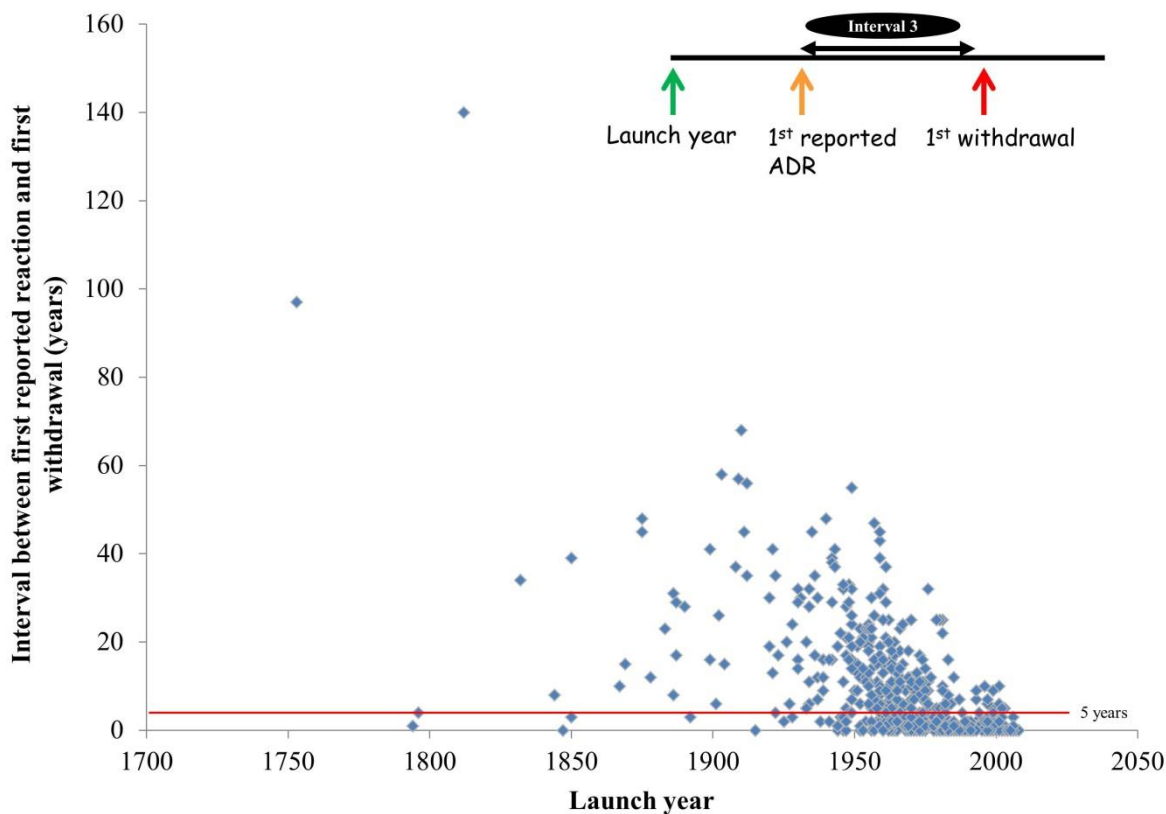
Figure 2.3: Time lapse between launch year and date of first withdrawal



2.3.7 Interval between the first reported adverse drug reaction and the first withdrawal

The median interval between the first reported adverse reaction and the year of first withdrawal was 6 years (IQR = 1 to 15 years) for all the medicinal products and 4 years for products launched after 1950 (IQR = 1 to 10 years). Figure 2.4 shows that there was a trend towards a shorter interval between the first reported adverse reaction and the first withdrawal. However, for products launched after 1950, there was no consistently shorter trend. Similar results were observed when we examined the delays to withdrawal after reports of adverse drug reactions in each of the six continents separately (data not shown).

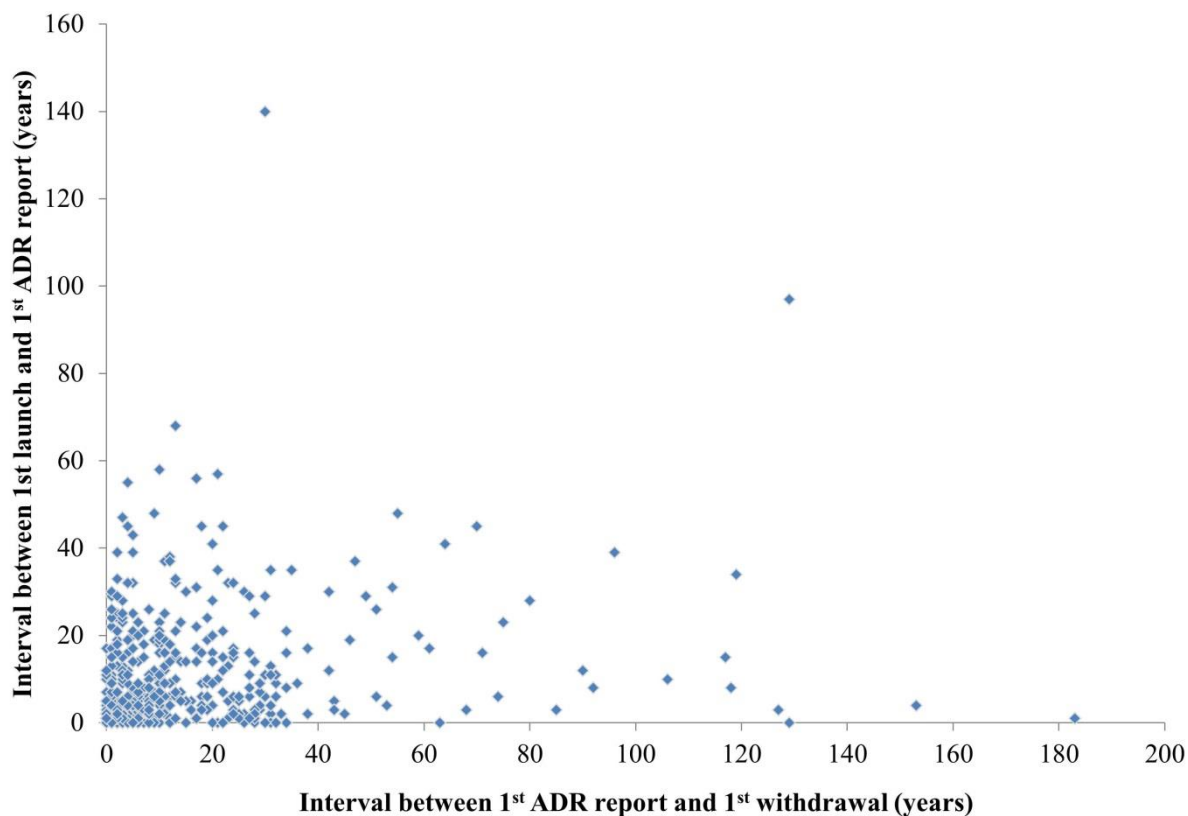
Figure 2.4: Time lapse between first adverse drug reaction (ADR) report and the date of first withdrawal



2.3.8 Relation between time of launch to first adverse drug reaction report *versus* the interval between the first adverse drug reaction report and the first withdrawal

Figure 2.5 shows that quicker reports of adverse drug reactions were not associated with a corresponding shortening of the time to regulatory action following such reports. This finding was also observed when medicinal products launched after 1950 were analysed separately.

Figure 2.5: Time lapse between first launch and first ADR report (Interval 1) versus time to withdrawal after first ADR report (Interval 3)



2.4 DISCUSSION

A total of 462 medicinal products have been withdrawn because of adverse drug reactions. The withdrawals occurred between 1953 and 2013. Hepatotoxicity and immune-mediated reactions were responsible for over 30% of withdrawals. Withdrawals were significantly less common in Africa than in Asia, Europe, and North and South America.

2.4.1 Evidence for withdrawal

Case reports were most often used as evidence on which withdrawal decisions were based: 71% of all the products, 70% of those launched after 1950, and 66% of those launched

after 1960. This suggests that formal studies are often not conducted when adverse drug reactions are reported anecdotally [15]. However, the frequency with which anecdotal reports have provided the dominant source of information has reduced with time, from 85% in the 1950s to 64% in the 1990s; since 2000 the frequency has fallen even further, to 35%, but the number of products affected during the last few years is relatively small. It is worth noting that while case reports are regarded as low levels of evidence, they are quite useful in detecting new adverse reactions, e.g., cases of serious adverse reactions where formal conduct of confirmatory studies may be unethical or time consuming. Expedited reviews of adverse reactions could be conducted if there is still uncertainty about the drug-adverse event relationship.

2.4.2 Patterns of withdrawal

There were significantly fewer withdrawals in Africa than in the other five continents. This suggests that there is better co-ordination among drug regulatory authorities in those geographical regions than in Africa. Furthermore, the delays between the first report of an adverse reaction and first withdrawal were more often than not longer in African countries than in Europe or North America, which were not significantly different from each other. Thus, harmful drugs are likely to stay on the market for longer in Africa.

There was a lower rate of withdrawal in African countries than elsewhere. Factors that can affect withdrawals include the strength of a local regulatory agency, and the availability of proper monitoring facilities or preventive strategies. According to the World Health Organization (WHO), only 4% of African nations have moderately developed pharmacovigilance systems and 39% lack adequate regulatory capacity [16]. Furthermore, the ability of a country to restrict access to harmful drugs is related to per caput gross

national product [17], and this contributes to the so-called medical poverty trap (increases in overall out-of-pocket expenses for health care in families who are already poor) [18].

2.4.3 Delays between launch dates and reports of adverse drug reactions

The interval between first launch and first report of adverse reactions has shortened over time (Figure 2.2). This is probably largely due to improved pharmacovigilance methods including the use of case-control networks and electronic health records [19]; observational phase IV trials [20], collaboration between PV databases [21], prescription event monitoring [22], use of web-based tools that collect primary information from patients [23], and improved quality of adverse reaction reporting in the published literature [24]. However, at least 5 years elapsed before the first report of an adverse drug reaction in 31% of instances for products launched after 1960. This suggests that detection of adverse reactions to approved medicinal products has improved with developments in drug regulation, but the improvements have not been substantial. This may be attributable to a variety of factors such as selective reporting of benefits and harms in clinical trials [25], and flawed regulatory assessment procedures [26]. These have led to calls for changes to current drug adverse event monitoring strategies [27,28]. Regulatory assessment of clinical trials data of medicinal products is seldom conducted in many African countries, where the drug regulatory processes are geared to grant marketing licences for imported products that have been assessed in other places and populations [29].

Under-reporting of adverse drug reactions

Under-reporting of adverse drug reactions could cause delays in making withdrawal decisions. There is evidence that clinicians selectively report adverse drug reactions [30,31], and the authors of a review of hospital admissions due to adverse drug reactions

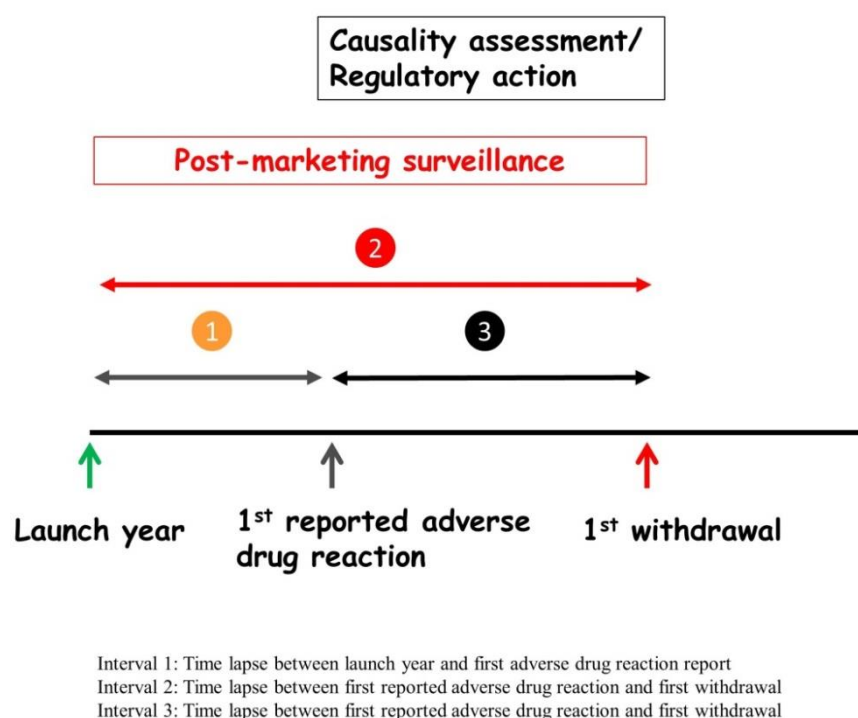
concluded that physicians seldom report such events when they occur [32]. A low rate of reporting among health-care professionals could be due to poor knowledge of how to use the spontaneous reporting systems [33], conflicts of interest [34], forgetfulness, lack of time, and uncertainty about causal relationships between drugs and adverse events [35]. Proactive measures to encourage physicians to report suspected adverse drug reactions have been suggested [36]. Indeed, provision of economic incentives and/or educational activities improves the reporting of adverse drug reactions among hospital clinicians [37,38,39,40,41]. Patients are also likely to under-report suspected adverse reactions to medications [42], and empowerment of patients has been advocated [43,44].

2.4.4 Delays to withdrawals after reports of adverse drug reactions

There was no consistent reduction in the interval between the first report of an adverse drug reaction and the first withdrawal from the market (Figure 2.5). This suggests that the shortened interval between the first launch and the first withdrawal was largely due to a shortening in the interval between the first launch and the first report of an adverse reaction. Therefore, difficulty in assessing causality and inconsistencies in how regulatory actions are enforced after reports of suspected adverse drug reactions could explain the observed delays and discrepancies (see Figure 2.6); this is corroborated by the absence of a relationship between the interval between first launch and first adverse drug reaction report (Interval 1) *versus* the interval between first adverse drug reaction report and first withdrawal (Interval 3) (Figure 2.5). It should be noted that from 1985 onwards, over 80% of withdrawals occurred within 5 years of initial adverse reactions reports compared with just over 50% for the 462 products; this suggests that the delays to withdrawal following reports of adverse reactions has generally improved since the thalidomide incident of the 1960s [45]. Difficulties in determining causality in part explain why drugs are withdrawn

in one country but remain available in another. The need to develop universally accepted methods for diagnosing adverse drug reactions through modification, improvisation, or combination of existing tools and/or algorithms has been suggested [46,47]; whether it is feasible to tailor these methods to suit specific settings is unclear and warrants further investigation.

Figure 2.6: Schematic diagram of the intervals following the launch of a medicinal product. The shortening in interval 2 is largely due to a shortening in interval 1.



2.4.5 Frequency of withdrawals compared with overall new drug approvals

The number of withdrawn medicinal products is probably only a small fraction of overall approvals. As examples, less than 2% of new drug approvals by the FDA between 1950 and 2011 have been withdrawn [48] and 3% of approved products in Canada and the USA

between 1992 and 2011 were withdrawn [49]. This suggests that drug regulatory authorities have made considerable efforts at ensuring that harmful drugs are not marketed.

2.4.6 Comparison with previous studies

This analysis confirms and extends the result of previous studies, all of which have been considerably smaller and of more limited time spans. This chapter also documents the levels of evidence used for making the withdrawal decisions, analysed time courses, and included data from African countries, not previously reported.

For example, an analysis of 19 medicinal products withdrawn in Europe between 2002 and 2011 showed that case reports were commonly used to justify withdrawal decisions, but less so with time [50]. A review of 22 products withdrawn in Spain between 1990 and 1999 showed that case reports were most commonly cited as evidence for withdrawal [51]. An analysis of 21 products withdrawn in France between 1998 and 2004 concluded that case reports were the most commonly used for making withdrawal decisions [52]; similar findings were observed for another series of 22 products withdrawn between 2005 and 2011 [53]. Another review of 121 withdrawn products showed that hepatotoxicity, cardiotoxicity, and carcinogenicity were the commonest reasons for withdrawals between 1960 and 1999 [54]. There were inconsistencies in the patterns of withdrawal of 26 products between 1971 and 1992 in the UK and the USA [55] and in drug withdrawal policies across countries [56], although an earlier study of 24 products suggested consistency in withdrawal patterns between the UK and USA from 1964 to 1983 [57]. In a study of 22 products withdrawn in Canada between 1990 and 2009 the median interval between approval and withdrawal was 3.5 (IQR 1.9–7.9) years [49]; the data in this

chapter, analysed over the same period, show a value of 3 (IQR 1 to 6) years (n=72). The results are therefore consistent with all of these findings.

2.4.7 Strengths and limitations

An extensive range of sources was searched to identify medicinal products withdrawn because of adverse reactions, the level of evidence on which the withdrawal decisions were based was documented. In addition, data was accessed from a variety of sources. However, some limitations are recognized. Data was not accessed from other sources (e.g. Index Medicus or journal editorials) that could have been used to verify launch year, first adverse reaction report or first withdrawal dates, especially for products introduced between 1800s and 1950 when access to the scientific literature was limited. There is no information on the delay between the actual occurrence of an adverse drug reaction due to a medicinal product and the date it first appeared in the literature. Nevertheless, such delays are unlikely to have significantly influenced the results. There is no data from countries in Africa that are blighted by armed conflict, e.g. Burundi, the Central African Republic, and Somalia; indeed, I did not identify any information on withdrawn medicinal products from these countries in the WHO drug lists. Furthermore, as of 2009, over half of all African countries did not have a drug regulatory website [58]. Data from non-English drug regulatory websites were not accessed; however, it is unlikely that the information from such sites would significantly alter the results, since a majority of such countries report their data to the WHO. In addition, the accuracy of the information from the databases used to document launch and withdrawal dates has not been assessed, but information from other selected texts was used to check for any inconsistencies. There is no data on countries in which withdrawn drugs were approved by regulatory authorities, where such exist; this difficulty has previously been reported by other authors [54]. Although the

results suggest that harmful drugs are more likely to remain in Africa for a longer period before withdrawal compared to the other continents, there was no information on when the products were specifically introduced into African countries; the extent to which the year of launch could have influenced the interval to withdrawal between Africa and the other continents is uncertain.

All medicinal products withdrawn in association with adverse drug reactions may not have been identified because of the possibility of negative publication bias, and consequently it is not known how many patients in all were affected by adverse reactions. This could also have influenced the speed with which regulatory decisions were taken. Some medicines are available only on prescription in some regions and may be available over the counter elsewhere. For example, antibiotics are generally available as prescription-only medicines in the UK [59]. In contrast, the results of surveys in Nigeria showed that self-medication with antibiotics and antimalarial drugs was common both in the general public and among health-care workers [60,61].

2.5 CONCLUSIONS

The interval between launch date and reports of adverse drug reactions has shortened over the past few decades, perhaps because of better reporting of suspected adverse reactions or stricter regulation. In addition, increasing numbers of individuals may have been exposed to the withdrawn products in recent years, leading to quicker detection of adverse reactions. However, withdrawal of products following reports of suspected adverse reactions, sufficiently serious to warrant withdrawal, has not improved consistently over the last 60 years. In addition, harmful drugs are less likely to be withdrawn in African countries. Greater co-ordination among drug regulatory authorities and increased

transparency in the reporting of suspected adverse drug reactions would help improve decision-making processes.

2.6 Chapter Summary

- 462 medicinal products have been withdrawn from the market because of adverse reactions since 1950, the most common reason being hepatotoxicity
- Case reports were cited as evidence for withdrawal in over 70% of instances
- Withdrawal was significantly less likely in Africa than in other continents
- The interval between launch dates and first ADR reports have decreased consistently over time, but this is less so for the delays to withdrawals following the ADR reports
- Greater co-ordination among drug regulatory authorities and increased transparency in reporting suspected adverse drug reactions would help improve current decision-making processes

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Chapter 3 Post-marketing withdrawal of medicinal products from the market because of drug-attributed deaths: a systematic review

3.1 INTRODUCTION

Drug regulatory authorities grant marketing authorizations that license pharmaceutical companies to market medicinal products when there is sufficient evidence that the product has a favourable benefit-to-harm balance [1]. If a new adverse drug reaction is suspected after approval, several courses of action can be taken by the regulator and/or manufacturer. These include adding a new product label with specific warnings [2]; adding a new contraindication [3]; issuing a Direct Healthcare Professional Communication (DPHC) [4]; allowing patients to decide whether they will take the drug [5]; and in the most serious cases, withdrawal or revocation of the licence [6].

The marketing authorization holder (MAH) may take some of these actions themselves without being required to do so by the regulators. When the final regulatory action would be to suspend or revoke the licence, the MAH sometimes withdraws a drug voluntarily before being forced to by the regulator. These options are not mutually exclusive and can be undertaken sequentially or in parallel, depending on the case and urgency.

In the previous chapter, the patterns of post-marketing withdrawal of medicinal products because of any type of adverse reaction were examined, irrespective of the intensity of such reactions. When a medicinal product is found to cause death as an adverse reaction, one would expect expedited investigation of the problem and, when indicated, withdrawal of the product from the market. However, the relation between occurrences of deaths and the time to withdrawal of responsible products has not hitherto been studied.

Building on the findings in Chapter 2 and a preliminary analysis of 284 medications that have been withdrawn or had major changes to their labels following reports of adverse drug reactions, including deaths [7], the objectives of this chapter were to identify medicinal products that were withdrawn in the last 60 years in association with deaths, searched for the evidence on which the withdrawal decisions were based, and analysed the delays and the worldwide patterns of post-marketing withdrawals.

The terms “withdrawal” and “withdrawn” indicate that the product has either been voluntarily withdrawn by the MAH or had its licence revoked by a regulatory agency. Other terms that are sometimes used to describe the latter include “banned”, “prohibited”, “recalled”, and “not [i.e. no longer] approved”.

3.2 METHODS

3.2.1 Search strategy

The first reviewer (IJO) used the same search strategy as in chapter 1 to identify products for which death was documented as a reason for withdrawal between 1950 and December 2015, from the following sources:

- the World Health Organization’s (WHO’s) database of Consolidated List of Products whose consumption and/or sale have been banned, withdrawn, severely restricted, or not approved by governments (Issues 6, 8, 12 and 14);
- the WHO’s Drug Information (Volumes 1–28);
- the WHO’s Pharmaceuticals Newsletter (1997–2015);
- the database of withdrawn drugs of the European Medicines Agency (EMA);
- the website of the UK Medicines and Healthcare products Regulatory Agency (MHRA);

- the website of the US Food and Drug Administration (FDA);
- PubMed, MEDLINE, and Google Scholar, using search terms including “drug withdrawal”, “fatal*”, “death(s)”, “voluntary recall”, “prohibited”;
- *Meyler’s Side Effects of Drugs* volumes 1–8 and editions 9–15 and the *Side Effects of Drugs Annuals* 1–36;
- *Stephens’ Detection of New Adverse Drug Reactions*, 5th edition [8].

[See appendix 1 for full search strategy].

3.2.2 Inclusion/exclusion criteria

To be included in the review, a product must have had death documented as a reason for withdrawal, irrespective of whether the deaths had occurred at therapeutic or toxic doses. Medicines that had previously been withdrawn in association with deaths but had been re-introduced or made available in other, safer, formulations were included. Products for which death was not specifically mentioned as a reason for withdrawal from the market were excluded, as were non-human medicines, herbal products, and non-prescription medicines.

3.2.3 Assessing the types of evidence

The highest levels of available evidence for reports of deaths related to the withdrawn drug were documented using the tool kit of the Oxford Centre for Evidence-based Medicine [9]. The first reviewer (IJO) documented the levels of evidence and a second reviewer (JKA) verified them independently. When there were discrepancies in the documented levels of evidence, both reviewers re-checked the data together and arrived at a consensus through discussion.

3.2.4 Data extraction

For each withdrawn product, the first reviewer (IJO) extracted data on: the date of marketing authorization, launch date, or date of first recorded use; the drug class or therapeutic indication [10]; the date of the first reported death; the first withdrawal date; the country or countries of withdrawal, even if death was not reported as a reason for withdrawal in all the countries; and the reported mechanism by which the drug resulted in death – these were independently verified by a second reviewer (JKA). It was assumed that if death was reported as a reason for withdrawal in at least one country, that was sufficient for inclusion of other countries in which the drug had been withdrawn, since it was likely to have caused deaths elsewhere, even if not cited as such. When the exact launch date of a drug was not available (two cases), its first record of use in humans, based on a PubMed search, was used as its launch date. The WHO Consolidated List was used as the primary source of information for dates of first launch and first withdrawal (if reported). These dates were cross-checked with the corresponding dates from the other sources listed above.

3.2.5 Statistical analysis

Medians and interquartile ranges (IQR) were used as the measure of central tendency and spread to report the intervals between launch year, the year of first reported death, and the first year of withdrawal. The intervals between products withdrawn because of deaths caused by overdose *versus* products withdrawn because of deaths caused at therapeutic doses were compared. Scatter plots were used to explore the relationship between launch years and delays to first reports of death or first withdrawal, and Pearson's chi-square tests used to compare differences in the frequencies of withdrawals within one year of the report of death; P values <0.05 were considered statistically significant.

3.3 RESULTS

A total of 118 medicinal products withdrawn because of drug-attributed deaths were identified (Figure 3.1). Out of these, one product was excluded because it was withdrawn before regulatory approval and three because they were herbal therapies. Finally, 114 products for which death was documented as a reason for withdrawal were included. Most of the drugs were used to treat neurological or psychiatric disorders ($n = 28$) or as analgesics or anti-inflammatory drugs ($n = 26$); 15 were used for cardiorespiratory disorders and 13 were antimicrobial drugs. The withdrawals occurred between 1957 and 2011. [The details of the withdrawn products are available in Table 3.1].

Figure 3.1: Schematic diagram showing the process for inclusion of medicinal products withdrawn from the market because of drug-attributed deaths

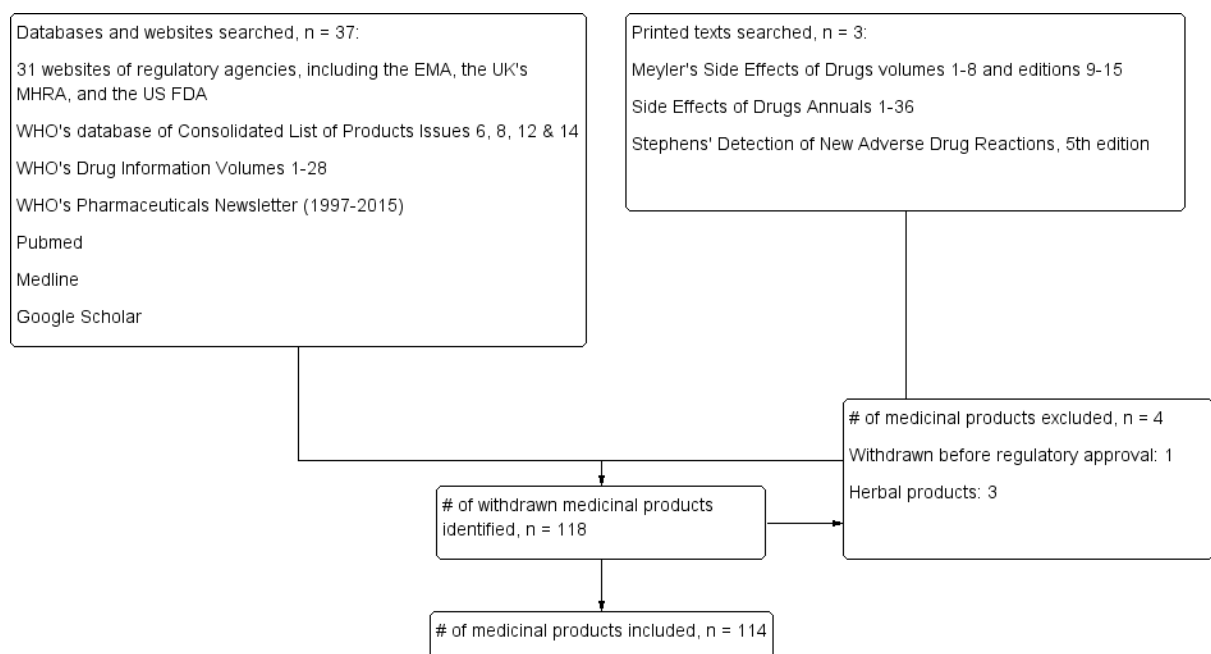


Table 3.1: List of medicinal products withdrawn from the market because of drug-attributed deaths

Medicinal product	Class	Launch year	First death reported	Year first withdrawn*	Countries of withdrawal ^{†‡}	Death attributed to	Level of evidence [§]
Alosetron	Antispasmodic	2000	2000	2000	USA; re-introduced with restrictions in 2002	Ischaemic colitis	4
Alpidem	Anxiolytic	1991	1994	1994	France	Hepatotoxicity	4
Aminophenazone	Analgesic	1887	1936	1965	10 European, 14 Asian, & 4 African countries; Australia; USA; Chile; Brazil; Venezuela	Agranulocytosis	4
Amobarbital [¶]	Sedative-hypnotic	1961	1979	1985	Sweden	Respiratory depression	4
Aprobarbital [¶]	Sedative-hypnotic	1920	1966	1985	Sweden	Respiratory depression	4
Azaribine	Antipsoriatic	1975	1976	1976	USA; Thailand; Mauritius; Saudi Arabia; Venezuela	Thromboembolism	4
Beclobrate	Antilipemic	1985	1990	1990	Switzerland	Hepatotoxicity	4
Benfluorex	Hypoglycaemic	1976	2003	2009	Europe	Cardiotoxicity	3
Benoxaprofen	Analgesic	1980	1982	1982	Worldwide	GI haemorrhage	4
Benzarone	Thrombolytic	1964	1992	1992	Germany	Hepatotoxicity	4
Benzyl alcohol	Antimicrobial	1972	1981	1982	Israel, USA, Oman, Iraq	Metabolic acidosis	4
Bezitramide [¶]	Analgesic	1961	1983	2004	Netherlands	Overdose	4
Bicalutamide (150 mg)	Chemotherapeutic agent	1995	2001	2003	Canada, UK	“Accelerated deaths”	2
Bismuth salts	Antidyspepsia	1875	1930	1978	France; Egypt; Japan; Greece; Austria; Bangladesh	Cardiotoxicity, neurotoxicity	4
Boric acid and borates	Antimicrobial	1875	1945	1981	Ireland; Malaysia	Neurotoxicity	4
Bromfenac Na	Analgesic	1997	1998	1998	USA, Saudi Arabia	Liver	4
Bromocriptine mesylate	Prolactin inhibitor	1976	1995	1994	USA	Cardiotoxicity, neurotoxicity	4
Buflomedil	Vasodilator	1970	1981	2006	France, Europe	Neurotoxicity, cardiotoxicity	4
Buformin	Hypoglycaemic	1957	1976	1978	Germany; Belgium; Ireland; Austria	Metabolic acidosis	4

Bunamiodyl	Radiography	1958	1962	1964	USA, Sweden	Nephrotoxicity	4
Buprenorphine [§]	Analgesic	1978	1991	1986	Egypt	Respiratory depression	4
Celecoxib	Analgesic	1999	2006	2011	European Union	Cardiotoxicity	1
Cell preparations	Antiageing	1931	1957	1987	Austria, Germany, Switzerland	Immunologic	4
Cerivastatin	Antilipemic	1990	1998	2001	Worldwide	Rhabdomyolysis; renal failure	4
Cianidanol	Antioxidant	1976	1985	1988	Worldwide	Haemolytic anaemia	4
Cisapride monohydrate	Prokinetic agent	1993	1993	2000	USA; UK; Canada; Philippines; Mauritius; Brunei; Armenia	Cardiotoxicity	4
Clofibrate	Antilipemic	1967	1973	1978	Germany, Israel, Norway, Bangladesh	Accelerated deaths	4
Clometacin	Analgesic	1977	1981	1987	France	Hepatotoxicity	4
Clozapine	Antipsychotic	1972	1975	1975	USA; Finland	Agranulocytosis	4
Coumarin (synthetic)	Anticoagulant	1996	1996	1996	France; Australia	Hepatotoxicity	4
Dextropropoxyphene + paracetamol (co-proxamol) [¶]	Analgesic	1978	1987	2005	UK	Respiratory depression; cardio- and hepato-toxicity	4
Dibenzepin hydrochloride [¶]	Antidepressant	1968	1973	1983	Sweden	Cardiotoxicity	4
Diiododiethyltin & isolinoleic ester	Antimicrobial	1954	1955	1957	France	Cerebral oedema	4
Dithiazanine iodide	Anthelmintic	1959	1960	1964	USA; France; Chad; Italy; Cuba	Metabolic acidosis	4
Domperidone (Inj)	Propulsive	1979	1982	1985	Worldwide	Cardiotoxicity	4
Doxycycline (IV)	Antimicrobial	1960	1984	1989	France	Anaphylaxis	4
Ebrotidine	Anti-ulcer	1997	1997	1998	Spain; Peru	Hepatotoxicity	4
Encainide	Antiarrhythmic	1980	1991	1991	UK	Cardiotoxicity	4
Ethyl nitrite	Antimicrobial	1850	1977	1980	USA	Methaemoglobinemia	4
Felbamate	Anti-epileptic	1993	1993	1994	USA, European Union	Hepatotoxicity; aplastic anaemia	2
Fenclofenac	Analgesic	1978	1984	1985	Worldwide	Toxic epidermal necrolysis	4
Fenoterol	Beta-2 adrenoreceptor agonist	1971	1987	1990	New Zealand	Increased mortality due to asthma	3

Fentanyl [†]	Analgesic	2006	2006	2009	Europe	Risk of overdose	4
Fipexide	Nootropic	1973	1992	1991	France	Hepatotoxicity	4
Flosequinan	Vasodilator	1992	1992	1993	UK	Cardiotoxicity	2
Gemtuzumab ozogamicin	Monoclonal antibody	2000	2010	2010	USA	Accelerated deaths	2
Grepafloxacin	Antimicrobial	1997	1999	1999	Worldwide	Cardiotoxicity	2
Heptabarb [†]	Sedative-hypnotic	1956	1984	1984	Sweden	Respiratory depression	4
Hexobarbital [†]	Barbiturate	1945	1962	1984	Sweden	Respiratory depression	4
Indoprofen	Analgesic	1976	1982	1983	Worldwide	Gastrointestinal haemorrhage	4
Interferon-gamma-1b	Immunomodulator	2002	2007	2007	USA	Accelerated deaths	2
Isaxonine phosphate	Neurotrophic	1981	1983	1984	France	Hepatotoxicity	4
Isoxicam	Analgesic	1983	1985	1985	Worldwide	Fatal skin reactions	4
Ketoconazole	Antimicrobial	1976	1981	2013	Europe, Australia	Hepatotoxicity	4
Ketorolac injection	Analgesic	1990	1993	1993	Germany; France	Gastrointestinal haemorrhage	4
Levamisole	Anthelmintic	1966	1978	1999	US, Canada, Vietnam	Haematologic, nervous system	3
Loperamide (syrops & drops)	Antidiarrhoeal	1975	1989	1990	Worldwide	Paralytic ileus	4
Loxoprofen	Analgesic	1983	1993	2000	Singapore	Colonic ulceration	4
L-tryptophan	Antidepressant	1963	1989	1989	Worldwide	Eosinophilia- myalgia syndrome (EMS)	3
Lumiracoxib	Analgesic	2007	2007	2007	Australia, USA, Canada, Europe, New Zealand, Brazil, Philippines, Colombia	Liver	4
Metamizole	Analgesic	1921	1952	1974	7 European and 11 Asian countries; Australia; USA; Ghana; Zimbabwe; Morocco	Agranulocytosis	4
Mibefradil	Antihypertensive	1997	1998	1998	USA; UK; Peru; South Africa; Jamaica; Bulgaria; Armenia	Drug interactions	4
Muzolimine	Antihypertensive	1985	1987	1987	Worldwide	Nephrotoxicity	4
Naftidrofuryl	Vasodilator	1984	1994	1995	France; Germany;	Anaphylaxis	4

oxalate IV					restricted in the UK		
Nebacumab	Monoclonal antibody	1991	1993	1993	Worldwide	“Accelerated deaths”	2
Nefazodone	Antidepressant	1994	2002	2003	European Union; Canada; Singapore	Hepatotoxicity	4
Nimesulide	Analgesic	1986	2000	2002	Ireland; Israel; Bangladesh; Spain	Hepatotoxicity	4
Nitrefazole	Anti-addiction	1980	1984	1984	Germany; Austria	Hepatotoxicity	4
Nomifensine	Antidepressant	1976	1985	1986	Worldwide	Haemolytic anaemia	4
Opium (in antitussives)	Antitussive	1812	1842	1982	Bangladesh, Italy	Drug dependence	4
Orgotein	Antiinflammatory	1968	1990	1990	Switzerland; Germany; Portugal	Anaphylaxis	4
Osmosin (indometacin)	Analgesic	1975	1983	1983	UK	Gastrointestinal haemorrhage	4
Oxomemazine [†]	Antitussive	1937	1979	1991	European Union; USA	Respiratory depression in children (SIDS)	4
Oxyphenbutazone	Analgesic	1955	1974	1984	Worldwide	Bone marrow suppression	4
Oxyphenisatine acetate	Laxative	1955	1972	1970	Worldwide	Hepatotoxicity	4
Pemoline	Psychostimulant	1975	1989	2005	Worldwide	Hepatotoxicity	4
Pentobarbital [†]	Barbiturate	1930	1953	1985	Sweden	Respiratory depression	4
Phenformin HCl	Hypoglycaemic	1957	1963	1970	14 European & 3 Asian countries; Canada; New Zealand; Brazil; USA; Ethiopia	Metabolic acidosis	4
Phenobarbital [†]	Barbiturate	1912	1929	1985	Sweden	Respiratory depression	4
Phenylbutazone	Analgesic	1949	1953	1984	6 European, 6 Asian & 3 African countries; Chile	Bone marrow suppression	4
Pirprofen	Analgesic	1982	1986	1990	Worldwide	Hepatotoxicity	4
Practolol	Antihypertensive	1970	1977	1994	Germany; Norway; Venezuela	Hypersensitivity	4
Prenylamine	Vasodilator	1960	1988	1989	Worldwide	Cardiotoxicity	4
Propofol (children)	Anaesthetic	1987	1992	1992	Israel, Norway, UK, Lithuania	Metabolic, hepatic, nervous	4

Propyphenazone	Analgesic	1951	1986	1989	Turkey, UAE, Bahrain, Ireland	Haematologic, Immunologic: Lyell's syndrome	4
Pumactant	Surfactant	1992	2000	2000	UK	"Accelerated deaths"	2
Rapacuronium bromide	Anaesthetic	1999	2000	2001	USA	Bronchospasm	4
Rimonabant	Psychostimulant	2006	2006	2007	Europe, India	Psychiatric	1
Rofecoxib	Analgesic	1999	2002	2004	Worldwide	Cardiotoxicity	1
Rosiglitazone	Hypoglycaemic	1999	2007	2011	UK; New Zealand; South Africa	Cardiotoxicity	1
Santonin	Anthelmintic	1911	1940	1978	Singapore	Neurotoxicity	4
Sertindole	Antipsychotic	1996	1996	1998	UK, Bulgaria	Cardiotoxicity	2
Sibutramine	Centrally-acting anti-obesity product	2001	2002	2010	European Union; 4 Asian countries; Australia; Canada; Mexico; New Zealand; USA	Cardiotoxicity	4
Sitaxentan sodium	Antihypertensive	2006	2002	2010	Worldwide	Hepatotoxicity	4
Somatropin (pituitary-derived)	Hormones	1973	1985	1985	Cyprus; Ireland; UK; Egypt; Turkey; New Zealand; Netherlands; USA; Oman	Creutzfeldt-Jakob disease	4
Sorivudine	Antimicrobial	1993	1993	1993	Germany; Japan	Interaction with 5-fluorouracil	4
Sulfadimethoxine	Antimicrobial	1958	1961	1966	USA	Skin	4
Suloctidil	Vasodilator	1975	1983	1985	Worldwide	Hepatotoxicity	4
Technetium (99mTc) fanolesomab	Radiography	2004	2005	2005	USA	Cardiotoxicity	4
Temafloxacin	Antimicrobial	1991	1992	1992	Worldwide	Haemolytic anaemia	4
Temazepam (gel capsules) [†]	Benzodiazepine	1969	1992	2004	Australia	Respiratory depression	3
Terfenadine	Antihistamine	1985	1991	1997	3 European, 2 African, 2 Asian & 3 South American countries; USA	Cardiotoxicity	4
Terodiline	Antispasmodic	1965	1989	1991	Worldwide	Cardiotoxicity	4
Thenalidine	Antihistamine	1953	1958	1958	USA; UK; Sweden; France; Cyprus; Australia; Finland; Norway	Neutropenia	4

Tienilic acid	Antihypertensive	1976	1980	1980	Greece; Philippines; USA; Brazil; Germany; Panama; France; India; Venezuela	Hepatotoxicity	4
Tocainide	Antiarrhythmic	1981	1986	1986	USA	Haematologic: agranulocytosis, aplastic anaemia	4
Tolcapone	Antiparkinsonian	1998	1998	1998	UK; Australia; Ireland; Spain; Portugal; Lithuania; Bulgaria	Hepatotoxicity	4
Tolrestat	Hypoglycaemic	1982	1995	1996	Worldwide	Hepatotoxicity	2
Troglitazone	Hypoglycaemic	1997	1997	1997	UK; Switzerland; Peru	Hepatotoxicity	4
Trovafloxacin	Antimicrobial	1997	1996	1999	European Union; Philippines; Syria	Hepatotoxicity	2
Vinbarbital [†]	Sedative-hypnotic	1939	1975	1984	Sweden	Respiratory depression	4
Vitamin E (IV)	Hematinic	1983	1984	1984	USA	Hepatotoxicity	4
Zipeprol HCl [†]	Antitussive	1982	1991	1993	Brazil; Philippines	Respiratory depression	4
Zomepirac	Analgesic	1979	1983	1983	Worldwide	Anaphylaxis	4

*For any reason; some drugs have been withdrawn for one or more indications but not for others

[†]The European Union refers to the European Medicines Agency member states; European, African, Asian, or South American countries refers to nations geographically located in these regions

[‡]Worldwide = in all countries in which it was marketed

[§]Drugs withdrawn because of fatal intoxication

[§]Based on the Oxford Centre for Evidence-Based Medicine Levels of Evidence [9]. Level 1: Systematic review of randomized trials, systematic review of nested case-control studies, Level 2: Individual randomized trial or (exceptionally) observational study with dramatic effect; Level 3: Non-randomized controlled cohort/follow-up study (post-marketing surveillance); Level 4: Case-series, case-control, or historically controlled studies; Level 5: Mechanism-based reasoning

3.3.1 Types of adverse reactions

Cardiotoxicity (n = 19), hepatotoxicity (n = 29), and respiratory depression (n = 12, all of which were attributed to overdose with central nervous system depressants), accounted for 53% of withdrawals. Two drugs (mibefradil and sorivudine) were withdrawn because interactions with other medications resulted in deaths. Nine products (bicalutamide 150 mg, clofibrate, fenoterol, flosequinan, gemtuzumab, interferon-gamma-1b, nebacumab, and pumactant) were withdrawn because their use was reportedly associated with increased mortality.

Boric acid was withdrawn because of deaths from systemic absorption associated with its use as a topical antiseptic. Pituitary-derived somatropin was withdrawn because of deaths due to Creutzfeldt–Jakob disease. L-tryptophan was withdrawn because of the eosinophilia–myalgia syndrome with resultant deaths.

3.3.2 Levels of evidence used for product withdrawals

The evidence for withdrawal in most cases came from case reports (94/114; 82%). In five cases (4%) the evidence was based on the results of case-control studies and in 11 cases (10%) on randomized controlled comparisons. The highest levels of evidence were cited for the withdrawal of evidence for withdrawal of four products (4%).

3.3.3 Patterns of withdrawals

At least 40% of the drugs were withdrawn in more than one country, but only 26 (23%) were reportedly withdrawn “worldwide” (i.e. in all the countries in which they had been marketed). Sixteen products continued to be marketed in some countries, despite having

been withdrawn in at least two others. Fifteen products (13%) were withdrawn because they caused deaths after overdose.

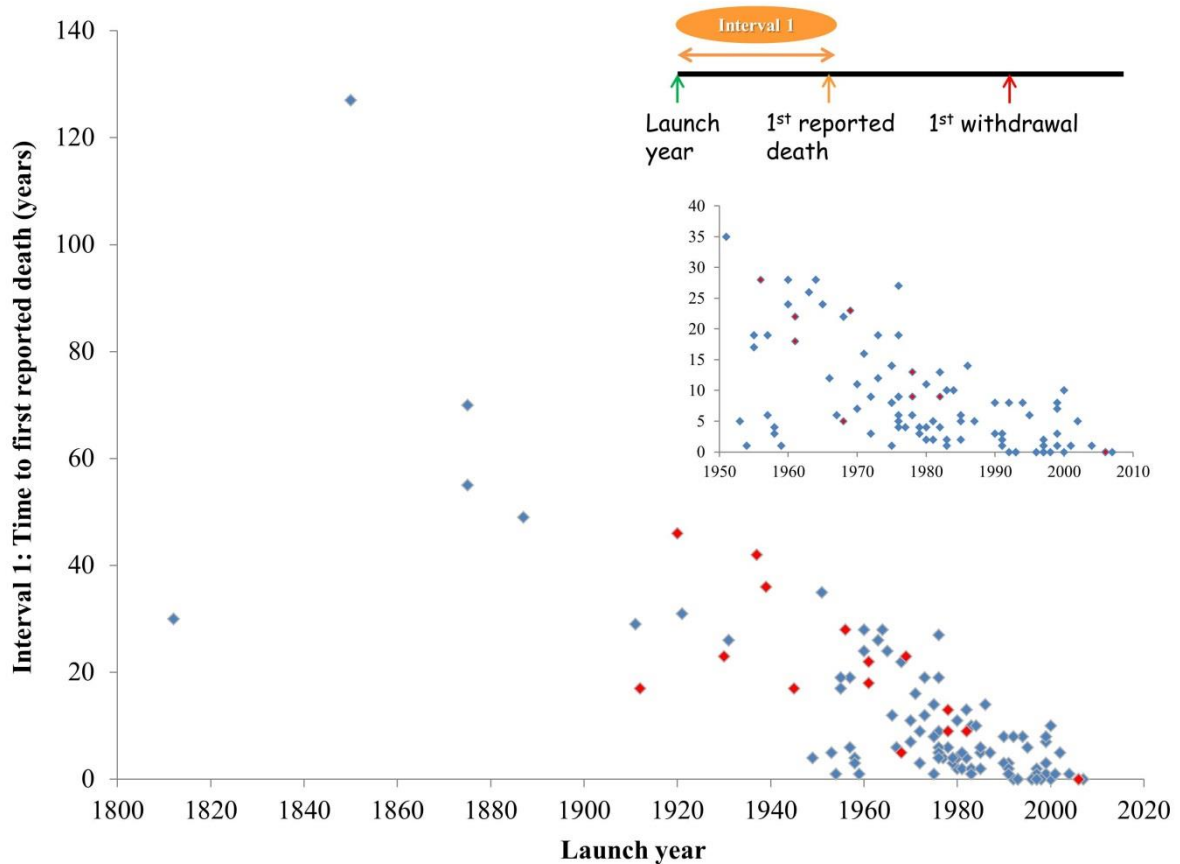
There were significantly fewer withdrawals in African and Asian countries than in other countries when comparing medications that were withdrawn within 1 year of the first report of a death and those that were withdrawn later ($P < 0.0005$). The frequency of respiratory events that occasioned withdrawal was also significantly lower in the former ($P = 0.04$).

Of published reports of deaths, 83 (73%) came from physicians; in 22 cases (19%) deaths were reported to regulatory agencies, and in two cases in clinical trials; other sources included a government inquiry and a coroner's report.

3.3.4 Interval between launch year and first reported death

The longest interval between launch year or year of first reported use and the first report of fatality was 127 years (ethyl nitrite; first reported use 1850, first reported death 1977) [11]. The median interval between launch year and the first reported death was 7 years (IQR= 2 to 17). The median interval to first reports was longer with products that caused deaths through overdose (18 years *versus* 6 years). The first reports of deaths occurred within a year of product launch in 25 cases (22%) within the first year, six cases within two years (5%), and more than two years in 83 instances (73%). Figure 3.2 shows the time lapse between the launch of a withdrawn product and the date of the first reported death (interval 1); the more recent the launch date, the sooner deaths were reported. These findings applied to the data after 1950 as well as to the whole set shown (see Figure 3.2 inset).

Figure 3.2: Launch year *versus* interval 1 (the time lapse between the launch of a withdrawn product and the date of the first reported death). The red boxes indicate products causing deaths in overdose.



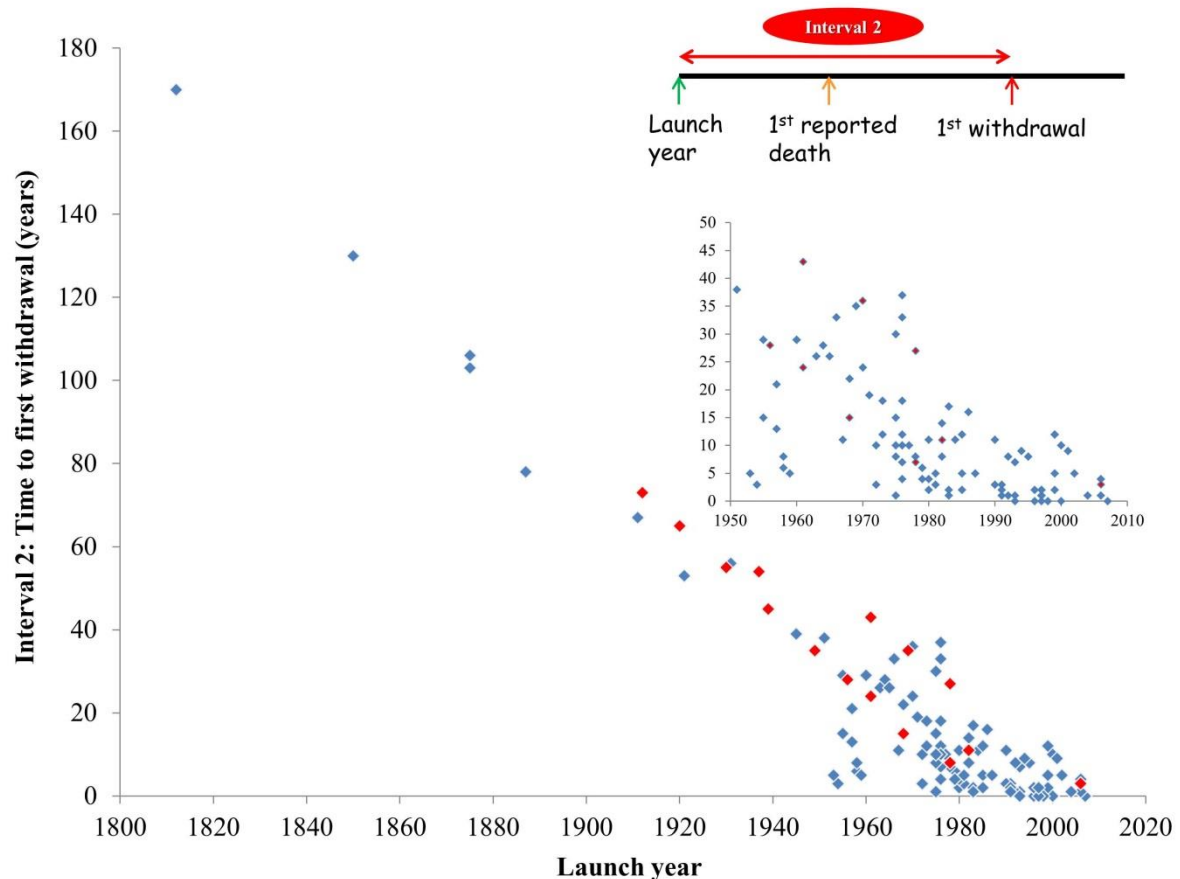
3.3.5 Interval between launch year and first withdrawal

The median interval between launch year and the first withdrawal was 10 years (IQR= 3 to 27). The median interval to withdrawal following product launch occurred within one year in 16 cases (14%), two years in eight cases (7%), and more than two year in 90 cases (79%). The median interval to first withdrawal was longer with products that caused deaths through overdose (35 years *versus* 9 years).

Figure 3.3 shows the time lapse between the launch of a withdrawn product and the date of the first withdrawal (interval 2); the more recent the launch date, the sooner products were

withdrawn from the market. These findings applied to the data after 1950 as well as to the whole set shown (see Figure 3.3 inset).

Figure 3.3: Launch year versus interval 2 (the time lapse between the launch of a withdrawn product and the date of the first reported withdrawal). Red boxes indication drugs causing deaths due to overdose.



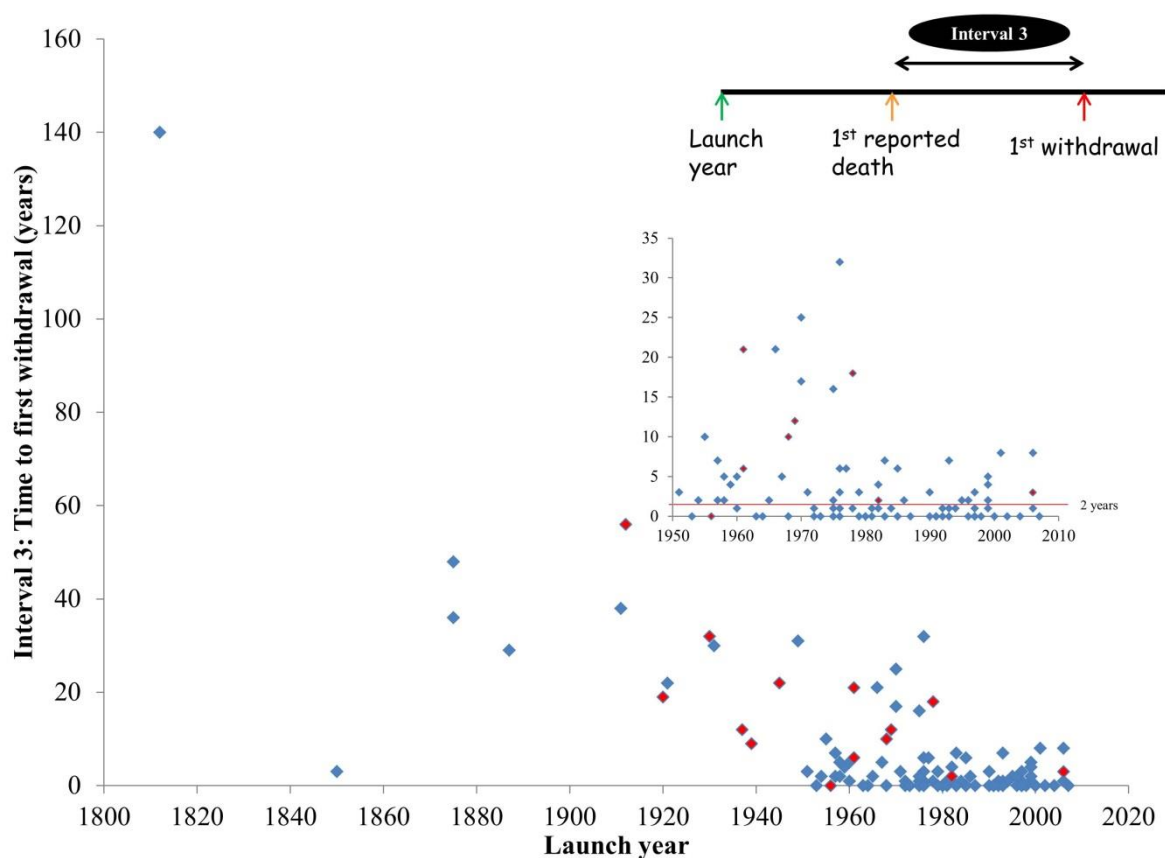
3.3.6 Interval between first report of death and first withdrawal

The longest interval between the first reported death and withdrawal of the medicine was 56 years (phenobarbital; first reported death 1929, withdrawn 1985 in Sweden [12]). The median interval to first withdrawal following reports of death was 2 years (IQR= 0 to 7 years). Of 99 products launched after 1950, 41 (41%) were withdrawn within 1 year of the first reported death, 15 (15%) within the second year, and 43 (43%) more than 2 years after the first reported death. In cases where deaths were due to overdose, the median interval to

withdrawal after the first report of death was 12 years (IQR= 3 to 21); the median interval to withdrawal when deaths occurred at therapeutic doses was 1 year (IQR= 0 to 5).

Figure 3.4 shows that the delay between the first death and the first withdrawal (interval 3) showed no consistent relation to the year in which the product was launched, and did not change consistently over time. Similarly, the delay between the first death and the first withdrawal showed no consistent relation to the year in which the first death was reported when eight medicinal products withdrawn after 1950 because of deaths due to overdose were examined (Figure 3.4 inset).

Figure 3.4: Launch year versus interval 3 (the time lapse between the first reported death and the first withdrawal in any country). The red boxes indicate products* withdrawn because of overdose-related deaths.



*Buprenorphine is not shown in the figure because its first withdrawal (Egypt) occurred before the first report of death appeared in the literature.

3.4 DISCUSSION

A total of 114 products for which death was cited as a reason for withdrawal between 1950 and 2013 were identified. Cardiotoxicity, hepatotoxicity, and respiratory depression accounted for over half of the withdrawals. Withdrawals were more common in European countries; few were reported in Africa.

3.4.1 Evidence for withdrawal

The criteria that determine whether a product should be withdrawn are not well established, although proposals have been made [13]. It is likely that in many cases agencies have applied the precautionary principle, defined by the Wingspread Consensus Statement as follows: “When an activity raises threats of harm to human health ... precautionary measures should be taken, even if some cause and effect relationships are not fully established scientifically, [in which case] the proponent of [the] activity ... should bear the burden of proof”. The “proponent” in this case would be the MAH [14].

The level of the evidence that led to the withdrawal of these medicinal products was on the whole low. In most instances it was limited to case reports, and in only eight instances was it based on randomized comparisons. This is consistent with the results of much smaller previous studies. Of 11 products that were withdrawn for different reasons during 1999–2001, evidence from spontaneous reports supported the withdrawal of eight products (73%); randomized trials and comparative observational studies were cited for only two products each [15]. In a study of 19 products that were withdrawn during 2002–11 (at least two studies were reported as evidence used for withdrawal of 10 products), case reports were cited in 18 of 19 withdrawals, case–control studies in four cases, cohort studies in four, randomized controlled trials in 12, and meta-analysis in five [16]. Similarly, in a

Spanish study of 22 drugs that were withdrawn in 1990–9 because of adverse reactions, case reports were the main source of information [17].

It should be noted that while case reports may be regarded as low level evidence, they are quite useful for investigating cases of drug-attributed deaths because conducting new confirmatory studies may be unethical (e.g. RCTs) or time consuming (e.g. case-control studies). However, case-control studies or systematic reviews may provide additional information to help drug regulators make withdrawal decisions when there is uncertainty about the relationship between a medicinal product and drug-attributed deaths.

In the world literature about 30% of all information on adverse drug reactions comes from case reports [18], but in our survey 83% of withdrawals were based on such evidence. This is consistent with the observation that suspected adverse reactions that are identified in case reports are infrequently followed up with formal studies to investigate the suspected associations; of 63 suspected adverse drug reactions that were the subjects of case reports in five medical journals in 1997, 52 were not subjected to further detailed evaluation and data from controlled studies that supported the postulated link between the product and the adverse event were available in only three cases [19]. However, when death is suspected to result from the use of a medicine, one might apply less strict criteria in attributing causality than for other, less serious, adverse reactions, in order to give higher priority to their investigation.

Nevertheless, for some of the medicines in this study, a cause and effect relation could be established. For example, overdose with sedative drugs (e.g. pentobarbital and co-proxamol) with consequent respiratory paralysis and death led to withdrawals [20]. For

some other drugs, such as fenoterol and nebacumab, a cause and effect relation was established indirectly by analysing patterns of mortality in patients taking the drugs. In some cases retrospective evidence of an association was also available; for example, a marked reduction in mortality rates from asthma was reported after fenoterol was removed from the market in New Zealand [21]; after L-tryptophan was withdrawn in 1989, when epidemiological studies linked its use to eosinophilia–myalgia syndrome, the incidence fell markedly [22]. In other cases [23,24], the cause and effect relation was not clearly demonstrated, and there have been controversies about whether such agents should have been removed from the market.

Negative publication bias is possible when deaths result from the use of medicinal products. For example, when rofecoxib was withdrawn the manufacturer’s statement referred to unpublished trial data and did not mention deaths [25]. While regulatory authorities in Europe withdrew nefazodone because of hepatotoxicity, the manufacturer stated that they withdrew the product for “commercial reasons” [26]. In the case of dithiazanine iodide, only two of eight deaths resulting from the use of the product were published; the other six were noted in a pharmaceutical company’s brochure [27]. More recently, a drug manufacturer received a large fine for withholding data on the safety of a medicinal product reported to have caused numerous deaths [28]. Another manufacturer is also under investigation for the non-reporting of deaths from patient support programmes [29].

3.4.2 Patterns of withdrawal

There were differences in the patterns of withdrawal in different countries. For example, in the UK troglitazone was withdrawn because of deaths due to liver damage, but in the USA

the label was changed to require more extensive monitoring of liver function. Furthermore, there were significantly fewer withdrawals in African and Asian countries than in other countries, when comparing medications that were withdrawn within 1 year of the first report of a death and those that were withdrawn later.

Only 26 products were reportedly withdrawn “worldwide”, i.e. in all countries in which they had been marketed, although it is unlikely that they were marketed everywhere. In 16 cases that we could identify the product continued to be marketed in some countries, despite having been withdrawn in others. Metamizole (dipyrone), which has been the subject of considerable controversy [30], provides an excellent example of this (Figure 3.5). Although the first death was recorded in 1952, metamizole was first withdrawn from the market (in Norway and Sweden) only in 1974, and other countries were slower to withdraw it. Indeed, it was reintroduced in Sweden in 1995 and withdrawn again in 1999, and it has only recently been withdrawn in India [31]. In other countries it remained on the market with changes to the label. In some cases combination formulations were withdrawn but single-product formulations remained.

Several reasons explain the withdrawal of a product in one country and not in another. The frequency of an adverse reaction may differ in different countries, as was controversially reported with metamizole [32]. In a few cases different indications for therapy may contribute to different risks of adverse reactions. In other cases the product may be cheaper than alternatives; there is a relation between a country's capacity to restrict dangerous drugs and its per capita gross national product [33]. Furthermore, competing interests may play a role in influencing the pattern of drug withdrawal, even when deaths have been associated [34]. A recent analysis of five of the largest private global health foundations

concluded that board members' interests and donors' investments (including those from pharmaceutical companies) are potential conflicts of interest that need to be addressed in order to prevent a distortion of science and public health outcomes [35]. Whether an independent group of reviewers should be tasked with making decisions about drug withdrawals because of adverse reactions is controversial. In the USA for example, some authors have advocated that an independent group of reviewers should be mandated with critically appraising and analysing post-marketing surveillance data [34,36]; this view has been contradicted by others who prefer that the FDA be bolstered in its drug monitoring strategies [37].

3.4.3 Delays between launch dates and reports of deaths

Several factors may have contributed to shortening the delay between the development and marketing of a drug and the first report of a drug-attributed death (interval 1). These include the likelihood that more patients are being treated nowadays with each new drug than was the case in the past, the increasing age of the treated population, and the increasing use of polypharmacy, whether appropriate or inappropriate. Improved pharmacovigilance and better reporting of suspected adverse reactions, better methods of signal detection and assigning causality, and stricter regulation could also contribute.

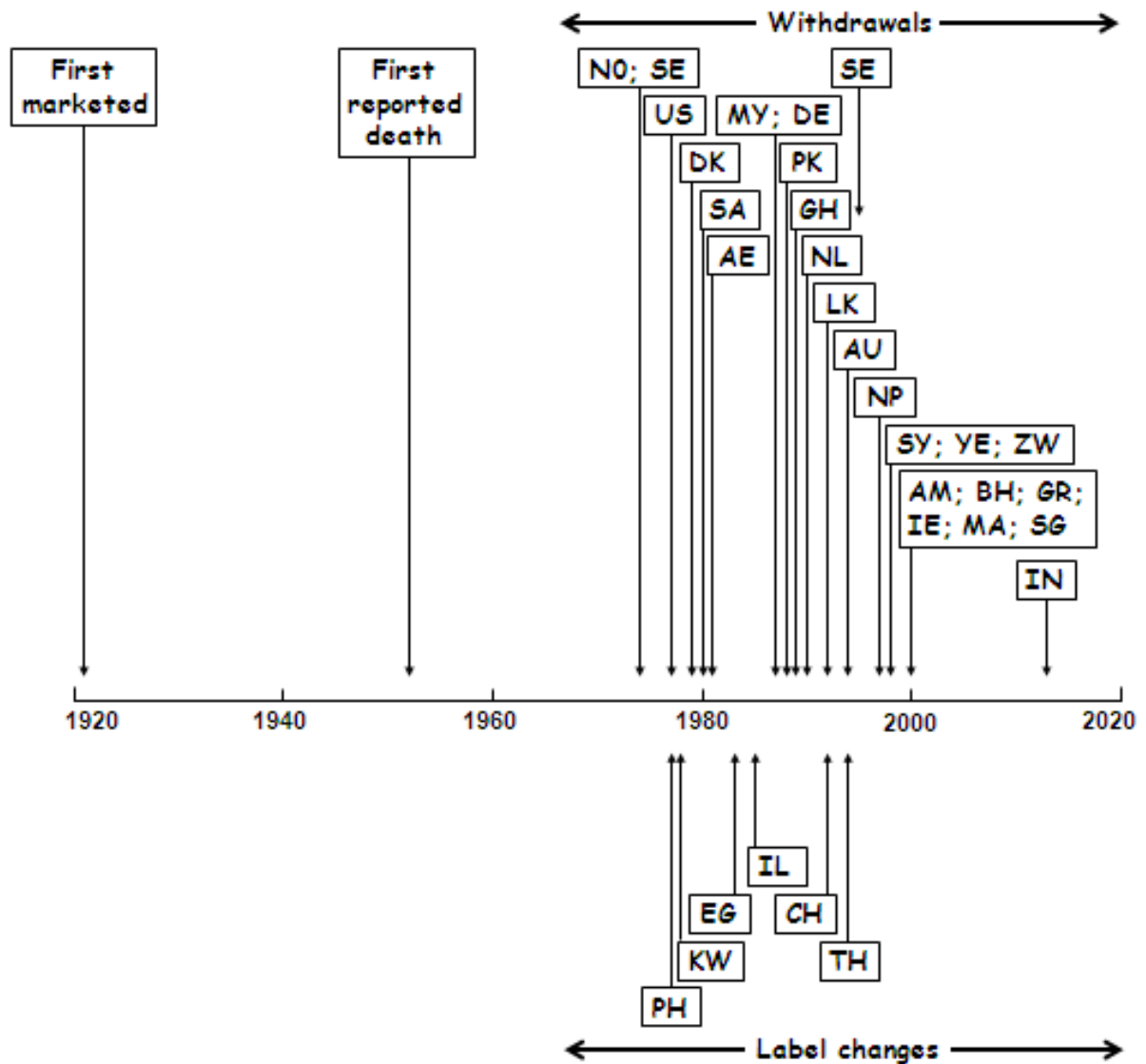
Improved pharmacovigilance Modern pharmacovigilance dates from the 1960s [38,39], and developments over the last 50 years include the acquisition of large numbers of case reports in international databases, combined with increasing use of statistical methods to analyse agglomerated case reports, endowing them with greater evidential power [40], the increasing use of meta-analysis of adverse drug reactions reports in clinical trials [41], and the introduction of patient reporting.

Causality assignment Some adverse drug reactions are definitive (“between-the-eyes” reactions) [42] and some are so-called “designated medical events” (i.e. reactions that are almost always or very often associated with a medicine when they occur) [43]. In this series, a death that occurred within minutes of injection of technetium (99mTc) fanolesomab [44] and a death that occurred immediately after the intravenous administration of bismuth tartrate [45] fell into the first of these categories. For other reactions several methods of determining causality (i.e. linking drug–adverse event pairs causally) have been devised over the last 35 years or so [46]. However, there are many drawbacks to their use [47]: they all rely to some extent on clinical judgement, and physicians tend to overestimate the likelihood of causality; the criteria used are neither sensitive nor specific and have poor predictive power; and in comparisons of different algorithms agreement has generally been very poor. It therefore seems unlikely that improvements in causality assessment in individual cases have contributed much to the improved time to withdrawal of products that cause deaths.

3.4.4 Delays between launch dates and withdrawals

The delay between launch date and market withdrawal (interval 2) shortened as the launch date became more recent (Figure 3.3). This is probably attributable to the shortening in the delay between launch and the first report of death (i.e. interval 1; Figure 3.2). One would expect faster withdrawal of a drug from the market if it caused deaths at therapeutic doses compared with another product that caused deaths through overdose; and the evidence from our review supports this assumption – the median times to withdrawal from both launch dates and first reports of deaths were longer with medicinal products that caused deaths through overdose.

Figure 3.5: Different times of withdrawal of metamizole in different countries; also shown are label changes in other countries; the country codes are according to the International Organization for Standardization [ISO 3166-1:2006. Codes for the representation of names of countries and their subdivisions—Part 1: Country codes. http://www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=39719.]



3.4.5 Delays to withdrawals after reports of deaths

In contrast, there was no consistent change in the delay between reports of death and market withdrawals (interval 3; Figure 3.4). Manufacturers and regulatory agencies need to address this problem, by putting in place processes to ensure rapid and internationally coordinated responses about decisions regarding withdrawal of medicinal products from

the market if deaths are suspected to be associated with their use. However, it should be noted that the market share and profitability of particular drugs would influence industry's attitude to withdrawal.

Drug regulatory activity continues to evolve [48]. For example, it is a current international regulatory requirement that fatal or life-threatening unexpected adverse reactions must be reported within 15 days [49]. However, there are discrepancies in the ways in which individual regulatory authorities expedite action on such reports. In Europe, the USA, India, and Australia there are established standard procedures for initiating drug withdrawals from the market because of deaths [50,51,52,53]. For instance in the USA, if there is a reasonable risk of death or other serious adverse reactions from use of a medicinal product, the FDA may ask the MAH to recall a drug, or mandate the MAH to conduct a recall (Class I recall), and may also issue a safety alert to notify the general public about the hazards of the drug [51].

In a 1984 review of 24 products that were withdrawn during 1974–1983 there was no difference in the rates of withdrawals in the UK and the USA [54]. However, in an investigation of 26 medicinal products that were withdrawn in the USA and/or UK during 1971–1992, products that were withdrawn for any reason in the USA were withdrawn sooner after marketing than in the UK, which was attributed to more stringent regulation in the USA, with slower regulatory approval [55]. However, our data suggest that, at least as far as products that cause deaths are concerned, changes in product licensing in recent years have not shortened the times to withdrawal. This might, however, be in part due to increased delays in the regulatory process, occasioned by waiting for the results of further studies into the nature of the suspected adverse reaction. This implies that while such

studies are being carried out the medication should be temporarily withheld pending the results.

3.4.6 Limitations

There was no access to information on the time lapse between the occurrence of the first death attributed to the drug and the date on which death was first reported. Indeed, some early deaths may have been observed but not reported. However, such delays are likely to have been short and unlikely to have affected the results significantly. The list of 114 withdrawn products may be incomplete, because of negative publication bias. The review authors have identified another list over 300 other products that were also withdrawn or had their labels changed during the period studied; some of those may have caused deaths, but since death was not specifically mentioned in relation to withdrawals in those cases we have excluded them. Although we included medicinal products that caused deaths at toxic doses, overdose is not usually classified as an adverse drug reaction [56]; however because overdose could be intentional or unintentional, one would expect cases of overdose to be spontaneously reported in a manner similar to conventional adverse reactions.

The review authors had no access to data on regulatory actions that may have been taken in advance of withdrawal. Some of the withdrawn drugs included in the review may also have been marketed as over-the-counter (OTC) medications in some countries; and in countries in which regulation is less stringent regulatory action would be more difficult.

Furthermore, some medicinal products (especially psychotropic drugs) are reported to have caused deaths, but have not been withdrawn from the market. This may have been because the benefit to harm balance was nevertheless still considered to be favourable or because of

poor regulatory action. The conclusions about international patterns of drug withdrawals are limited by the relative paucity of data in some countries.

3.5 CONCLUSIONS

A total of 114 products have been withdrawn from the market because of drug-attributed deaths. The interval between launch date and reports of deaths has shortened over the past few decades, and this could be because of better reporting of suspected adverse reactions or stricter regulation. However, many withdrawals still occurred more than two years after the reports of deaths begin to appear. Furthermore, there are discrepancies in the patterns of drug withdrawals in different countries, with greater delays in Africa and Asia. These delays and discrepancies could be mitigated by encouraging prescribers and investigators to report serious suspected adverse reactions, by swifter regulatory action when reports appear, and by international co-ordination of reports.

3.6 Chapter Summary

- 114 medicinal products have been withdrawn from the market because of drug-attributed deaths since 1950
- Case reports were cited as evidence for withdrawal in over 80% of instances
- There were significantly fewer withdrawals in African and Asian countries
- The more recent the launch date, the sooner deaths were reported.
- In 43% of cases more than 2 years elapsed between the first report of a death and withdrawal of the drug
- The interval between the first report of a death attributed to a medicinal product and eventual withdrawal of the product has not improved over the last 60 years

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Chapter 4 Worldwide withdrawal of medicinal products because of adverse drug reactions: a systematic review and analysis

4.1 INTRODUCTION

After drug manufacturers have successfully conducted clinical trials demonstrating favourable benefit-to-harm balance for medicinal products, they apply for marketing licences to allow sale of such products. In some cases, the products may be marketed in one or two countries; but in other instances, the products could be marketed in many countries, or even worldwide.

Although adverse events associated with a newly approved medicinal product are observed in the period before and around the time of regulatory approval, the frequency and intensity of such events is generally not quantifiable during the pre-approval phase. In addition, rare but potentially important adverse drug reactions may not be apparent. Consequently, the benefit-to-harm balance of a newly approved medicinal product may change over time [1]. In cases where the harms outweigh the benefits, one of several courses of action may be taken by the regulatory authority or the manufacturer, including addition to the label of an adverse reaction or a warning or a contraindication, and/or revision of the risk minimization plan [2]. In the most extreme cases, the product may be withdrawn from the market [3,4].

When medicinal products are withdrawn from the market because of adverse reactions, one would expect uniformity in the pattern of withdrawal across the countries where such products were marketed. In chapters 2 and 3, the results showed that there are inconsistencies in the patterns of withdrawals across countries when adverse reactions or

deaths are attributed to the use of medicinal products. For example, drugs were not always withdrawn in every country in which they have been marketed, even when there were concerns about harms in some of the countries. In chapter 2, the pattern of post-marketing withdrawal of medicinal products in any country or countries was examined, i.e, products withdrawn in one, two or more countries irrespective of the number of countries where the products were marketed. There has been no specific research on the pattern of withdrawals when medicinal products are withdrawn worldwide (i.e. all countries in the world) because of suspected adverse drug reactions. In this chapter, medicinal products that were withdrawn worldwide because of adverse drug reactions are specifically documented, the level of evidence used for making the withdrawal decisions are assessed, and the patterns of withdrawals over time are explored.

4.2 METHODS

4.2.1 Search strategy

The first reviewer (IJO) used the information from the results of chapter 2 to identify products for which adverse reactions were documented as a reason for worldwide withdrawal between from 1950 onwards [see also appendix 1 for search strategies]. The searches were updated in June 2016 to identify any further worldwide withdrawals from the following databases:

- the WHO's Drug Information;
- the WHO's Pharmaceuticals Newsletter;
- the website of the UK Medicines and Healthcare products Regulatory Agency (MHRA);
- the website of the US Food and Drug Administration (FDA);
- the database of withdrawn drugs of the European Medicines Agency (EMA).

4.2.2 Inclusion/exclusion criteria

To be included in the review, a product must have been withdrawn worldwide from the market because of reports of a suspected adverse reaction or reactions, or problems related to hazards or harms. Such products must also have been introduced into the market from 1950 onwards. By worldwide withdrawal we mean the withdrawal of a product in all the countries in which it had been marketed, even if it was not marketed globally; furthermore, it must have been specifically stated, either by the manufacturer or a regulatory authority, that the drug was being withdrawn worldwide.

Medicinal products that had previously been withdrawn because of adverse reactions but had been re-introduced or made available in other, safer, formulations were included.

Medicines for which there was documented regulatory evidence that they had been voluntarily withdrawn by marketing authorization holders solely for “commercial reasons” were excluded. Herbal products, non-human medicines, and non-prescription medicines were also excluded.

4.2.3 Assessing the types of evidence

As in the previous chapters, the first reviewer (IJO) documented the highest level of available evidence before the year of first worldwide withdrawal of products, based on the Oxford Centre for Evidence-based Medicine (OCEBM) criteria [5]. These were independently verified by a second reviewer (JKA). Any discrepancies were resolved through consensus.

4.2.4 Classification of adverse drug reactions

The possible clinical mechanisms through which the reported adverse reactions occurred were described using the DoTS system [6], which examines three domains, namely: Dose-relatedness (Do), which determines toxic, collateral, or hypersusceptibility reactions; Time-course (T), varying from immediate to delayed; and Susceptibility factors (S).

4.2.5 Data extraction

For each withdrawn product, the information from chapter 2 was used to document data on: the date of marketing authorization, the launch date, or the date of first recorded use; the drug class, and therapeutic indication [7]; the year in which an adverse drug reaction (ADR) related to the reason for withdrawal was first reported and the sources of the report(s); the year of first withdrawal; and the reported organ or system that was affected by the product. In addition, we extracted data on the year of worldwide withdrawal; the party or parties that initiated the withdrawal; and the possible clinical mechanisms for the adverse reactions based on the DoTS system. The first reviewer (IJO) extracted and documented the data and a second reviewer (JKA) verified them independently. When there were discrepancies, both reviewers re-checked the data together and arrived at a consensus through discussion.

4.2.6 Data presentation

Summary tables were used to document the intervals between launch year and the year of first reports of adverse drug reactions, the interval between launch year and the year of first withdrawal, and the interval between the first report of an adverse drug reaction and the year of first withdrawal. Because these intervals were skewed, medians and interquartile ranges (IQR) were used as measures of central tendency and spread. Scatter plots were

used to explore the relationships between launch dates and times to first reports of adverse drug reactions and withdrawals.

4.3 RESULTS

There were 40 medicinal products withdrawn worldwide since 1950; the first worldwide withdrawal occurred in 1969, and the last worldwide withdrawal occurred in 2011. Non-steroidal anti-inflammatory drugs (NSAIDs) (mainly COX-1 and COX-2 inhibitors) accounted for 10 (25%) of the withdrawals, followed by antihypertensives and antidepressants (three each) (see Table 4.1).

In seven cases (17.5%), the first withdrawals were initiated by drug regulatory authorities; manufacturer-initiated withdrawals accounted for 27 cases (67.5%). In five cases, the drug manufacturer and drug regulatory authorities simultaneously withdrew the products from the market. The worldwide withdrawal of one product (fenclofenac) by the manufacturer was as a result of a refusal by the UK regulatory authorities to renew the product licence.

The adverse reactions that occasioned withdrawals were due to off-target effects in all but two cases, paralytic ileus due to loperamide, a μ opioid receptor agonist, and cardiovascular adverse reactions to prenylamine, a calcium channel blocker.

Table 4.1: List of 40 medicinal products withdrawn worldwide because of adverse drug reactions

Medicinal product	Class	Mechanism of action	Launch date	Year of first ADR report	Year first withdrawn	First withdrawal initiated by	Reason for withdrawal	LoE [†]
Anagestone acetate	Hormone	Inhibition of ovulation	1968	1969	1969	FDA	Tumorigenicity	5
Aprotinin	Antifibrinolytic	Pancreatic trypsin inhibitor	1959	1964	2007	EMA; re-introduced with restrictions in 2012	Anaphylaxis	4
Benoxaprofen*	NSAID	COX-1 & COX-2 inhibition	1980	1982	1982	Danish Health and Medicines Authority	Liver, skin, urinary tract	4
Cerivastatin*	Lipid modifier	HMG CoA reductase inhibition	1997	1998	2001	Manufacturer	Renal, musculoskeletal	4
Chlormezanone	Muscle relaxant	GABA receptor modulation	1960	1983	1996	Simultaneous action by regulatory authorities and manufacturer	Skin, drug dependence, liver	4
Cianidanol*	Flavonoid	Free radical scavenger	1976	1980	1985	Simultaneous action by regulatory authorities and manufacturer	Haematologic	4
Dilevalol	Antihypertensive	Nonselective beta blocker; beta-2 adrenoceptor agonist	1989	1989	1990	Manufacturer	Liver	4
Domperidone (injectable)*	Antiemetic	Dopamine receptor antagonist	1979	1982	1985	Manufacturer	Cardiovascular, drug overdose, endocrine, nervous system	4
Drotrecogin alfa (activated)	Antithrombotic	Recombinant human activated protein C	2001	2001	2011	Manufacturer	Insufficient evidence; bleeding risk	1
Fenclofenac*	NSAID	COX-1 & COX-2 inhibition	1978	1984	1984	Manufacturer, following refusal of renewal of licence in the UK	Skin, urinary tract, tumorigenicity,	4
Fenfluramine	Psychotropic	Serotonin receptor antagonist	1973	1996	1997	Simultaneous action by regulatory authorities and manufacturer	Cardiovascular, respiratory	3
Glafenine	NSAID	COX-1 & COX-2 inhibition	1965	1973	1984	Italian Medicines Agency (AIFA)	Urinary tract	4
Grepafloxacin*	Antimicrobial	Inhibition of DNA gyrase	1997	1999	1999	Manufacturer	Cardiovascular	2, 4
Indoprofen*	NSAID	COX-1 & COX-2 inhibition	1976	1982	1983	Simultaneous action by regulatory authorities and manufacturer	Gastrointestinal	4
Isoxicam*	NSAID	COX-1 & COX-2 inhibition	1983	1985	1985	Simultaneous action by regulatory authorities and manufacturer	Skin	4
Lapdap (chlorproguanil + dapsone)	Antimalarial	Dihydrofolate reductase inhibitor + dihydropteroate	2003	2008	2008	Manufacturer	Haemolytic anaemia	2

		synthase inhibitor						
Laropiprant / nicotinic acid	Antilipemic	Prostaglandin receptor blocker	2008	2008	2008	Manufacturer	Higher frequency of non-fatal but serious side effects	2
Loperamide (syrup & drops)*	Antidiarrhoeal	Opioid receptor agonist	1975	1990	1990	Manufacturer	Paralytic ileus	4
L-Tryptophan*	Antidepressant	Converted to serotonin	1963	1989	1989	Several drug regulatory authorities	Eosinophilia-myalgia syndrome (EMS)	4
Methyl-hexanamine	Nasal decongestant	Norepinephrine & dopamine transporter blockade	1971		1983	Manufacturer	Cardiovascular, nervous	4
MMR vaccine (Urabe)	Vaccines	Antibody production	1983	1987	1988	Manufacturer	Nervous system, psychiatric	2
Muzolimine*	Antihypertensive	Diuresis by inhibition of Na/K/Cl transport	1983	1987	1987	Manufacturer	Nervous system	4
Nebacumab*	Monoclonal antibody	Endotoxin-specific IgM	1991	1993	1993	Manufacturer	Infection risk; accelerated deaths	2
Nomifensine*	Antidepressant	Norepinephrine-dopamine reuptake inhibitor	1976	1980	1986	Manufacturer	Haematologic, liver, respiratory	4
Oxyphenbutazone*	NSAID	COX-1 & COX-2 inhibition	1955	1974	1984	Drug regulatory authorities in UK, Germany	Haematologic: Bone marrow suppression	4
Pemoline*	Psychostimulant	Dopamine agonist?	1960	1973	2005	Manufacturer	Liver: hepatotoxicity	4
Pirprofen*	NSAID	COX-1 & COX-2 inhibition	1982	1986	1990	Manufacturer	Gastrointestinal, liver, urinary tract	4
Polyoxyethylated castor oil	Adjuvant		1970	1973	1984	Manufacturer	Anaphylaxis, hyperlipidemia	4
Prenylamine*	Antianginal	Calcium channel blocker	1960	1973	1989	Manufacturer	Cardiovascular: multifocal ventricular tachycardia	4
Remoxipride	Antipsychotic	Dopamine D2 receptor antagonist	1991	1993	1994	Manufacturer	Haematologic	4
Rofecoxib*	NSAID	COX-2 inhibitor	1999	2002	2004	Manufacturer	Cardiotoxicity	1
Sitaxentan sodium*	Antihypertensive	Endothelin receptor antagonist	2006	2009	2010	Manufacturer	Hepatotoxicity	4
Suloctidil*	Vasodilator	Calcium channel blockade, inhibits thromboxane B2	1975	1983	1985	Manufacturer	Liver: hepatotoxicity	4
Suprofen	NSAID	COX-1 & COX-2 inhibition	1983	1986	1986	‡Regulatory authority	Urinary tract	4
Temafloxacin*	Antimicrobial (fluoroquinolone)	Inhibits DNA gyrase	1991	1992	1992	Manufacturer	Haematologic, immunologic, liver, metabolism, urinary tract	4
Terodiline*	Antispasmodic	Calcium channel blockade,	1965	1989	1991	Manufacturer	Cardiovascular	4

		blocks cholinergic receptors						
Thioridazine	Antipsychotic	Dopamine receptor antagonist	1959	1961	2000	Manufacturer	Retinopathy, cardiovascular	4
Tolrestat*	Hypoglycaemic	Aldose reductase inhibitor	1982	1995	1996	Manufacturer	Liver	2
Zimeldine	Antidepressant	5 HT reuptake inhibitor	1982	1982	1983	Manufacturer	Liver, nervous system	4
Zomepirac*	NSAID	COX-1 & COX-2 inhibition	1979	1981	1983	Manufacturer	Immunologic, urinary tract	4

ABBREVIATIONS: ADHD: Attention deficit hyperactivity disorder; ADR: Adverse drug reaction; COX-1: Cyclooxygenase 1; COX-2: Cyclooxygenase 2; DNA: Deoxyribonucleic acid; EMA: European Medicines Agency; FDA: US Food and Drug Administration; GABA: Gamma-aminobutyric acid; HMG CoA: 3-hydroxy-3-methyl-glutaryl-CoA; 5 HT: 5-hydroxytryptamine; LoE: Level of evidence; NSAID: non-steroidal anti-inflammatory drug

*Products withdrawn in association with deaths

‡While it was withdrawn because of ADRs in the UK, the manufacturer suspended sales worldwide on the grounds of diminished sales

†Based on the Oxford Centre for Evidence-Based Medicine Levels of Evidence [5]. Level 1—systematic reviews, n-of-1 trials, or dramatic observational studies; Level 2—randomized clinical trials or exceptional observational studies; Level 3—non-randomized, cohort or follow-up studies; Level 4—case-series or case-control studies; Level 5—mechanism-based reasoning

Table 4.2: Reported mechanisms through which medicinal products withdrawn worldwide caused adverse reactions

Medicinal product	ATC class†	Therapeutic mechanism of action	Mechanism of action for adverse reaction	ADR dose-response relationship‡
Anagestone acetate	Hormone	Inhibition of ovulation	Stimulation of mammary gland tumors in beagle bitches	Collateral
Aprotinin	Antifibrinolytic	Pancreatic trypsin inhibitor	Anaphylaxis	Hypersusceptibility
Benoxaprofen*	NSAID	COX-1 & COX-2 inhibition	Immunologic	Hypersusceptibility
Cerivastatin*	Lipid modifier	HMG CoA reductase inhibition	Inhibition of CYP2C9 by gemfibrozil leading to accumulation and rhabdomyolysis	Collateral
Chlormezanone	Muscle relaxant	GABA receptor modulation	Steven-Johnson syndrome; Toxic epidermal necrosis	Hypersusceptibility
Cianidanol*	Flavonoid	Free radical scavenger	Hemolytic anemia and thrombocytopenia	Hypersusceptibility; collateral
Dilevalol	Antihypertensive	Nonselective beta blocker; beta-2 adrenoceptor agonist	Hepatitis via hypersensitivity reaction	Hypersusceptibility
Domperidone (injectable)*	Propulsive	Dopamine receptor antagonist	QT interval prolongation (the therapeutic doses recommended by the manufacturers were insufficient for an antiemetic effect and clinicians therefore used higher doses than recommended)	Toxic
Drotrecogin alfa (activated)	Antithrombotic	Recombinant human activated protein C	Increased bleeding via anticoagulant effect; activated protein C combines with protein S on platelets and then degrades factor Va and factor VIIIa	Collateral
Fenclofenac*	NSAID	COX-1 & COX-2 inhibition	Immune-complex mechanism: nephrotic syndrome, nephritis	Hypersusceptibility
Fenfluramine	Centrally acting	Serotonin receptor antagonist	Valvular heart disease, possibly via 5HT ₂ receptor agonist activity	Collateral
Glafenine	NSAID	COX-1 & COX-2 inhibition	Direct renal damage	Collateral
Grepafloxacin*	Antiinfective (fluoroquinolone)	Inhibition of DNA gyrase	QT interval prolongation	Collateral
Indoprofen*	NSAID	COX-1 & COX-2 inhibition	Gastrointestinal bleeding via prolonged bleeding time and reduced platelet aggregation; worldwide withdrawal by manufacturer due to suspected carcinogenicity in animals	Collateral
Isoxicam*	NSAID	COX-1 & COX-2 inhibition	Immunologic mechanism: Steven-Johnson's syndrome, toxic epidermal necrolysis	Hypersusceptibility
Lapdap (chlorproguanil + dapsone)	Antimalarial	Dihydrofolate reductase inhibitor + dihydropteroate synthase inhibitor	Hemolytic anemia in patients with G6PD deficiency	Hypersusceptibility
Laropiprant / nicotinic acid	Antilipemic	Prostaglandin receptor blocker	GI, skin, bleeding, infections, musculoskeletal	Collateral
Loperamide (syrup & drops)*	Antipropulsive	Opioid receptor agonist	Paralytic ileus	Toxic; collateral
L-Tryptophan*	Antidepressant	Converted to serotonin	Eosinophilia-myalgia syndrome (EMS): mechanism unknown, perhaps due to a contaminant	Collateral
Methylhexanamine	Nasal decongestant	Norepinephrine & dopamine transporter blockade	Sympathomimetic: vasoconstriction	Collateral
MMR vaccine (Urabe)	Vaccines	Antibody production	Aseptic meningitis due to the Urabe strain of mumps vaccine	Collateral
Muzolimine*	Diuretic	Diuresis by inhibition of Na/K/Cl transport	Neuromyeloencephalopathy at high doses in patients with renal	Toxic

			impairment; mechanism unknown	
Nebacumab*	Immunoglobulin	Endotoxin-specific IgM	Unexplained “accelerated deaths”	Unknown
Nomifensine*	Antidepressant	Norepinephrine-dopamine reuptake inhibitor	Immune-mediated hemolytic anemia	Hypersusceptibility
Oxyphenbutazone*	NSAID	COX-1 & COX-2 inhibition	Bone marrow suppression	Collateral
Pemoline*	Psychostimulant	Dopamine agonist?	Liver toxicity: precise mechanism unclear; several hypotheses have been proposed, including hypersensitivity reactions, dose-related phenomena, and autoimmune-mediated reactions	Hypersusceptibility; toxic
Pirprofen*	NSAID	COX-1 & COX-2 inhibition	Massive, predominantly centrilobular hepatic cell necrosis and microvesicular steatosis	Collateral
Polyoxyethylated castor oil	Contact laxative		Anaphylaxis	Hypersusceptibility
Prenylamine*	Vasodilator	Calcium channel blocker	Multifocal ventricular tachycardia via QT interval prolongation	Collateral
Remoxipride	Antipsychotic	Dopamine D2 receptor antagonist	Aplastic anemia via apoptosis of human bone marrow progenitor (HBMP) cells	Collateral
Rofecoxib*	NSAID	COX-2 inhibitor	Myocardial infarction: increased susceptibility of human LDL and membrane lipids to oxidative damage	Collateral
Sitaxentan sodium*	Antihypertensive	Endothelin receptor antagonist	Competitive inhibition of a bile salt transporter pump, leading to intracellular accumulation of bile salts and causing fulminant hepatitis	Collateral
Suloctidil*	Peripheral vasodilator	Calcium channel blockade, inhibits thromboxane B2	Hepatocellular necrosis and cholestasis	Collateral
Suprofen	NSAID	COX-1 & COX-2 inhibition	Renal damage via uric acid nephropathy	Collateral
Temafloxacin*	Antibacterial (fluoroquinolone)	Inhibits DNA gyrase	Immune hemolytic anemia, possibly secondary to immune complex formation	Hypersusceptibility
Terodiline*	Antispasmodic	Calcium channel blockade, blocks cholinergic receptors	QT interval prolongation and polymorphous ventricular tachycardia with torsade de pointes	Collateral
Thioridazine	Antipsychotic	Dopamine receptor antagonist	Retinopathy via ocular oxidative stress at low doses; ventricular arrhythmias at high doses	Collateral; toxic (CVS)
Tolrestat*	Hypoglycemic	Aldose reductase inhibitor	Hepatic necrosis	Collateral
Zimeldine	Antidepressant	5 HT reuptake inhibitor	Liver toxicity via a hypersensitivity mechanism	Hypersusceptibility
Zomepirac*	NSAID	COX-1 & COX-2 inhibition	Immune complex-mediated anaphylaxis; mechanism for renal toxicity unclear	Hypersusceptibility

Abbreviations: ADHD: Attention deficit hyperactivity disorder; ADR: Adverse drug reaction; ATC: Anatomical Therapeutic Chemical; COX-1: Cyclooxygenase 1; COX-2: Cyclooxygenase 2; DNA: Deoxyribonucleic acid; EMA: European Medicines Agency; FDA: US Food and Drug Administration; GABA: Gamma-aminobutyric acid; HMG CoA: 3-hydroxy-3-methyl-glutaryl-CoA; 5 HT: 5-hydroxytryptamine; NSAID: non-steroidal anti-inflammatory drug

*Products withdrawn in association with deaths

†The ATC classification divides medicinal products into groups based on their therapeutic, pharmacological and chemical properties (http://www.whooc.no/atc/structure_and_principles/)

‡Based on the DoTS system [6]: Dose-relatedness (Do) which determines toxic, collateral, or hypersusceptibility reactions; Time-course (T), varying from immediate to delayed; and Susceptibility factors (S)

4.3.1 Evidence for withdrawal

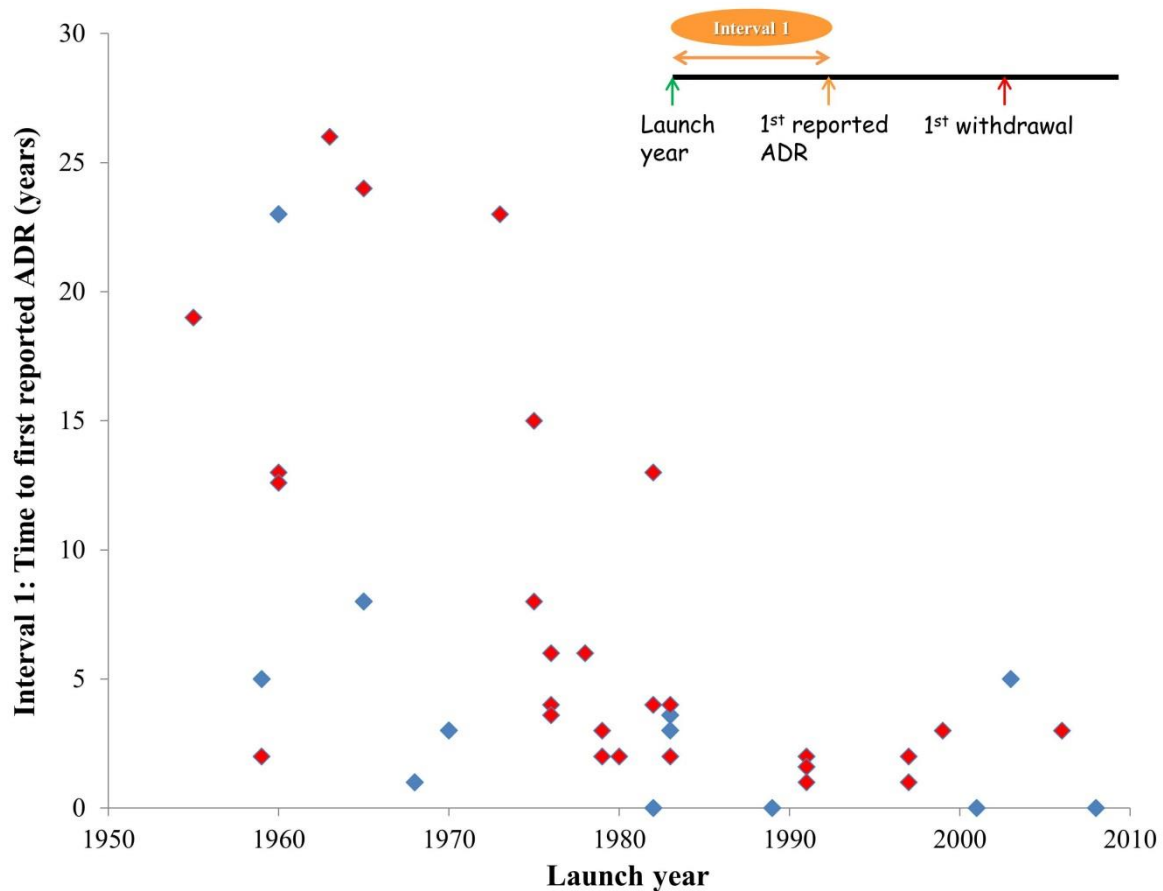
Case reports were used as evidence for withdrawal in 30 cases (75%), while systematic reviews were used in only two cases (5%) (Table 4.1). Evidence from animal research was used as the basis for withdrawal in one case. In 27 cases (68%), deaths were attributed to the withdrawn products. The most common mechanisms through which the adverse drug reactions occurred were hepatotoxicity (25%), cardiotoxicity (20%), and nervous system toxicity (12.5%).

In 24 cases (60%), the adverse reactions resulted from collateral reactions, i.e. reactions that occurred at therapeutic doses (Table 4.2), while hypersusceptibility reactions (reactions at doses below the usual therapeutic range) accounted for 13 cases (33%). Toxic reactions were responsible for adverse reactions in five cases (13%). The dose relationship for one product (nebacumab) was unknown.

4.3.2 Interval between launch year and first adverse drug reaction reports

The longest interval between launch and the first ADR report was 26 years (L-tryptophan and eosinophilia–myalgia syndrome). The median interval between launch year and first ADR report was 4 years (IQR = 2 to 8). The more recent the launch year, the quicker the ADR reports appeared in the literature (Interval 1; Figure 4.1). In 14 cases (35%), such reports appeared within 2 years of the product launch; in 30% of cases, the first reports of ADRs occurred at 2 to 5 years after the launch of the product. When deaths were reported, the median delay before the reports of the deaths appeared in the literature was 1 year (IQR = 0 to 4); in 75% of cases (18/24) the adverse reaction reports occurred within 2 years of launch. The more recent the launch year, the quicker reports of deaths appeared in the literature (Figure 4.1).

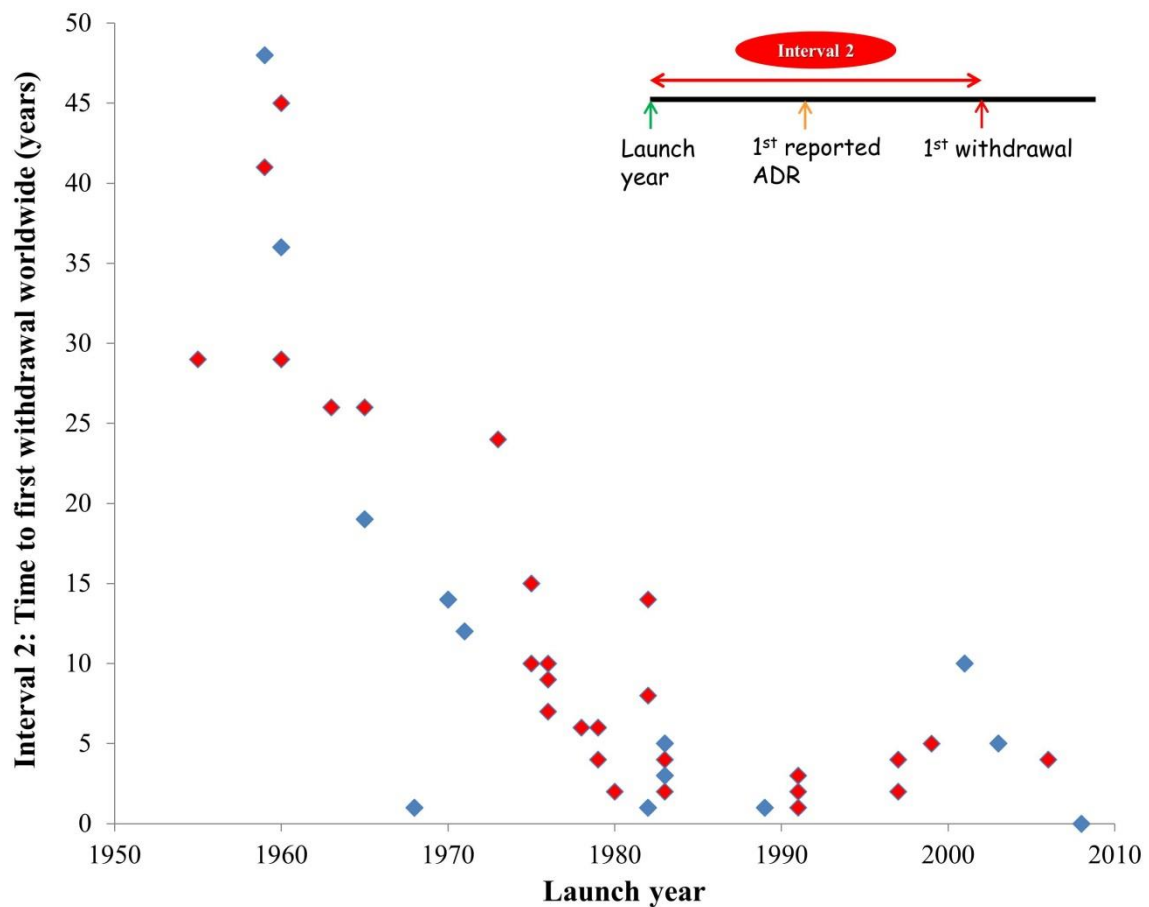
Figure 4.1: Interval between launch and first ADR reports for medicinal products withdrawn worldwide because of adverse reactions. The red boxes indicate products that caused deaths.



4.3.3 Interval between launch year and worldwide withdrawal

The longest interval between launch year and worldwide withdrawal was 48 years (aprotinin and anaphylaxis). The median interval between first launch and worldwide withdrawal was 4 years (IQR = 1 to 12.5). Worldwide withdrawals occurred within two years of product launch in nine cases (23%). The more recent the launch year, the sooner a product was withdrawn from the market worldwide following ADR reports (Figure 4.2). When deaths were attributed to the use of a product, the median interval between launch and worldwide withdrawal was 7 years (IQR = 4 to 24). There was a decadal stepwise shortening in the intervals between launch year and worldwide withdrawals when deaths were attributed to a medicinal product (Figure 4.2).

Figure 4.2: Launch year *versus* interval 2 (the time lapse between the launch of a withdrawn product and the date of the first reported withdrawal worldwide). Red boxes indicate products that caused deaths.

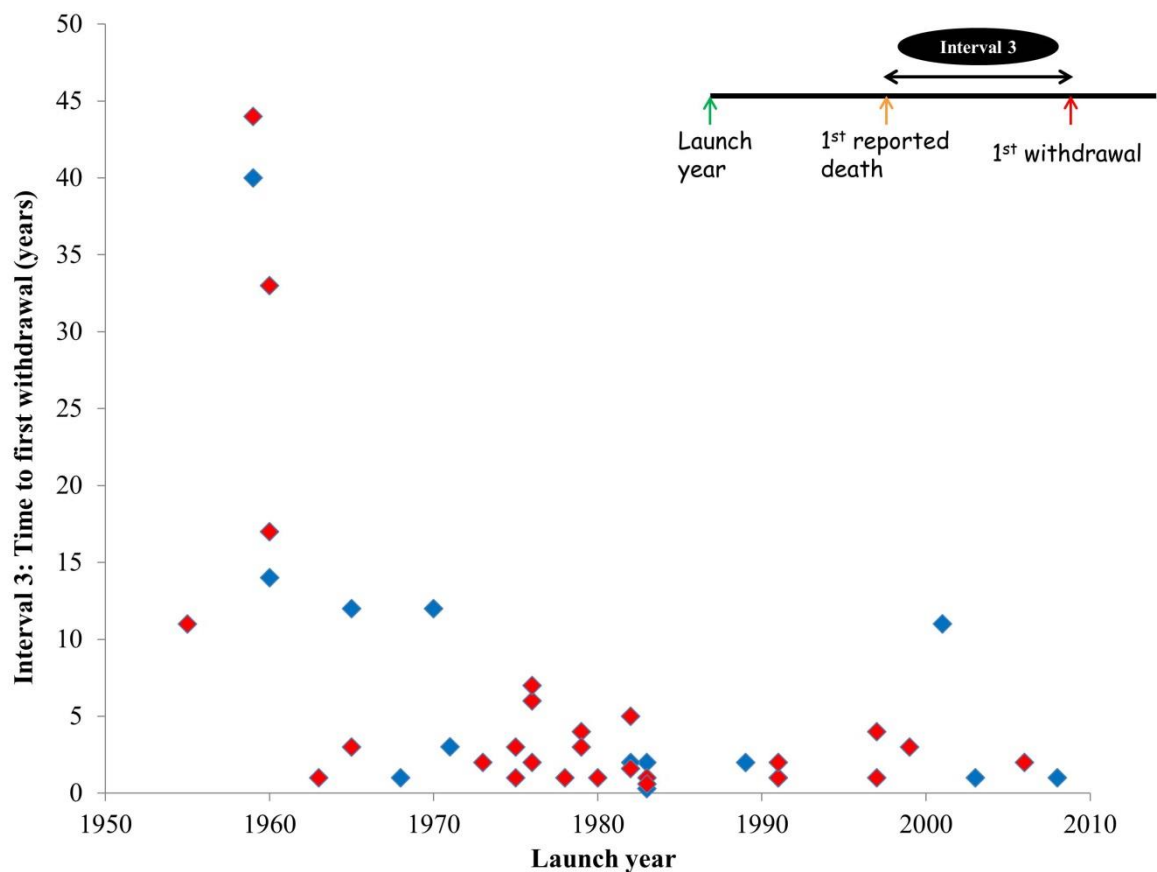


4.3.4 Interval between first reports of adverse drug reactions and worldwide withdrawal

The longest interval between the first adverse drug reaction reports and worldwide withdrawal was 43 years (aprotinin). The median interval was 1 year (IQR = 0 to 6). The more recent the launch year, the sooner a product was withdrawn worldwide after adverse drug reaction reports; however, the interval to first withdrawal over time did not change consistently (Figure 4.3). In 26 cases (65%), worldwide withdrawals occurred within 2 years of adverse drug reaction reports; and worldwide withdrawals occurred within the first year of initial withdrawal in any country in 39 cases (see Table 4.1). In 18 cases (75%), withdrawals because of deaths occurred within 2 years of the first adverse drug reaction

reports. There was also a shortening in the intervals to worldwide withdrawals when death was attributed to a product (Figure 4.3).

Figure 4.3: Launch year versus interval 3 (the time lapse between the first reported ADR and the first withdrawal worldwide). Red boxes indicate products withdrawn because of drug-attributed deaths.



4.3.5 Comparison of worldwide withdrawals with all withdrawals

There was a marked distinction between products withdrawn before and after 1980.

Between 1950 and 1979 only one product was withdrawn worldwide out of a total of 71 products (1.4%) that were withdrawn anywhere; from 1980 onwards, the number of worldwide withdrawals was on average 14% of all withdrawals (40 out of 283), without much variation from decade to decade.

4.4 DISCUSSION

A total of 40 medicinal products withdrawn worldwide because of adverse drug reactions were identified. Hepatotoxicity, cardiotoxicity and neurotoxicity accounted for over half of the withdrawals, and most of the adverse reactions showed collateral dose-responsiveness. The proportion of worldwide withdrawals compared with all withdrawals increased considerably from 1980 onwards.

The evidence used for withdrawal in 75% of cases was anecdotal reports, and deaths were attributed to the use of withdrawn products in over a third of cases (68%). In almost all cases (98%), the product was withdrawn worldwide within the first year after withdrawal in any country. The interval between the first adverse drug reaction reports and worldwide withdrawals shortened inconsistently over time. These results confirm the previous observations in chapters 2 and 3 which showed that case reports are most often cited as evidence for the need to withdraw medicinal products after marketing. These results also confirm that the interval between launch and the first adverse drug reaction reports and first withdrawals has shortened over time.

4.4.1 Evidence for withdrawals

Most of the worldwide withdrawals were based on evidence obtained from case reports. This is consistent with evidence that formal studies are not often conducted when adverse reactions are suspected [8]. However, worldwide withdrawals may have been justified because of the precautionary principle [9], especially when deaths were reported. However, one would expect confirmatory studies to be conducted if a medicinal product is withdrawn from the market because of suspected non-fatal adverse reactions. In addition, it has been argued that the precautionary principle may not be applicable in health care,

because it is based on the avoidance of risk, and not on assessment of the benefit-harm balance [10], although this has been disputed [11]. Some authors have suggested further modification of this principle to make it more relevant to decision-making processes in health care [12,13]. However, where adverse drug reactions are concerned the crux is the balance of benefit to harm. When this is clearly favourable drugs will not be withdrawn. When it is clearly unfavourable, withdrawal will be likely. However, when the balance is in doubt the precautionary principle may tip the decision towards withdrawal.

One product, anagestone acetate, was withdrawn worldwide because of the risk of tumours, based on evidence from animal studies. Subsequent confirmatory studies after worldwide withdrawal confirmed an increased risk of mammary gland tumours in animals [14,15]. The extrapolation of animal results to human research is controversial and generates strong debate [16,17]. Some authors have suggested that systematically combining the evidence on harms from several animal studies could improve translation of the data into clinical practice [18], but this has been vehemently contradicted by others [19,20]. Furthermore, systematic reviews of animal studies show that they are often methodologically poor [21,22]. A meeting of experts to seek a consensus on “the way forward” has been suggested [23].

Most of the withdrawals were initiated by drug manufacturers, suggesting that they are likely to withdraw their products from the market when there is evidence that the harms outweigh the benefits; this may have been driven by the fact that the suspected adverse reactions in over two-thirds of cases were fatalities. However, the processes for the withdrawals in the face of accumulating evidence for harms do not appear to be consistent. For example, worldwide withdrawal of fenclofenac was initiated because renewal of its

licence was refused in the UK [24] after data from the UK's erstwhile Committee on Safety of Medicines showed records of seven deaths and almost 895 suspected adverse drug reactions within a year of approval [25].

4.4.2 Strengths and limitations

Similar to the previous two chapters, an extensive range of sources was searched to identify medicinal products that have been withdrawn worldwide, and data on their launch dates and withdrawal dates were systematically documented. In addition, the extensive searches were conducted to identify the first reports of adverse drug reactions, the quality of the evidence for which worldwide withdrawal decisions were based was accounted for, and the clinical pathways through which the adverse reactions occurred were examined. However, some limitations are recognized. Worldwide withdrawal has been defined as the withdrawal of a product in all the countries in which it was marketed, even if it was not marketed globally. However, it is uncertain whether all medicinal products that have been withdrawn worldwide were identified through the searches. This difficulty implies that all countries in which drugs have been marketed should be registered (e.g. with the WHO), so that the progress of the drugs can be monitored as widely as possible, and so that even countries in which local information about adverse reactions is not readily available may benefit from access to information gathered in other countries. There was no access to information that enables computation of the intervals between actual occurrences of the first adverse reactions, as opposed to their being reported, and subsequent worldwide withdrawals. Nevertheless, it is unlikely that such information would have significantly affected the trends observed.

4.4.3 Implications for future monitoring and reporting of harms

Although it is unclear the extent to which withdrawals of the specific products identified in this chapter influenced subsequent drug development, it is known that compounds that have caused serious adverse drug reactions (e.g. thalidomide, benoxaprofen, TGN1412) have markedly affected subsequent pharmacovigilance, stressing the importance of studying such withdrawals. The inconsistency in the delays between reports of adverse reactions and worldwide withdrawals suggest difficulty in making withdrawal decisions when reports of such reactions accumulate. Therefore, the need for greater co-ordination across regulatory authorities cannot be overemphasized. Low- to middle-income economies with limited pharmacovigilance capabilities could be assisted in setting up standardized operating procedures for drug recalls. When there has been accelerated approval of products for marketing [26], there should be correspondingly accelerated withdrawal or at least suspension of licences when serious treatment-emergent adverse events are detected.

Evidence syntheses on harms should be expedited when adverse drug reactions are suspected. This could prevent unnecessary exposure of patients to harmful products before withdrawal from the market. As an example, researchers queried why drug regulatory authorities and the drug manufacturer failed to monitor and summarize accumulating data on harms for rofecoxib after regulatory approval [27]. Therefore, rapid systematic reviews could be conducted swiftly when adverse reactions are suspected, to help strengthen the evidence used for withdrawal decisions [28]. Drug manufacturers should also be encouraged to investigate whether a withdrawn medicinal product may have a possible favourable benefit-to-harm balance in other indications, especially when the product had a good population benefit; e.g. thalidomide caused birth defects when it was first introduced

as a hypnotic in pregnancy, but it has since been used beneficially in multiple myeloma [29]. Because an overwhelming majority of the worldwide withdrawals were due to off-target effects, there are opportunities for drug developers to design medicinal products with less risk of harms, but at the same time maintaining the desired pharmacologic, on-target effects [30].

4.5 CONCLUSIONS

The time it takes for drugs to be withdrawn worldwide after reports of adverse drug reactions has shortened over time. However, the speed with which worldwide withdrawals occurred after initial withdrawal suggests possible selective reporting of potentially serious harms in the pre-approval phase, improving with time. There are inconsistencies in current withdrawal procedures when adverse drug reactions are suspected. A uniform method for establishing worldwide withdrawal of approved medicinal products when adverse drug reactions are suspected should be developed, to help facilitate global withdrawals. Rapid synthesis of the evidence on harms data in the pre- to post-approval phases should be a priority when adverse reactions are suspected.

4.6 Chapter Summary

- Anecdotal reports have largely been used as evidence for making worldwide withdrawals when serious adverse reactions are attributed to medicinal products
- Worldwide withdrawals of medicinal products are initiated by the drug manufacturer in a majority of instances

- The delay to worldwide withdrawal following reports of adverse reactions has shortened over time; however, there are inconsistencies in withdrawal procedures across geographical regions
- Rapid synthesis of the evidence on harms should be a priority when serious adverse reactions are suspected

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Chapter 5 Post-marketing withdrawal of human medicinal products because of adverse reactions in animals: a systematic review and analysis

5.1 INTRODUCTION

Before new chemical entities are tested in humans, their safety and effectiveness are assessed using animals. Only after the new product is deemed to be ready for human study (based on findings from *in vitro* and animal studies) are clinical studies initiated, with a view to obtaining marketing authorization.

However, in some cases, evidence of harms in animal research may not become apparent until after the product has been granted marketing authorization, causing a shift in the benefit-to-harm balance in the light of the new evidence, requiring new regulatory action. In the most serious cases, the marketing licence may be revoked or voluntarily withdrawn from the market by the manufacturer [1]. In such cases there may be large financial implications for drug manufacturers and loss of public confidence in pharmaceutical products [2]. Such withdrawals can also be contentious, especially when a causal association between the new product and the adverse reaction is not proven.

In 1963, meclozine became the first product in the modern era to be withdrawn from the market because of a suspected risk of teratogenicity based on evidence from animal research [3]; however, this was later disproved by other published studies [4,5], and the product is still available in several countries. Over the last few decades, regulatory authorities have based withdrawal decisions on evidence observed in animal research.

In chapter 2, the results showed that 11% of the post-marketing withdrawals of medicinal products because of adverse reactions since 1950 were based on evidence obtained from animal research. Until now, there has been no systematic review of the trends in post-marketing withdrawal of medicinal products for which the decisions were based on evidence obtained from animal data. Therefore, the objectives of this chapter were to document medicinal products for which animal research was used as evidence for withdrawal, to determine whether the adverse drug reactions (ADRs) that occurred in the animals were also reported in humans, to investigate whether confirmatory human studies were conducted, and to explore the trends in reporting and withdrawal intervals over time.

5.2 METHODS:

5.2.1 Search strategy

Using the information from the results of updated searches in Chapter 2, the first reviewer (IJO) documented medicinal products that were withdrawn after regulatory approval because of adverse drug reactions based on evidence from animal research between 1950 and June 2016 from the following sources:

- the World Health Organization's (WHO's) database of Consolidated List of Products whose consumption and/or sale have been banned, withdrawn, severely restricted, or not approved by governments (Issues 6, 8, 12 and 14);
- the WHO's Drug Information (Volumes 1–29);
- the WHO's Pharmaceuticals Newsletter (1997–2016, Vol. 1);

For each medicinal product withdrawn, the first reviewer (IJO) then searched the following databases for the first reports of harms in animal:

- PubMed;

- Medline;
- Google Scholar;

[See appendix 1 for comprehensive search strategy].

The bibliographies of retrieved full texts were also searched for any earlier dates of reports of suspected adverse reactions in animals. If an article had evidence of an earlier reported date, that date was chosen as the first adverse reaction date.

The first reviewer (IJO) conducted electronic searches on PubMed, Medline, and Google Scholar to identify human reports of similar adverse reactions resulting from use of the same product. The bibliographies of relevant articles were also searched to verify if earlier reports of such reactions had already been published (except when authors specifically stated that their report was the first known case published). In addition, searches to identify formal studies of the adverse reactions in humans were conducted in electronic databases using the following order of priority: systematic review/meta-analyses > clinical trial > observational studies > case series.

5.2.2 Inclusion/exclusion criteria

To be included in the review, a product must have been withdrawn from the market because of reports of a suspected adverse reaction or reactions, or problems related to hazards or harms based on evidence from animal research. Such products must also have been launched onto the market from 1950 onwards.

Medicinal products that had previously been withdrawn because of adverse reactions but had been re-introduced or made available in other, safer, formulations were included.

Medicinal products were also included irrespective of the route of administration. Products for which there was documented regulatory evidence that they had been voluntarily withdrawn by marketing authorization holders (MAHs) solely for “commercial reasons”, or because of evidence from human adverse reactions reports were excluded, as were herbal products, non-human medicines, and non-prescription medicines.

5.2.3 Assessing the level of evidence and overall evaluation of the evidence

The first reviewer (IJO) used a checklist adapted from the International Agency for Research on Cancer (IARC) criteria [6], to rate the quality of the evidence for withdrawals based on suspected harms in animals (and humans in cases where such harms were subsequently reported). The IARC criteria were used for assessing the evidence because the majority of post-marketing withdrawals of medicinal products from the market because of harms in animals are due to increased risks of carcinogenicity. Where the reason for withdrawal was not related to carcinogenicity (or teratogenicity), the levels and overall evaluation of the evidence was determined by comparing the results of research in such studies with the corresponding levels on the IARC scale, and “extrapolating” the evidence. The level of evidence was rated as follows: Level 1 (highest)—sufficient evidence of harm; Level 2— limited evidence of harm; Level 3— inadequate evidence of harm; Level 4— evidence suggesting lack of harm. The first reviewer (IJO) used the ratings separately for animal or human studies. The IARC’s overall evaluation rating for justification for withdrawal was determined by combining the rating scores of animal and/or human data as follows: Group 1—the agent is harmful to humans; Group 2a—the agent is probably harmful to humans; Group 2b—the agent is possibly harmful to humans; Group 3—the agent is not classifiable as to its harmfulness to humans; Group 4—the agent is probably

not harmful to humans. A second reviewer (JKA) independently verified the level of evidence and the overall evaluation rating. Discrepancies were resolved by discussion.

5.2.4 Data extraction and presentation

For each withdrawn product, the following data were extracted: the date of marketing authorization, the launch date or the date of first recorded use; the drug class and therapeutic indication [7]; the year in which harms related to the reason for withdrawal were first reported in animals; the year in which a suspected adverse reaction was first reported in humans (if any); the year of first withdrawal; the country or countries of withdrawal; the reported organ or system that was affected by the drug; and the species of animals used as evidence for the harms. The first reviewer (IJO) extracted the data and a second reviewer (JKA) verified them independently. When there were discrepancies, both reviewers re-checked the data together and arrived at a consensus.

Summary tables were used to document the following intervals:

- launch year to the year of first reports of adverse reactions in animals;
- launch year to the year of first withdrawal;
- the first report of an adverse drug reaction to the year of first withdrawal;
- the first report of harms in animals to suspected adverse reaction reports in humans.

Because the distributions of these intervals were skewed, medians and interquartile ranges (IQR) were used as measures of central tendency and spread. Scatter plots were used to explore the relationships between launch dates and times to first reports of adverse drug reactions (ADRs) and withdrawals.

5.3 RESULTS

A total of 37 medicinal products for which evidence from animal studies was documented as a reason for withdrawal were included; the withdrawals occurred between 1963 and 2000. The key details of these products and the reasons for withdrawal are shown in Table 5.1. One withdrawn product, pronethalol, was used in clinical studies in the UK but was withdrawn before a licence was issued.

Of the 37 products, 21 were withdrawn in only one country, and only one product was withdrawn worldwide. Suspected risks of carcinogenicity justified withdrawal in 23 cases, and risk of teratogenicity was cited as evidence for withdrawal in four instances. In 11 cases, the adverse reactions were subsequently reported in humans (Table 5.2). Analgesics (n = 4), antimicrobials (n = 4) and contraceptives (n = 4) accounted for 12 withdrawals (33%).

Table 5.1: List of human medicinal products withdrawn from the market because of reports of adverse reactions in animals

Medicinal product	Therapeutic indication	Launch year	First ADR report	Year first withdrawn	*LoE	*Overall rating	Reason for withdrawal	Countries withdrawn
Acetylfuratrizine	Bacterial infections	1962	1976	1977	2	2b	Carcinogenicity	Japan, Saudi Arabia, Venezuela
Acitretin	Psoriasis	1989	1989	1990	1	1	Teratogenicity	Netherlands, France
Anagestone acetate	Contraception	1968	1969	1969	2	2a	Carcinogenicity	Worldwide
Brotizolam	Hypnosedative	1982	1983	1989	4	4	Carcinogenicity	UK
Bucetin	Analgesia	1968	1985	1986	2	2b	Carcinogenicity	Germany
Bumadizone injection	Arthritis	1972	1978	1986	2	2a	Haematologic	Oman
Canrenone	Aldosteronism, heart failure, hypertension	1966	1976	1986	2	2b	Carcinogenicity	Germany
Chenodeoxycholic acid	Cholelithiasis	1975	1976	1987	2	2a	Carcinogenicity	Norway
Chlormadinone acetate	Contraception	1965	1970	1972	3	3	Carcinogenicity	USA, UK, Italy, Egypt, Venezuela
Chlorphentermine	Obesity	1962	1970	1969	2	2b	Respiratory	Germany, Venezuela
Cupric bisquinoline	Arthritis	1958	1967	1978	2	2b	Neuromuscular	France
Dantron (chrysazin)	Constipation	1959	1985	1987	2	2b	Carcinogenicity	Norway, Germany, Japan, USA, Singapore, Canada
Dihydroxy-methylfuratrizine	Bacterial infection	1975	1975	1977	2	2b	Carcinogenicity	Japan, Saudi Arabia, Venezuela
Etretinate	Psoriasis	1981	1982	1992	2	2b	Carcino-teratogenicity	Norway, Brazil, France, USA, Canada
Flosulide	Analgesia	1994	1995	1996	2	2b	Renotoxicity	Germany
Fluvoxamine	Obsessive compulsive disorder; depression	1984	1987	1987	3	3	Teratogenicity	Iceland
Genaconazole	Fungal infection	1970	1992	1992	2	2b	Carcinogenicity	USA
Lynestrenol	Contraception	1962	1970	1980	2	2b	Carcinogenicity	Australia
Lysine amidotriazolate	Vascular diagnostics	1975	1981	1980	2	2b	Cardiotoxicity	Germany
Meclozine (meclizine)	Motion sickness	1953	1963	1995	2	3	Teratogenic potential	Indonesia
Megestrol acetate	Contraception	1963	1972	1963	2	2a	Carcinogenicity	Greece, Norway, Germany, New Zealand
Metofoline	Analgesia	1962	1965	1976	2	2b	Ocular toxicity	USA
Molsidomine	Angina pectoris	1972	1975	1985	2	2b	Carcinogenicity	Germany
Nitroxoline	Urinary tract infection	1965	1966	1985	2	2b	Ototoxicity	Ireland, Thailand, Venezuela
Noscapine	Cough	1959	1984	1990	2	2a	Genotoxicity	Ireland, UK, Netherlands

Oxeladin	Cough	1972	1991	1990	2	2b	Carcinogenicity	Germany, France, Armenia, Canada
Phentolamine mesilate	Erectile dysfunction	1998	1998	1994	2	2a	Carcinogenicity	Singapore
Potassium canrenoate	Hypertension, ascites	1968	1985	1986	2	2b	Carcinogenicity	Germany
Pronethalol†	Angina pectoris	1963	1963	1965	2	2b	Carcinogenicity	UK
Pyrrolizidine	Cough, sinusitis	1967	1968	1992	1	1	Carcinogenicity	Germany, Belgium, UK
Sodium dibunate (ethyl dibunate)	Cough	1963	1968	1982	2	2b	Nervous system toxicity	Philippines
Suxibuzone	Analgesia	1974	1982	1986	2	2a	Carcinogenicity	Oman, Italy
Trazodone	Depression	1973	1983	1985	2	2b	Carcinogenicity	Norway
Tretinoin	Acne	1973	1977	1988	2	2b	Carcinogenicity	Germany
Vigabatrin	Refractory complex partial seizures in adults & infantile spasms	1989	1989	1989	1	1	Ocular toxicity	Norway
Zipeprol HCl	Cough	1971	1984	1991	1	1	Nervous system toxicity	Philippines, Brazil, Spain, Switzerland, Turkey
Zopiclone	Hypnosedative	1985	1985	1986	2	2b	Carcinogenicity	Israel, Norway

ABBREVIATIONS: ADR: Adverse drug reaction; COX: Cyclooxygenase; GABA: Gamma aminobutyric acid; LoE: Level of evidence

*Adapted from the International Agency for Research in Cancer (IARC) criteria [6]. Level 1 (highest)—sufficient evidence of harm; Level 2- limited evidence of harm; Level 3- inadequate evidence of harm; Level 4- evidence suggesting lack of harm. Group 1-agent is harmful to humans; Group 2a-agent is probably harmful to humans; Group 2b-agent is possibly harmful to humans; Group 3-agent is not classifiable as to its harmfulness to humans; Group 4- agent is probably not harmful to humans.

†Patented and marketed, but never licensed for medical use

Table 5.2: Reports of first adverse drug reactions in humans, and the type of animal species used to examine drug-adverse event associations for medicinal products withdrawn because of adverse reactions in animals

Medicinal product	Launch date	First ADR in animals	Year first withdrawn	First ADR in humans	Animal species used as evidence for harms
Acetylfuratrizine	1962	1976	1977	None	Rodents: rats
Acitretin	1989	1989	1990	1994	Rodents: mice, rabbits, rats
Anagestone acetate	1968	1969	1969	None	Non-rodents: beagle bitches
Brotizolam	1982	1983	1989	None	Rodents: mice
Bucetin	1968	1985	1986	None	Rodents: hamsters, mice
Bumadizone injection	1972	1978	1986	None	Rodents: mice, rats
Canrenone	1966	1976	1986	None	Rodents: rats
Chenodeoxycholic acid	1975	1976	1987	1981	Rodents: mice, rats
Chlormadinone acetate	1965	1970	1972	1975	Rodents & non-rodents: rats, beagle bitches
Chlorphentermine	1962	1970	1969	None	Rodents: mice, rats
Cupric bisquinoline	1958	1967	1978	None	Rodents: rats
Dantron (chrysazin)	1959	1985	1987	1989	Rodents: mice, rats
Dihydroxymethylfuratri zine	1975	1975	1977	None	Rodents: rats
Etretinate	1981	1982	1992	1986	Rodents: mice, rabbits, rats
Flosulide	1994	1995	1996	None	Rodents: mice, rats
Fluvoxamine	1984	1987	1987	None	Rodents & non-rodents: mice, rats, dogs
Genaconazole	1970	1992	1992	None	Rodents: mice
Lynestrenol	1962	1970	1980		Rodents: rats
Lysine amidotriazoate	1975	1981	1980	None	Non-rodents: dogs
Meclozine (meclizine)	1953	1963	1995	1962	Rodents: rats
Megestrol acetate	1963	1972	1963	1975	Rodents & non-rodents: mice, rats, cats, dogs
Metofoline	1962	1965	1976	None	Non-rodents: dogs
Molsidomine	1972	1975	1985	None	Rodents: rats
Nitroxoline	1965	1966	1985	None	Rodents: mice
Noscapine	1959	1984	1990	None	Rodents: hamster
Oxeladin	1972	1991	1990	None	?
Phentolamine mesilate	1998	1998	1994	None	Rodents: mice, rats
Potassium canrenoate	1968	1985	1986	None	Rodents: rats
Pronethalol	1963	1963	1965	None	Rodents & non-rodents: mice, dogs
Pyrrolizidine	1967	1968	1992	1970	Rodents: rats

Sodium dibunate (ethyl dibunate)	1963	1968	1982	None	Rodents: mice
Suxibuzone	1974	1982	1986	None	Rodents: rats
Trazodone	1973	1983	1985	None	Rodents: rats
Tretinoin	1973	1977	1988	None	Rodents: mice
Vigabatrin	1989	1989	1989	1997	Rodents & non-rodents: rats, dogs
Zipeprol	1971	1984	1991	1985	Non-rodents: monkeys
Zopiclone	1985	1985	1986	2005	Rodents: rats

Abbreviation: ADR: adverse drug reaction

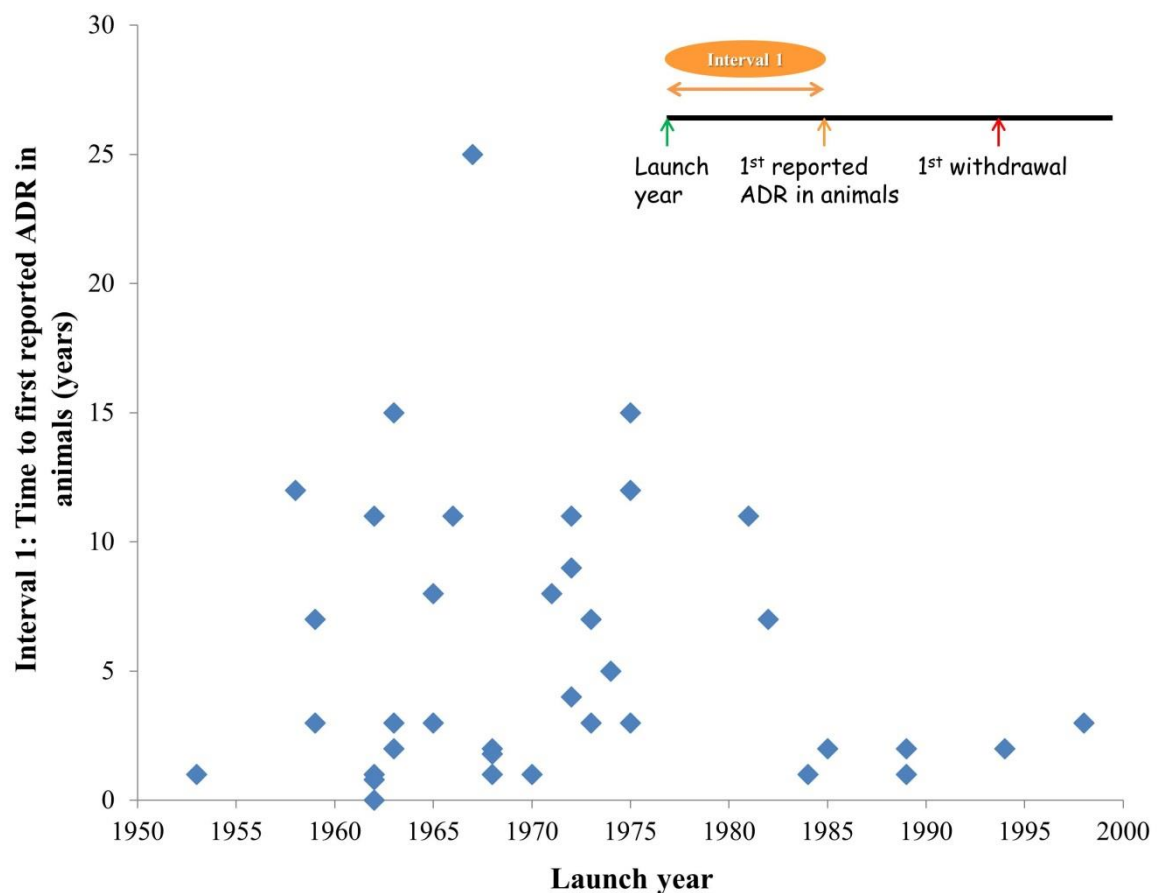
5.3.1 Levels and quality of the evidence

Four products were withdrawn because of IARC Level 1 evidence, and 30 products because of Level 2 evidence (Table 5.1). Two products were withdrawn based on Level 3 evidence and only one was withdrawn based on Level 4 evidence. In 22 cases (59%), the products were possibly harmful to humans. In five instances we identified subsequent published reports of formal studies investigating the association between the product and the suspected adverse reaction in humans (see section 5.4.2).

5.3.2 Intervals between launch and first reports of adverse reactions in animals

The longest interval between launch year and the first adverse reaction report in animals was 26 years (Danthron). The median interval between launch and animal reports of suspected harms was 6 years (IQR = 1 to 11). The more recent the launch date, the quicker the reports of possible harms in animal studies appeared in the literature (Figure 5.1). In six cases (16%), such reports appeared within one year of launch, and the reports appeared within 2 years of launch for 7 cases (19%). For the remaining 34 cases (65%), at least 3 years elapsed before the first reports of adverse reactions in animals.

Figure 5.1: Interval between launch year and first report of adverse reactions in animals



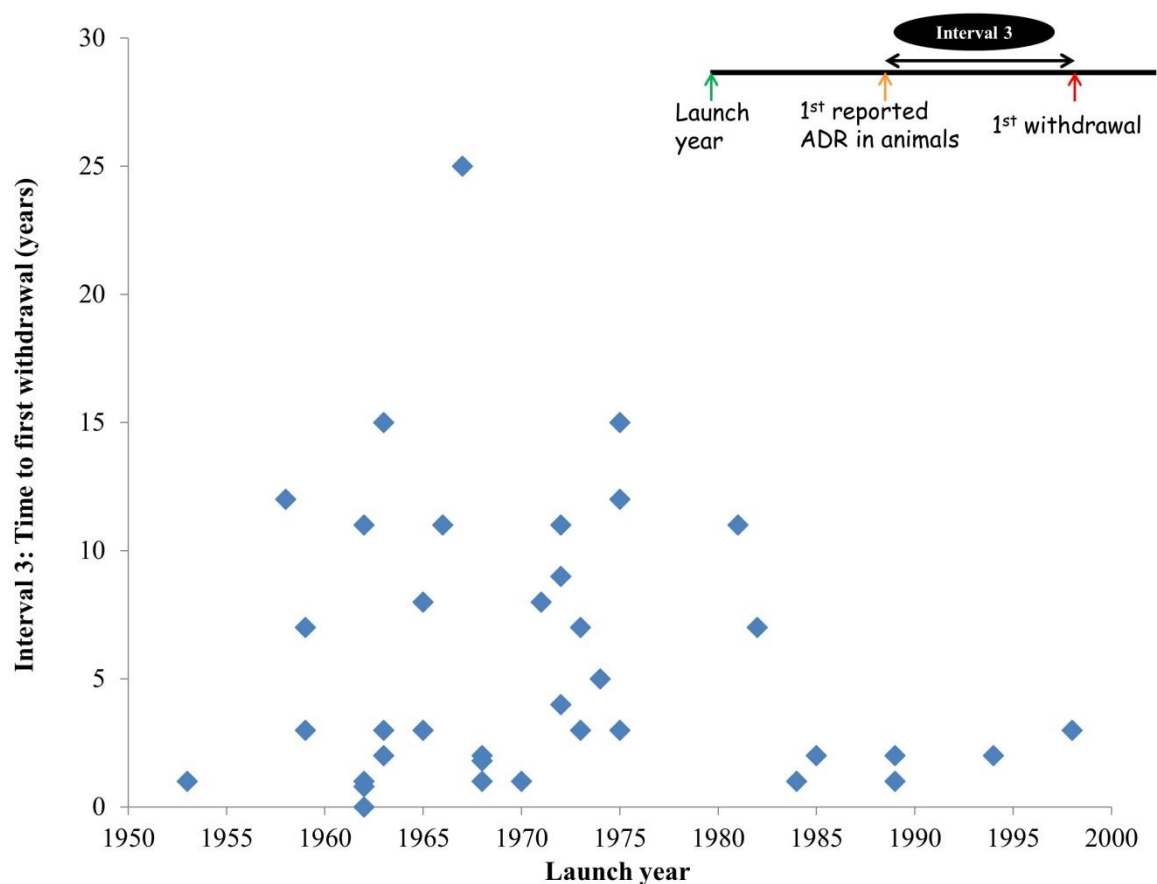
5.3.3 Interval between launch year and the year of first withdrawal

The longest interval between launch year and first withdrawal from the market following adverse reaction reports in animals was 31 years (noscaphine). The median interval between launch and first withdrawal following reports of suspected harms in animals was 12 years (IQR = 3 to 20). The more recent the launch year, the faster the withdrawals were enforced following reports of harms in animals (data not shown). Eight products (22%) were withdrawn from the market within two years of launch.

5.3.3 Interval between first adverse reaction report in animals and the year of first withdrawal

The longest interval between the first adverse reaction report in animals and the year of first withdrawal was 24 years (pyrrolizidine). The median interval to withdrawal following reports of suspected adverse reactions in animals was 2 years (IQR = 1 to 9). Figure 5.2 shows an inconsistent shortening in the interval to withdrawal with more recent launch; in 54% of cases, the withdrawals occurred within two years of reports of harms to animals appearing in the literature.

Figure 5.2: Interval between first report of adverse reactions in animals and withdrawal of human medicinal products from the market



For 11 withdrawn products, when suspected adverse reactions were reported in humans after the initial withdrawals based on animal studies, the median interval between the reports in animals and subsequent reports of suspected adverse reactions in humans was 4 years (IQR = 1 to 5). For one withdrawn product, zipeprol, while the first withdrawal (in the Philippines) was based on evidence from animal data, subsequent withdrawals in other countries were based on human reports of adverse drug reactions (deaths).

5.3.4 Classification of animal species used for withdrawals

In 27 cases (73%) evidence from rodent-only species was used to determine withdrawal decisions (Table 5.2), while evidence from only non-rodent species was used as evidence for determining withdrawal in 4 cases (11%). In 5 instances (14%) evidence from rodent and non-rodent species was used as reasons for withdrawals. We were unable to identify the animal species used as evidence for withdrawal in one case (oxeladin).

5.4 DISCUSSION

5.4.1 Main findings

Thirty seven medicinal products were identified to have been withdrawn from the market between 1963 and 2000 based on evidence from animal research. Carcinogenicity was the main reason for withdrawal in 70% of cases. Toxicity to the nervous and sensory systems accounted for the majority of the other reasons for withdrawal (14%). In over 80% of cases, the level of evidence for which withdrawal decisions were based was limited, and in about two-thirds of cases there was evidence of possible harm. The median interval to withdrawal following the reports of suspected harms was 2 years, and in 11 cases similar reactions were subsequently reported in humans. In an overwhelming majority of cases, research reports involving only rodent species were used as evidence for withdrawals.

Based on the IARC levels of evidence and the overall ratings, the decisions to withdraw all but one of the products appear to have been justified if the precautionary principle was applied, i.e. withdrawal of a medicinal product when there is a suspected risk of harm and uncertainty about the benefit to harm balance [8]. However, the pattern of withdrawal across countries was inconsistent, suggesting that there are discrepancies in how the results of animal research are interpreted and applied across regulatory authorities. We have previously reported that withdrawals are inconsistent for a range of drugs used in humans and further this supports our previous recommendations about the need for a uniform method to facilitate withdrawals of medicinal products when serious adverse reactions are suspected [9].

The results show that confirmatory animal studies involving at least two different animal species are seldom conducted when adverse reactions are suspected from the use of medicinal products, and evidence synthesis research on harms using animals could not be identified. This suggests that the decisions for withdrawals were largely based on anecdotal evidence of suspected harms in animals. This is crucial, especially as there were inconsistencies in the results of animal research for some of the withdrawn products. That carcinogenicity and teratogenicity were the most common reasons for withdrawals could be because medicines are more likely to be withdrawn when animal studies demonstrate the serious potential adverse effects of cancers and foetal malformations than when they demonstrate other risks.

The overall shortening in the interval between launch and withdrawal suggests that there have been improvements in pharmacovigilance methods for detecting and assessing drug-

adverse event relationships in animals. The median interval to withdrawal following reports of harms was shorter for products launched from 1980 onwards (1 year) than those introduced earlier (3 years). The delay in withdrawals from 1980 onwards may be shorter because of emergence of novel techniques and improvements in the facilities used for conducting animal research [10], increasing use of other alternatives for conducting harms assessment [10,11], or a combination of the two. The reports of adverse reactions in humans after withdrawals based on the evidence in animal reports (11 cases) could have been due to either the time lapse between actual occurrences of the adverse reactions and subsequent publication in the literature, or the withdrawal of products in one country based on the reports of adverse reactions in animals in another country.

The results of this chapter also show that there is a failure to conduct further human studies when initial reports of suspected harms are inconclusive. For instance, zopiclone was withdrawn from the market because of an increased risk of adenocarcinomas, based on results of research in animals. The authors of a retrospective study in humans concluded that a prospective study to investigate the effects of the product in humans was warranted [12]. The first reviewer (IJO) has not found any such study (latest search on PubMed, MEDLINE and Google Scholar: from 1 January, 2005 to 9 January, 2017). Failure on the part of drug manufacturers or regulatory authorities to conduct further research investigating drug-adverse event relationships adds to uncertainties about the validity of the reasons for withdrawal of products.

5.4.2 Disconnect between animal and human research

The value of using animal research to predict harms of medicinal interventions in humans is highly debatable, because of challenges on how to extrapolate the results [13,14]. This is

especially concerning when the results of formal human studies on harms are at variance with the findings in animals.

Of the five withdrawn products for which confirmatory studies were conducted in humans, in four cases (chlormadinone [15,16], fluvoxamine [17], meclizine [18,19,20], and nitroxoline [21]) the results contrasted with those of the animal research on which withdrawal decisions were based, while the results with the fifth product (zopiclone) [12] were inconclusive (Table 5.3). The difficulty in predicting harms in humans using evidence from animal studies has led to calls from some authors to abandon the use of animals for research [22,23].

Table 5.3: Cases in which there were discrepancies between the results of animal studies and human studies for medicinal products withdrawn because of adverse drug reactions in animals

Medicinal product	Launch year	Withdrawal year	Reason for withdrawal	Conclusions from human studies	Level of evidence†
Chlormadinone acetate	1965	1972	Increased risk of mammary gland tumours in beagle bitches	No association between chlormadinone acetate and increased risk of cancers ^{15,16}	3
Fluvoxamine	1984	1987	Increased risk of congenital malformations	No association between fluvoxamine and increased risk of congenital malformations ¹⁷	1
Meclozine	1953	1963	Increased risk of congenital malformations	No apparent risk when used in early pregnancy ^{18,19,20}	2*
Nitroxoline	1965	1973	Increased risk of cataracts in rats	No significant association between nitroxoline exposure and risk of eye disorders ²¹	1
Zopiclone	1985	1986	Increased risk of adenocarcinoma in rats and mice	Further research required to estimate possible risk of cancer with zopiclone exposure ¹²	3

*Upgraded from Level 3 to Level 2 because there were two very large sample sized observational studies which reported similar findings

†Based on the Oxford Centre for Evidence-Based Medicine Levels of Evidence [<http://www.cebm.net/wp-content/uploads/2014/06/CEBM-Levels-of-Evidence-2.1.pdf>]. Level 1: Systematic review of randomized trials, systematic review of nested case-control studies, Level 2: Individual randomized trial or (exceptionally) observational study with dramatic effect; Level 3: Non-randomized controlled cohort/follow-up study (post-marketing surveillance); Level 4: Case-series, case-control, or historically controlled studies; Level 5: Mechanism-based reasoning.

Furthermore, in some instances it is difficult to predict whether the intensity of the harms observed in animals will result in an unfavourable benefit-to-harm balance in humans. For instance, vigabatrin was refused marketing authorization in Norway because the regulatory

authorities there concluded that the therapeutic indication was not medically justified because of an increased risk of ocular damage. This has been demonstrated in both animal and human studies [24,25,26,27]. However, the product has been approved in several other countries for use in refractory epilepsy, despite evidence of damage to visual fields. Such inconsistencies in withdrawal decisions support our previous assertion in chapter 3 that different indications may contribute to variations in the interpretation of the risk of adverse reactions attributed to a product.

5.4.3 Strengths and limitations

This is the first review that has systematically identified and evaluated the reasons for withdrawal of medicinal products based on evidence from animal research. A range of sources was used to search for the withdrawn products, and the levels and quality of the evidence which influenced the withdrawal decisions were accounted for. However, some limitations are noted. All medicines that were withdrawn based on evidence from animal research may not have been identified and all countries in which products were withdrawn may not have been identified; however, it is unlikely that this would significantly alter the conclusions. There was no information to determine the interval between the observations of the suspected adverse reactions in animals and the first publications of such reports, but it is not likely that such intervals would change the trends we observed.

5.4.4 Implications for research and policy

Current international guidelines on non-clinical safety studies stipulate the use of at least one rodent and one non-rodent species for drug toxicity studies, and that clinical trials of longer duration should be supported by evidence of repeated animal toxicity studies of at least equivalent duration [28,29,30]. However, as our results show, in only very few

instances (<14%) did we identify research evidence based on both rodent and non-rodent species.

It is doubtful whether the use of one rodent and one non-rodent animal species is sufficient to adequately predict the risks of harms in humans. For instance, aminorex was withdrawn from the market by regulatory authorities because of suspected pulmonary hypertension attributed to its use as an anti-obesity medication. Attempts at replicating pulmonary hypertension by administration of aminorex were unsuccessful in rats [31], patas monkeys [32], and beagle dogs [33]. However, pulmonary hypertension was subsequently elicited in mongrel dogs [34]. Therefore, further research on which animal models can more accurately predict drug-tissue/organ interactions in humans could be encouraged. [See Box 5.1 for list of recommendations].

Of note, research evidence from animal studies has not been cited as a reason for withdrawal of medicinal products from the market over the past 15 years. This could be the result of more rigorous methods of animal testing before the start of human studies, e.g. longer durations of intervention. However, it may also be indicative of negative publication bias by investigators when the results of such studies were unfavourable [35], resulting in skewed reporting in favour of effectiveness over harms [36]. In fact, the authors of some of the published reports of animal studies referred to the use of unpublished reports of animal research provided by drug sponsors. The reporting of results of animal research should be mandatory, irrespective of the direction of the effect (Box 5.1). A collaborative network to encourage greater transparency in the reporting of data from animal research has been established and continues to develop [37].

The quality of harms reporting in animal studies is often poor [38], and this could limit the validity of the results. A guideline to improve reporting of animal research has been developed [39], and it is imperative that future reports of animal toxicity studies should adhere to such guidelines to improve the quality of harms reporting (Box 5.1).

Furthermore, evidence synthesis of harms in animals should be conducted to improve the predictability of such results in humans [40,41]. A navigation guide for evaluating the strength of human evidence with respect to reproductive and developmental toxicity has been proposed [42,43], but has not yet been validated.

Box 5.1: The Onakpoya *et al* recommendations for improvement of translational evidence in harms assessment.

Recommendation	Reason
Develop a registry of animal trials and ensure mandatory reporting	Overcomes negative publication bias
Obtain data on harms from two or more animals	It is doubtful whether the use of one rodent and one non-rodent animal species is sufficient to adequately predict the risks of harms in humans
Conduct human studies when animal studies are inconclusive	The value of using animal research to predict harms of medicinal interventions in humans is highly debatable; in some instances it is difficult to predict whether the intensity of the harms observed in animals will result in an unfavourable benefit-to-harm balance in humans
Undertake systematic reviews	Decisions for withdrawals have been largely based on anecdotal evidence of suspected harms in animals
Adhere to animal toxicity guidelines	The quality of harms reporting in animal studies is often poor
Create an international body that reviews newer developments in animal testing	Some authors have advocated further research aimed at refining existing methods or developing new methods for predicting the carcinogenic risks of new chemical entities

The most common cause for withdrawals in our study was the risk of carcinogenicity. Most of the animal testing for predicting the risk of carcinogenicity in humans have been conducted using the lifetime rodent bioassay (LRB) – a two year test intended to simulate lifetime exposure to a compound [44]. However, the extent to which LRB accurately predicts the risk of cancer in humans has not been validated [45], it has been reported to be very expensive and time-consuming [46], and the appropriateness of the two year study duration has been questioned [47]. Similarly, most in vitro mutagenicity testing was based on the Ames method developed in the 1970s, which relies on observing effects on the bacterium *Salmonella typhimurium* [48]. Although this test has been modified several times over the years, it has been reported to show poor sensitivity (false positives) [49,50], and the test does not detect non-genotoxic carcinogens. Newer tests aimed at obviating the limitations of the Ames test have become available, but some authors have advocated further research aimed at refining existing methods or developing new methods for predicting the carcinogenic risks of new chemical entities [51]. Indeed, the combination of the Ames test with other in vitro and animal studies (in vitro micronucleus assay and mouse lymphoma assay) as a test battery has been shown to increase the sensitivity for carcinogen detection to over 90% [52]. We therefore advocate the creation of an international body to evaluate such new techniques (Box 5.1).

5.5 CONCLUSION

Suspected risks of carcinogenicity or teratogenicity are the most common reasons for withdrawal of medicinal products from the market based on animal research.

Confirmatory animal and human studies are seldom conducted when medicinal products are withdrawn because of evidence from animal research. Investigators should be encouraged to publish the data of harms research conducted in animals, irrespective of the

direction of the results; this would aid better harms assessment of new medicinal products. There should be more consistency in the methods with which the results of animal studies are interpreted. Further research to determine the most robust methods for extrapolation of the results of animal research to humans should be a priority.

5.6 Chapter Summary

- Regulatory authorities and drug manufacturers are likely to withdraw medicinal products quickly from the market when animal experiments suggest increased risks of cancers or congenital malformations
- The level of evidence used for making withdrawal decisions when adverse reactions are observed in animals is limited in an overwhelming majority of cases
- Confirmatory animal studies involving at least two different animal species are seldom conducted when adverse reactions are suspected from the use of medicinal products
- Human studies are seldom conducted when harms are suspected in animals
- Future research should explore better methods of extrapolating harms data from animal research to humans

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Chapter 6 Post-marketing withdrawal of analgesic medicinal products because of adverse drug reactions: a systematic review

6.1 INTRODUCTION

Pain is one of the most common presenting symptoms to primary care physicians [1,2]. Estimates of its prevalence in the general population varies, but have been reported to be 30-66% in Scandinavia [3,4], approximately 46% in Asia [5], and over 66% for adults in the UK [6]. The prevalence of chronic pain in general population ranges from 31% in the USA [7] to 44% in the UK [8]. Chronic pain accounts for 41% and 62% of general practice presentations in South Africa and Germany respectively [9,10]. Pain has a substantial impact on the quality of life [11,12], and can result huge economic burdens for governments. Common pain conditions have been reported to cause annual lost productivity to the tune of \$61 billion in the US [13], \$13 billion in the Europe [14], and \$3 billion in Australia [15]. Indeed, pain has been described as a global public health priority [16]. Strategies to manage pain include patient education [17], transcutaneous electrical nerve stimulation (TENS) [18,19], other complementary therapies [20], and pharmacotherapy usually in the form of anti-inflammatories (hereafter referred to as analgesics) [21,22].

Dioscourides, a Greek physician of the Roman army, prescribed extracts of willow bark for joint pain, an approach that was later propagated by Hildegard von Bingen in continental Europe and, of course, by the Reverend Stone in his famous letter to the Royal Society of Medicine in London [23]. This was followed by the discovery of aspirin in 1853 by Gerhardt [24]. By 1897, the use of aspirin as an anti-inflammatory remedy was trialled, and by 1899, aspirin was already being marketed as an analgesic [24,25]. During this period (1875), another analgesic, antipyrine (phenazone) was discovered, and this

compound has been referred to as the “mother of modern analgesia” [26]. Since the discovery of these two compounds, development of analgesics has evolved, with the synthesis and marketing of new products over the last two centuries.

Analgesic and anti-inflammatory products (hereafter referred to as analgesics) have been used for the management of various pain conditions for thousands of years [27].

Analgesics are the most common over the counter medication [28] and the most commonly used drug in palliative care [29]. This high frequency of use has led some authors to advocate continuous education of clinicians on appropriate prescribing to ensure their rational use [30,31].

In chapter 2, the results showed that analgesics accounted for 13% of medicinal products withdrawn from the market because of adverse drug reactions (second only to the antimicrobials). In chapter 4, the results showed that analgesics are the most common medicinal products (25%) withdrawn worldwide because of adverse drug reactions. However, controversy still surrounds the use of some for pain management [32,33] and there has been no systematic examination of the patterns and reasons for withdrawal. In this chapter therefore, analgesic medicinal products that have been withdrawn because of adverse drug reactions have been specifically documented, the reasons for withdrawal examined, the levels of evidence used for making the withdrawal decisions ascertained, the mechanisms through which the adverse reactions occurred are determined, and the trends in withdrawals over time are explored.

6.2 METHODS

6.2.1 Search strategy

The first reviewer (IJO) identified analgesic medicinal products withdrawn from the market using the results of chapter 2. The searches were updated in June 2016 to identify any further withdrawals using the following sources:

- the WHO's Drug Information;
- the WHO's Pharmaceuticals Newsletter;
- the website of the UK Medicines and Healthcare products Regulatory Agency (MHRA);
- the website of the US Food and Drug Administration (FDA);
- the database of withdrawn drugs of the European Medicines Agency (EMA);

For each analgesic product, the first reviewer (IJO) also conducted updated searches in the following databases to confirm the year of first reported adverse drug reaction (ADR):

- PubMed [up till June 2016];
- Google Scholar [up till June 2016];
- the database of withdrawn drugs of the European Medicines Agency (EMA);
- the website of the UK Medicines and Healthcare products Regulatory Agency (MHRA);
- the website of the US Food and Drug Administration (FDA).

The search terms included “analgesic”, “withdrawal”, “adverse reaction”, “adverse event”, “toxicity”, “fatal*”, “voluntary recall”, “suspension”, “prohibition”, “banned”, “remov*”, “revoke*”, “discontinued”. [See appendix 2]. If the information for an analgesic product using its chemical name could not be found, the trade name or code name was used for our electronic searches. The first reviewer (IJO) also searched the bibliographies of retrieved articles for any earlier reports of suspected adverse reactions. If an article contained

evidence of an earlier reported date, that date was chosen as the first adverse reaction date. If an analgesic was withdrawn because of two or more adverse reactions, the first published date of any such reactions was used.

6.2.2 Inclusion/exclusion criteria

To be included in the review, an analgesic product must have been withdrawn from the market because of reports of suspected adverse reactions, or problems related to hazards or harms. The products must have been launched into the market from 1950 onwards.

Analgesic products that had previously been withdrawn because of adverse reactions but had been re-marketed or re-introduced in other formulations were included. Analgesics for which there was documented regulatory evidence that they had been voluntarily withdrawn by marketing authorization holders (MAHs) solely for “commercial reasons” were excluded. Also excluded were herbal products, non-human medicines, and non-prescription medicines.

6.2.3 Assessing the types of evidence

The first reviewer (IJO) documented the highest level of available evidence before the year of first withdrawal of products, based on the Oxford Centre for Evidence Based Medicine (OCEBM) criteria [34]. These were independently verified by a second reviewer (JKA). Discrepancies were resolved through discussion.

6.2.4 Data extraction

The first reviewer (IJO) extracted data based on the strategy used in the previous chapters. For each withdrawn analgesic product, data were extracted on: the date of first marketing authorization or launch date; the drug class and therapeutic indication [35]; the year in

which an adverse drug reaction related to the reason for withdrawal was first reported; the year of first withdrawal; the country or countries of withdrawal; and the reported organ or system that was adversely affected by the drug. A second reviewer (JKA) verified the extracted data independently. When there were discrepancies, both reviewers re-checked the data together and arrived at a consensus through discussion.

6.2.5 Statistical analysis

Summary tables were used to document the intervals between launch year and the year of first reports of adverse drug reactions, the interval between launch year and the year of first withdrawal, and the interval between the first report of an adverse drug reaction and the year of first withdrawal. Because these intervals were skewed, medians and interquartile ranges (IQR) were used as measures of central tendency and spread. Scatter plots were used to explore the relationships between launch dates and times to first reports of adverse drug reactions and withdrawals. The chi-square statistic was used to compare withdrawal patterns between different geographical regions and different mechanisms of action; a P value of <0.05 was considered statistically significant.

6.3 RESULTS

A total of 83 withdrawn analgesic products were identified (Figure 6.1). Thirty-four products were excluded because they were withdrawn from the market before regulatory approval and another two because they were marketed as herbal preparations. Finally, a total of 47 products were included. The withdrawals occurred between 1965 and 2011. The key characteristics of the withdrawn products, including the reasons for withdrawal, are shown in Table 6.1.

Figure 6.1: Flow diagram showing strategy used to analgesic medicinal products withdrawn from the market because of adverse reactions

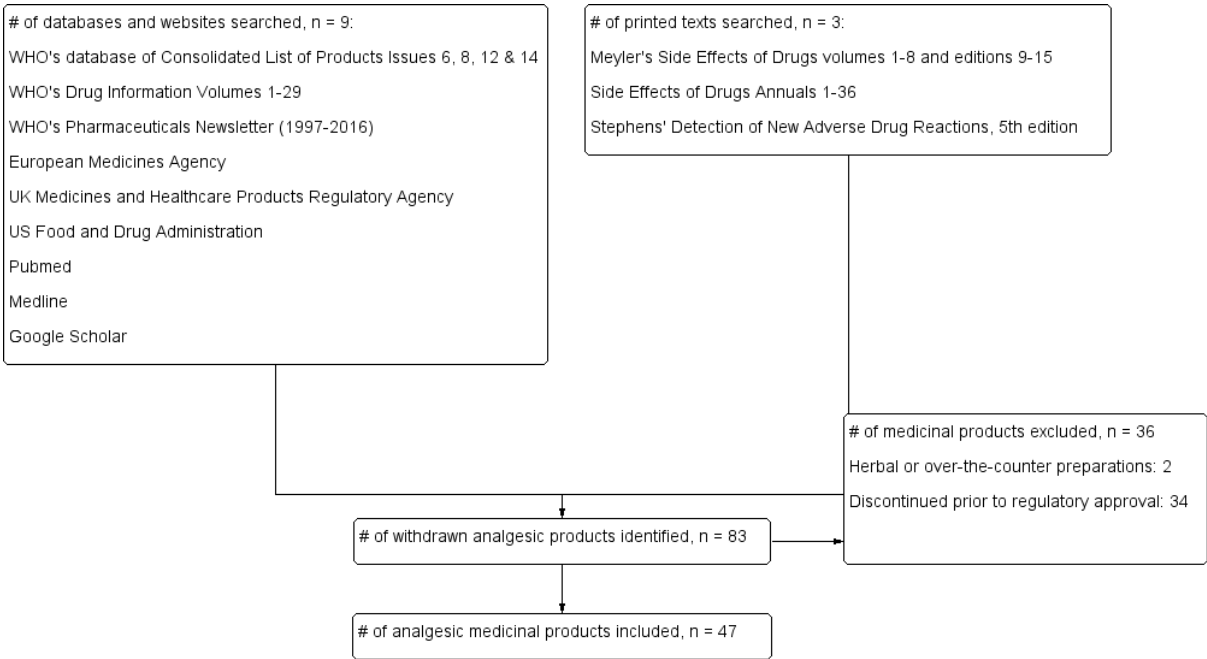


Table 6.1: List of analgesic medicinal products withdrawn from the market because of adverse drug reactions

Medicinal product	Class	Mechanism of action	Launch year	First ADR report	Year first withdrawn	Countries withdrawn	Reason for withdrawal†	LoE†
Alclofenac	NSAID	COX-1 & COX-2 inhibition	1972	1974	1977	Ireland, Cyprus, Germany, UK, Italy, New Zealand, Egypt, Greece, India, Denmark, Indonesia, Jordan, Morocco	Vasculitis, dermatitis	4
Alphacetylmethadol	Opioid	β-opioid receptor agonist	1993	2001	2003	USA	Cardiac arrhythmia	4
Antrafenine	NSAID	COX-1 & COX-2 inhibition	1977	1979	1984	France	Acute interstitial nephritis	4
Bendazac*	NSAID	COX-1 & COX-2 inhibition	1983	1987	1993	Spain	Hepatotoxicity	4
Benoxaprofen	NSAID	COX-1 & COX-2 inhibition	1980	1982	1982	Worldwide	Hepatotoxicity	4
Benzydamine (Difflam)	NSAID	COX-1 & COX-2 inhibition	1967	1980	1995	Germany (available in the UK)	Photodermatitis	4
Bezitramide	Opioid	Opioid receptor agonist	1961	1983	2004	Netherlands	Abuse	4
Bromfenac tablets	NSAID	COX-1 & COX-2 inhibition	1997	1998	1998	USA, Saudi Arabia	Hepatotoxicity	4
Bucetin	Anilide	Phenacetin analogue: precise mechanism unknown	1968	1985	1986	Germany	Carcinogenicity	5
Bufexamac	NSAID	COX-1 & COX-2 inhibition	1973	1973	1990	France; Europe in 2010	Hyper-susceptibility	4
Bumadizone injection	NSAID	COX-1 & COX-2 inhibition	1972	1978	1986	Oman	Degenerative bone changes	5
Buprenorphine*	Opioid	Agonist-antagonist opioid receptor modulator	1978	1983	1986	Egypt	Abuse	4
Celecoxib (Onsenal)	NSAID	COX-2 inhibition	2003	2006	2011	Europe	MI, stroke	3
Clomacron	NSAID	COX-1 & COX-2 inhibition	1966	1970	1982	UK	Hepatotoxicity	4
Clometacin*	NSAID	COX-1 & COX-2 inhibition	1971	1981	1990	France	Hepatotoxicity	4
Co-proxamol (PCM+ dextropropoxyphene)	Anilide + opioid	G-protein receptor modulation + β-, κ- & μ-opioid receptor agonist	1957	1960	2007	Europe, India, USA, Zimbabwe, New Zealand	Abuse	4
Diclofenac sodium**	NSAID	COX-1 & COX-2 inhibition	1979	1979	1983	Philippines, Norway	Carcinogenicity	4

Diphenazine (quetidine)	Anxiolytic	GABA-receptor agonist?	1962	1967	1967	Hungary, Venezuela	Photodermatitis	4
Droxicam	NSAID	COX-1 & COX-2 inhibition	1990	1992	1994	Europe	Hepatotoxicity	4
Fenclofenac*	NSAID	COX-1 & COX-2 inhibition	1978	1984	1984	Worldwide	Hepatotoxicity; carcinogenicity	4
Fenclozic acid	NSAID	COX-1 & COX-2 inhibition	1969	1970	1970	UK, USA	Hepatotoxicity	2
Fentanyl hydrochloride	Opioid	μ -opioid receptor agonist	2006	2006	2009	Europe	Abuse	4
Feprazone (prenazone)	NSAID	COX-1 & COX-2 inhibition	1978	1981	1984	UK, Germany, Greece, Egypt	Skin reactions	4
Floctafenine	NSAID	COX-1 & COX-2 inhibition	1976	1976	1987	Belgium	Dermatitis	4
Flosulide	NSAID	COX-2 inhibitor	1994	1995	1996	Germany	Renal damage	5
Fluproquazone	NSAID	COX-1 & COX-2 inhibition	1979	1984	1989	USA	Hepatotoxicity	4
Glafeine	NSAID	COX-1 & COX-2 inhibition	1965	1973	1984	Worldwide	Anaphylaxis, hepatorenal toxicity	4
Ibufenac	NSAID	COX-1 & COX-2 inhibition	1961	1964	1968	UK	Hepatotoxicity	4
Indometacin * (Osmosin)	NSAID	COX-1 & COX-2 inhibition	1963	1978	1983	UK	GI bleeding	4
Indoprofen	NSAID	COX-1 & COX-2 inhibition	1976	1982	1983	Worldwide	Carcinogenicity	4
Isoxicam	NSAID	COX-1 & COX-2 inhibition	1983	1985	1985	Worldwide	Dermatitis	4
Ketoprofen (gel)	NSAID	COX-1 & COX-2 inhibition	1980	1983	2008	Egypt, France	Photodermatitis	4
Ketorolac	NSAID	COX-1 & COX-2 inhibition	1989	1992	1992	Germany, France, Jamaica	GI bleeding	4
Loxoprofen sodium*	NSAID	COX-1 & COX-2 inhibition	1983	1993	2000	Singapore	Colonic ulceration	4
Lumiracoxib*	NSAID	COX-2 inhibitor	2006	2007	2007	Australia, USA, Canada, Europe, New Zealand, Brazil, Philippines, Colombia	Hepatotoxicity	4
Metofoline	Opioid	Opioid receptor agonist	1962	1965	1965	USA	Ocular damage	5
Nimesulide*	NSAID	COX-2 inhibition	1986	1998	1999	Portugal, Israel, Spain, Bangladesh, Nigeria, India, Ireland, Ghana	Hepatotoxicity	4
Oxyphenbutazone*	NSAID	COX-1 & COX-2 inhibition	1955	1974	1984	Worldwide	Bone marrow suppression	4
Parecoxib	NSAID	COX-2 inhibition	2002	2005	2005	USA, European Union	Cardiorespiratory toxicity	2

Pifoxime	NSAID	COX-1 & COX-2 inhibition	1975	1975	1976	France	Neuropsychiatric	4
Pirprofen	NSAID	COX-1 & COX-2 inhibition	1982	1986	1990	Worldwide	Hepatotoxicity	4
Propyphenazone*	NSAID	COX-1 & COX-2 inhibition	1951	1980	1989	Turkey, UAE, Bahrain, Ireland	Lyell's syndrome; bone marrow suppression	4
Rofecoxib	NSAID	COX-2 inhibition	1999	2002	2004	Worldwide	MI	1
Suprofen	NSAID	COX-1 & COX-2 inhibition	1983	1986	1986	Worldwide	Renal damage	4
Suxibuzone	NSAID	COX-1 & COX-2 inhibition	1974	1982	1986	Oman, Italy	Carcinogenicity	5
Valdecoxib	NSAID	COX-2 inhibition	2001	2003	2005	USA, Canada, Europe, India	Cardiovascular and skin reactions	2
Zomepirac*	NSAID	COX-1 & COX-2 inhibition	1979	1981	1983	Worldwide	Anaphylaxis	4

ABBREVIATIONS: ADR: Adverse drug reaction; COX: Cyclooxygenase; LoE: Level of evidence; NSAID: Non-steroidal, anti-inflammatory drug

*Withdrawn products for which deaths were attributed

**Withdrawn because of risk of bone marrow suppression in children in the Philippines

†Based on the Oxford Centre for Evidence-Based Medicine Levels of Evidence [34]. Level 1: Systematic review of randomized trials, systematic review of nested case-control studies, Level 2: Individual randomized trial or (exceptionally) observational study with dramatic effect; Level 3: Non-randomized controlled cohort/follow-up study (post-marketing surveillance); Level 4: Case-series, case-control, or historically controlled studies; Level 5: Mechanism-based reasoning

Table 6.2: Post-marketing withdrawals of analgesic medicinal products by continent*

Continent	No. of analgesics withdrawn (% of total withdrawn)	Statistical comparison (Europe vs other continents)
Europe	39 (83%)	Reference
Asia	21 (45%)	P = 0.005
N. America	20 (43%)	P < 0.0001
Africa	14 (30%)	P < 0.0001
Australasia & Oceania	13 (28%)	P < 0.0001
S. America	12 (26%)	P < 0.0001

*The analysis is based on 47 medicinal products, and includes 10 products withdrawn worldwide

When analysed by continent, 39 products were withdrawn in Europe, 21 in Asia, 20 in North America, 14 in Africa, 13 in Australasia and Oceania, and 12 in South America. A total of 10 products were withdrawn worldwide (21%), and 19 (40%) were withdrawn in only one country: Europe 13, North America 3, Asia 2, and Africa 1. There was a significantly greater proportion of withdrawal in Europe compared with each of the other five continents: $P < 0.001$ for each comparison except for Asia ($P = 0.005$) (Table 6.2). For 16 products marketed in both Europe and the USA (Table 6.3), there was a higher rate of withdrawal in Europe than in the USA: relative risk (RR) 6.00, 95% CI 0.81 to 51, $P = 0.08$.

Systematic reviews (Level 1) were used as evidence for withdrawal in one case (2.1%) (Table 6.1). The results of randomized trials (Level 2) were used as evidence in three instances (6.4%), and observational studies (Level 3) were cited as evidence in one case (2.1%). In 42 instances (89%), case reports (Level 4) were used as evidence for withdrawals. In five cases (11%), the withdrawals were based on evidence from animal studies (Level 5). In 11 cases (23%), deaths were attributed to the use of the analgesics. Thirty-two withdrawn products (68%) were inhibitors of cyclo-oxygenase types 1 and 2 (COX-1 and COX-2) and seven (15%) were predominantly COX-2 inhibitors; six products (13%) acted via opioid receptors and the precise mechanism for one product, bucetin, was unknown.

Hepatotoxicity was reported as the primary reason for withdrawal in 14 cases (30%), immunologic adverse reactions in 12 cases (26%), cardiovascular reactions in 5 cases (11%), and carcinogenicity in 5 cases (11%) (Table 6.1). Renal toxicity ($n = 4$), drug abuse ($n = 4$), gastrointestinal haemorrhage ($n = 3$), haematologic abnormalities ($n = 2$), and

ocular damage (n = 1) were the other adverse reactions on which withdrawal decisions were based. Among the COX-1 and COX-2 inhibitors, hepatotoxicity was the commonest reason for withdrawal (38%). In the case of the selective COX-2 inhibitors, cardiovascular adverse reactions accounted for 57% of withdrawal decisions. The selective COX-2 inhibitors were significantly more likely to be withdrawn because of cardiovascular adverse reactions compared with the non-selective COX-inhibitors (P = 0.0004). Drug abuse was the commonest reason for withdrawal of analgesics with actions at opioid receptors (67%).

Table 6.3: List of 16 withdrawn analgesics that were marketed in both Europe and the USA

Product	Withdrawn in Europe	Reason for withdrawal in Europe	Withdrawn in USA	Reason for withdrawal in the USA	Action when the product was not withdrawn
Benoxaprofen	Yes	Liver toxicity	Yes	Liver toxicity	–
Bufexamac	Yes	Allergic reactions	No		New formulation marketed to reduce drug absorption
Buprenorphine	No		No		Uses restricted [in both cases]
Celecoxib	Yes	Myocardial infarction, stroke	No		“Black box” warning†
Co-proxamol	Yes	Drug abuse	Yes	Drug abuse	–
Diclofenac sodium*	Yes	Carcinogenicity	No		No change (evidence of carcinogenicity regarded as inconclusive)
Fenclozic acid	Yes	Liver toxicity	Yes	Liver toxicity	–
Fentanyl hydrochloride	Yes	Drug abuse	No		Re-formulated
Ketorolac	Yes	Gastrointestinal haemorrhage	No		“Black box” warning‡
Oxyphenbutazone	Yes	Bone marrow suppression	Yes	Bone marrow suppression	–
Pirprofen	Yes	Liver toxicity	Yes	Liver toxicity	–
Propyphenazone	Yes	Lyell's syndrome; bone marrow suppression	Yes	Lyell's syndrome; bone marrow suppression	–
Rofecoxib	Yes	Myocardial infarction	Yes	Myocardial infarction	–
Suprofen	Yes	Renal toxicity	Yes	Diminished sales	–
Valdecoxib	Yes	Cardiovascular and skin reactions	Yes	Cardiovascular and skin reactions	–
Zomepirac	Yes	Anaphylaxis	Yes	Anaphylaxis	–

*Refused registration because carcinogenicity testing in rats was inconclusive and involved the use of only one rodent species

†Consider alternative therapy; use lowest effective dose if appropriate

(<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2004/ucm108384.htm>)

‡Contraindications: peptic ulcer, renal impairment, bleeding diathesis, following heart surgery (http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/019645s016lbl.pdf)

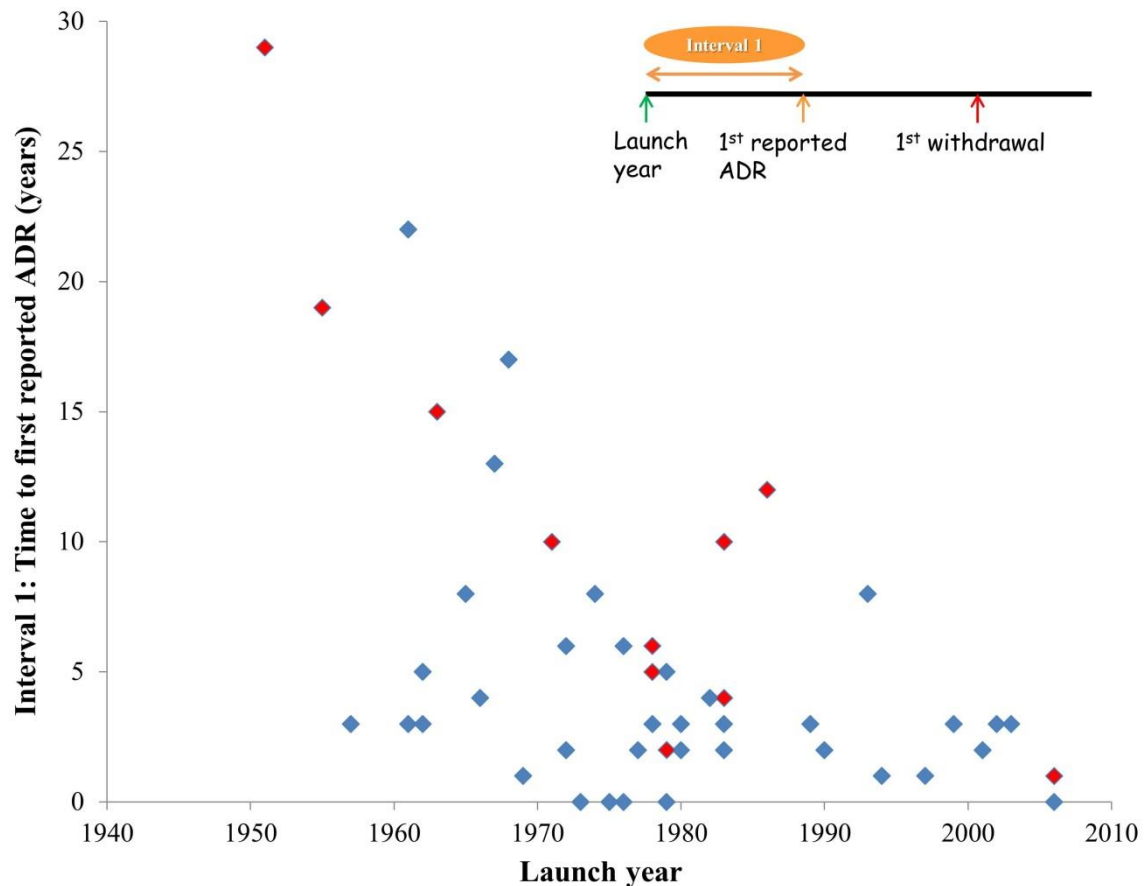
6.3.1 Interval between launch year and first reported adverse drug reaction

The interval between launch and the first reports of adverse reactions ranged from 0 to 29 years (Table 6.1). In 16 instances (34%), the adverse reactions were detected within two years of marketing; in five of these, the adverse reactions occurred within the first year – these were immune-mediated reactions, carcinogenicity, drug abuse and neuropsychiatric reactions. The median interval between launch and the first adverse reaction report was 3 years (IQR = 6 to 8). There was a trend towards quicker reports of adverse reactions with more recently launched drugs (Figure 6.2). There was no difference in the median interval to the first reports of adverse reactions between the COX inhibitors that are regarded as selective and non-selective (3 years). The median interval to first reports of adverse reactions for opioid receptor agonists was 5 years (IQR = 2 to 15).

6.3.2 Interval between launch year and first withdrawal

The intervals between the first reports of adverse drug reactions and the first withdrawals ranged from 0 to 47 years (Table 6.1). In 21 instances (45%), the withdrawals occurred within two years of the reports of adverse reactions; of the five products that had adverse reactions observed within the first year of approval, only one was withdrawn from the market within a year.

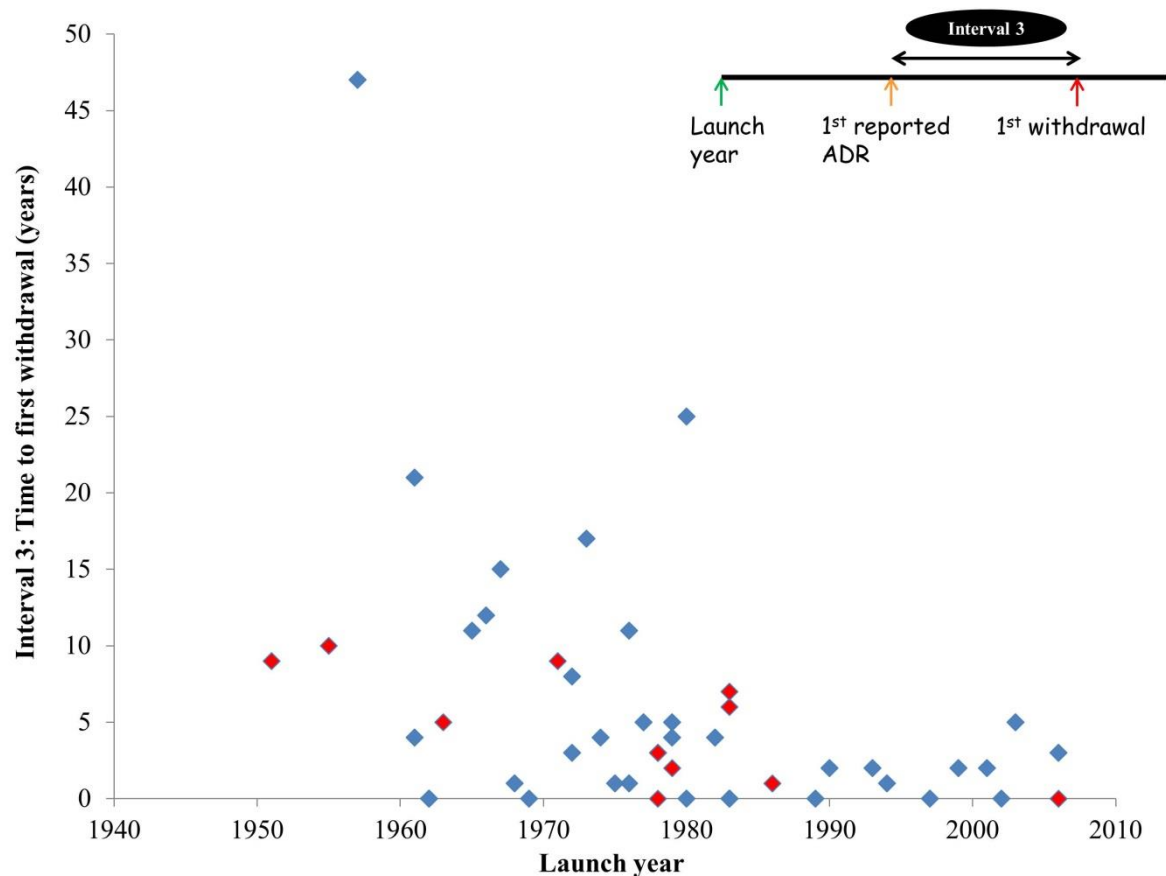
Figure 6.2: Launch year *versus* interval 1 (the time lapse between the launch of analgesic medicinal products and the date of the first reported ADR). The red boxes indicate products that caused deaths.



6.3.3 Interval between the first reported adverse drug reaction and the first withdrawal

The median interval between the first reports of adverse reactions and the first withdrawals was 3 years (IQR = 1 to 8). Figure 6.3 shows an inconsistent shortening in the time to withdrawals following reports of adverse reactions with more recently launched drugs. The median interval to withdrawal was shorter for analgesics withdrawn worldwide, 2 years (IQR = 0 to 6). The median interval to withdrawal was shorter with the selective COX-2 inhibitors compared with the non-selective COX inhibitors, 1 year (IQR = 0 to 2) *versus* 4 years (IQR = 1 to 10). The median interval to the first withdrawal of opioid receptor agonists was 3 years (IQR = 1 to 12).

Figure 6.3: Launch year *versus* interval 3 (the time lapse between the first reported ADR and the first withdrawal). The red boxes indicate products withdrawn because of drug-attributed deaths.



6.4 DISCUSSION

6.4.1 Main findings

A total of 47 analgesic medicinal products have been withdrawn from the market because of adverse drug reactions. The withdrawals occurred between 1965 and 2011. Anecdotal reports (low-level evidence) were most commonly cited as the evidence for withdrawal. There were discrepancies in the patterns of withdrawals across regulatory authorities, only one fifth were withdrawn worldwide, and over 80% of the withdrawn drugs were selective or non-selective COX inhibitors. Hepatotoxicity and/or immunological reactions accounted for over half of the withdrawal decisions, and in 11 instances deaths were reported as the

reason. The speed with which reports of adverse reactions appeared after product launch has shortened over time. The speed with which analgesics were withdrawn from the market shortened until the mid-1980s; though the intervals to withdrawals after this period have not been consistent, the median interval to withdrawal has shortened compared with pre-1980 (1.5 *versus* 4 years).

The use of case reports in most instances as evidence on which withdrawal decisions were based supports our findings in chapters 1 to 5, that formal confirmatory studies are seldom conducted when adverse reactions are attributed to medicinal products [36]. Failure to conduct formal studies may have resulted in prolonged delays to withdrawal of some products following initial reports of adverse drug reactions, e.g. ketoprofen gel (25 years) and clomacron (12 years). Lack of formal studies also makes the causal establishment of drug-adverse event relationships uncertain, and can result in controversies (and discrepancies) associated with some withdrawn medicines.

The shortened interval to the first reports of adverse reactions with more recently launched analgesics indicates better methods of detection of adverse reactions after the granting of marketing licences. However, the speed with which the adverse reactions appeared in the literature following launch also arouses suspicion of lack of transparency in harms reporting in clinical trials conducted in the pre-approval phases, or flaws in the ways in which harms were assessed by regulators. This is also supported by the speed with which the analgesics were withdrawn from the market following the reports of such reactions. Indeed one such product, pifoxime, was withdrawn within three months of regulatory approval in France following reports of serious neuropsychiatric adverse reactions [37].

The shortened median interval to withdrawal following adverse reaction reports until the mid-1980s suggests improved pharmacovigilance methods over the last few decades, and is consistent with our previous findings in chapter 2, that most withdrawals occurred within 5 years of adverse reaction reports. However, the delay to withdrawals has not been consistent since then (Figure 6.3); this suggests that there are still challenges in how to assign causality when adverse reactions are suspected after new analgesics are granted marketing authorization.

The discrepancies in withdrawal patterns across regulatory authorities suggest that either the criteria used for making withdrawal decisions vary across countries, or that there are differences in the numbers of adverse reactions reports available to regulators that could result in withdrawal decisions, or a combination of the two. For example, buprenorphine was withdrawn in Europe in 2010 because of severe allergic reactions attributed to its use [38]; however, it remained available in Taiwan where there have been no reports of severe adverse reactions [39]. Furthermore, transdermal fentanyl was withdrawn in Europe in 2009 because of the risk of drug abuse [40]; however, it remained available in the USA because the adverse reactions were due to either inappropriate prescribing or incorrect use by patients [41]; the formulation was subsequently changed from a “gel pouch and membrane” to a “drug in adhesive matrix” design to prevent inappropriate use [42].

The greater proportion of withdrawals in Europe (83% of all products withdrawn) compared with other continents (26–45%) suggests that marketing licences for analgesics are more often granted in Europe than elsewhere. Of the 13 products withdrawn in only one country in Europe, nine were marketed only in that country (see Table 6.4). However, the greater rate of withdrawals in Europe than in the USA suggests that European

regulators are more risk averse than those in the USA; indeed, the EMA has been accused of being excessively risk averse [43], by withdrawing products from the market that could have caused more benefits than harms. The difference between the agencies is highlighted, for example, by the withdrawal of celecoxib in Europe [44,45] but its continued availability in the USA with “black box” warnings [46], the difference being partly explained by how the agencies interpreted the available evidence (see Box 6.1).

Table 6.4: Marketing profile of 13 analgesics products withdrawn only in one European country

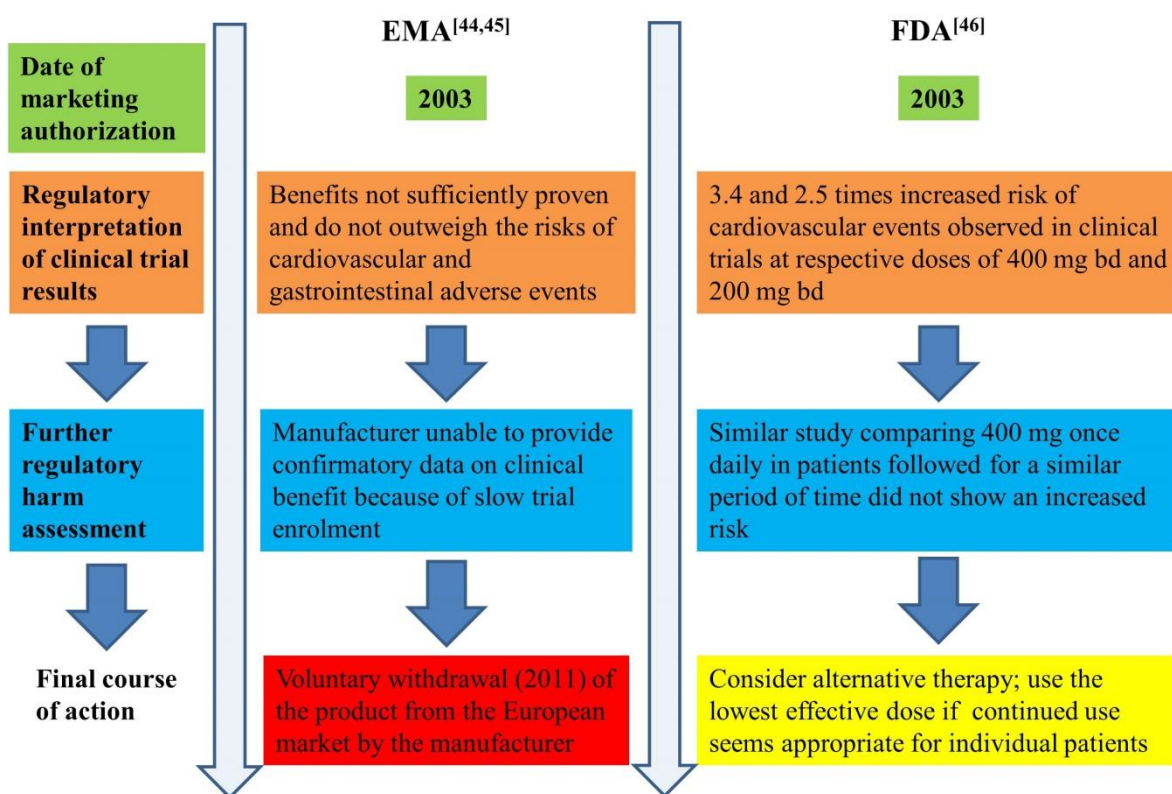
Product	Launch year	Year withdrawn	Countries where marketed
Antrafenine	1977	1984	France
Bendazac	1983	1993	Spain
Benzydamine	1967	1995	Germany, UK, USA
Bezitramide	1961	2004	Belgium
Bucetin	1968	1986	Germany
Bufexamac*	1973	1990	Europe, USA
Clomacron	1966	1982	UK
Clometacin	1971	1990	France
Floctafenine	1976	1987	Belgium, Canada
Flosulide	1994	1996	Germany
Ibufenac	1961	1968	UK
Osmosin	1963	1983	UK, Japan, USA
Pifoxime	1975	1976	France

*Withdrawn initially only in France; subsequently withdrawn in the whole of Europe in 2010

The development of analgesics during the last 100 years has largely focussed on chemical entities that either inhibit the cyclo-oxygenase enzyme or act as agonists or partial agonists at opioid receptors. The limited number of targeted mechanisms identified suggests that it is very challenging to achieve better control of pain other than interfering with the cyclooxygenase or opioid receptor pathways. The differences in the patterns of post-marketing withdrawal observed with the selective COX-2 inhibitors compared with their non-selective analogues could have arisen because the former can cause life-threatening adverse reactions more often than the latter [47,48], as emphasized by the worldwide

withdrawal of rofecoxib [49] and the withdrawal of celecoxib in Europe [50] because of increased risks of serious cardiovascular adverse reactions. Although some authors have called for a separate investigation of the cardiovascular risks of COX-2 inhibitors [51], others have argued that those risks are no different from the risks of NSAIDs in general [52,53,54].

Box 6.1: Differences in regulatory courses of action between the European Medicines Agency (EMA) and Food and Drug Administration (FDA) when serious adverse reactions to celecoxib were reported



6.4.2 Comparison with the existing literature

The results of this chapter corroborate the reports of others who have analysed trends in the regulatory approval of analgesics. In an analysis of 59 medicinal products approved by the FDA for use as analgesics, the author concluded that there have been no significant

breakthroughs in the development of new analgesic drugs over the last 50 years [55]. In a systematic review of NSAIDs that were withdrawn from the market because of hepatotoxicity, the authors concluded that the limited data on harms from clinical trials may have contributed to the failure to detect the potential risks from exposure to analgesics in the pre-approval phases [56]. In contrast to those reviews, we included all analgesics withdrawn from the market because of adverse reactions, assessed the quality of the evidence used for making withdrawal decisions, and explored trends in withdrawal over time.

6.4.3 Strengths and weaknesses

An extensive range of sources was searched to identify analgesics that have been withdrawn after regulatory approval. There was also extensive cross-checking of dates to ensure accuracy of the data for initial launch dates, first reports of adverse reactions, and first withdrawals. Furthermore, the levels of evidence used in making withdrawal decisions for first withdrawals were accounted for. However, some limitations should be noted. Some countries in which some analgesics were withdrawn may not have been identified; this is especially true for low-resource settings, where pharmacovigilance structures are either weak or non-existent. There was no information on the interval between the actual occurrence of adverse reactions and their first appearance in the published literature. In addition, there was access to data to enable identification of all countries in which the approved analgesics were marketed; indeed, some of the withdrawn products may have been marketed in some countries and not others. For example, rofecoxib was reported to have been withdrawn worldwide, but the product was actually marketed in only 80 countries [57].

6.4.4 Implications for policy

Regulatory authorities could, in conjunction with drug manufacturers, develop a database that can track the marketing of approved analgesics (and other medicinal products) in different countries. This would make it easier to identify countries in which such products are being marketed. This is especially important in developing countries, most of which lack adequate regulatory capacity. This would also ensure uniformity in the reasons given for withdrawal of products from the market and expedite withdrawal, thereby enhancing public trust.

Greater transparency in the reporting of harms by drug sponsors should be encouraged. This would facilitate more robust assessment of the benefit-to-harm balance of new medicinal products, and also minimize the risk of exposure of the public to products with harmful properties. The swift and voluntary worldwide withdrawal of indoprofen by the manufacturer following evidence of increased risk of cancers [58] is a commendable example. The manufacturer immediately instigated worldwide recall of the products when testing in rats suggested evidence of carcinogenicity; however, the product had also been reported to have caused deaths in humans around the same time. Regulatory authorities could delay the granting of marketing licences of new products until the drug sponsors demonstrate convincing evidence that the product has a favourable benefit-to-harm profile. In addition, rapid evidence synthesis of harms associated with a newly approved product could be conducted when serious adverse reactions are suspected. Research aimed at strengthening the methods of conducting such reviews should also be a priority for regulators, drug manufacturers, and healthcare organizations. Indeed, a checklist for reporting of harms in clinical trials of analgesic medicinal products has recently been proposed [59].

When new analgesics are granted accelerated marketing authorization, regulators should consider early suspension of such products when serious adverse reactions are suspected, i.e. the precautionary principle should be applied speedily [60]. For example, celecoxib was approved for treatment of familial adenomatous polyposis in Europe in 2006 under “exceptional circumstances”, despite research evidence showing an increased risk of myocardial infarction and stroke [61]. It took another five years before the product was withdrawn from the market after initial reports of serious cardiovascular adverse reactions. Earlier suspension of the product would have protected the public from unnecessary exposure to the harms associated with it.

6.4.5 Implications for future drug development

The profile of the withdrawn analgesics identified in our review shows that very few targets have been tested for pain control over the last few decades. Indeed, about half the currently available analgesics are structural analogues of original molecules [62]. Recently, there have been calls for new molecules to be developed for the treatment of pain, because of the limited number of analgesics currently in use [63,64]; indeed, several new chemical entities with other mechanisms, including transient receptor potential cation channel subfamily V member 1 (TRPV1), cannabinoid receptors, and sodium channel subunits, have been tested in the last two decades [63,64,65]. However, there have also been some notable failures, e.g. the recent premature termination of the development of BIA-10-2474 (a fatty acid amide hydrolase inhibitor) in France because of drug-attributed deaths [66].

The dearth of innovative chemical molecules for pain management (and the possible financial costs involved in developing new chemical entities) could encourage drug manufacturers to test whether some already available medicinal products could be of value

in pain management. Indeed, a previous review showed that 34% of medicinal products approved by the FDA between 1960 and 2009 for pain management were initially developed for treating other conditions [55]. Furthermore, modified formulations of currently available compounds have been used successfully to improve pain control [67,68,69].

Perhaps one of the most difficult challenges in the development of new analgesics is that those currently being marketed are quite effective in relieving pain; however, most of the approved products, especially those with stronger analgesic actions (opioids) are also associated with increased risks of serious adverse reactions [70,71]. Drug manufacturers could therefore focus their research on the development of new chemical entities that can provide similar levels of pain relief, but with fewer and/or less severe harmful effects, compared with currently marketed analgesics.

6.5 CONCLUSION

The interval to the withdrawal of analgesics following reports of adverse reactions has shortened with time. However, the speed with which withdrawals have occurred recently after reports of adverse drug reactions suggests flaws during pre-marketing development. Low-level evidence has primarily been used to make the withdrawal decisions, but formal confirmatory studies are seldom conducted to explore analgesics-adverse event relationships. Few mechanisms have been targeted for the development of new analgesic medicinal products over the last six decades. Future development of analgesics should include targeting other mechanistic pathways.

6.6 Chapter Summary

- The interval to the withdrawal of analgesics following adverse reaction reports has shortened with time
- Case reports (Level 4 evidence) were cited as evidence for withdrawal in over 90% of instances
- The speed of withdrawals, after adverse reaction reports, suggests current regulatory systems do not adequately detect harms in the premarketing phase
- Selective COX-2 inhibitors are significantly more likely to be withdrawn because of cardiovascular adverse reactions compared with non-selective COX-inhibitors
- Few mechanisms have been targeted for the development of new analgesic medicinal products over the last six decades

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Chapter 7 Post-marketing withdrawal of anti-obesity medicinal products because of adverse drug reactions: a systematic review

7.1 INTRODUCTION

The prevalence of overweight and obesity has more than tripled in the last decade [1], giving rise to substantially increased healthcare costs [2,3]. According to the World Health Organization, overweight and obesity are the fifth leading cause of mortality worldwide [4]. Strategies to reduce weight include diet and lifestyle adjustments, behavioural techniques, and drug therapy [5]; however, they have had little effect on the growing obesity epidemic.

Modern drug therapy for obesity treatment began in 1933 with the use of 2,4 dinitrophenol (2,4 DNP), a thermogenic agent, for weight reduction [6]. However, its use was associated with serious adverse reactions, and the FDA banned it in 1938 [7]. In the late 1930s drugs acting on monoamine neurotransmitters, prescribed as appetite suppressants, were introduced [8]. One such drug, Hydrin (amfetamine), gained FDA approval under controversial circumstances, because the FDA's then acting medical director served as a consultant to the Council on Pharmacy and Chemistry of the American Medical Association (AMA) [9]. The Council later withdrew its approval of Hydrin, citing lack of evidence on harms [10]. This was followed by the development of other anti-obesity medications, mainly congeners of amfetamine and monoamine reuptake inhibitors [11]. In recent years, there has been a growing focus on the development of novel therapies for the treatment of obesity [12], including drug combinations, a few of which have recently gained marketing approvals from regulatory authorities [13].

In chapter 2, trends in the post-marketing withdrawal of all medicinal products because of adverse reactions were analysed. By observing trends in the post-marketing withdrawal of products approved for specific therapeutic indications, the first reviewer (IJO) discovered that several products approved for use as anti-obesity therapies have been withdrawn from the market because of adverse reactions over the past six decades. It was therefore, reasonable to specifically examine the trends in the post-marketing withdrawals of this group of products.

7.2 METHODS

7.2.1 Search strategy

The first reviewer (IJO) used the results of Chapter 2 to identify and document anti-obesity medicinal products withdrawn from the market because of adverse reactions. In addition, the first reviewer (IJO) conducted updated searches on the under listed sources using anti-obesity related search terms [See appendix 3]:

- the US Food and Drug Administration website;
- the database of withdrawn drugs of the European Medicines Agency (EMA).

For each withdrawn anti-obesity medicine identified, first reviewer (IJO) conducted updated searches on the following sources for the first reported adverse drug reaction: Medline and Google Scholar. Search terms used included “anti-obesity”, “withdrawal”, “fatal*”, “adverse reaction”, “adverse event”, “toxicity”, “voluntary recall”, “suspension”, “prohibition”, “banned”, “remov*”, “revoke*”, “discontinued”. [See appendix 3]. If the information for an anti-obesity medication when using its chemical name for searches could not be found, trade or code names were used. The first reviewer (IJO) also hand searched references in retrieved full texts for earlier reports of adverse reactions. If an article contained information about an earlier reported date, that date was chosen as the

first adverse reaction date. If an anti-obesity product was withdrawn because of two or more adverse reactions, the date of the first reported reaction was used.

7.2.2 Inclusion/exclusion criteria

To be included in the review, an anti-obesity medicinal product must have been withdrawn from the market because of reports of suspected adverse reaction(s), or problems related to hazards or harms. Anti-obesity medicines for which there was documented regulatory evidence that they had been voluntarily withdrawn by marketing authorization holders (MAHs) solely for “commercial reasons” were excluded. Also excluded were herbal products, non-human, and non-prescription medicines (i.e. medicines that were not approved via the conventional regulatory pathway for drug licensing) used as weight loss products.

7.2.3 Assessing the types of evidence

The first reviewer (IJO) documented the highest level of available evidence before the year of first withdrawal of anti-obesity medicines, based on the Oxford Centre for Evidence-based Medicine (OCEBM) criteria [14] as reported in the previous chapters. The documented levels of evidence were independently verified by a second reviewer (JKA). Disagreements were resolved through discussion.

7.2.4 Data extraction

For each withdrawn anti-obesity product, the following data were extracted: the marketing authorization or launch date (or the date of first recorded use); the drug class, mechanism of action, and therapeutic indication(s) [15]; the year an adverse reaction related to the reason for withdrawal was first reported; the year of first withdrawal; the country or

countries of withdrawal; and the reported mechanism by which the drug caused the adverse reaction. The first reviewer (IJO) extracted the data and a second reviewer (JKA) verified them independently. Discrepancies were resolved through discussion.

7.2.5 Statistical analysis

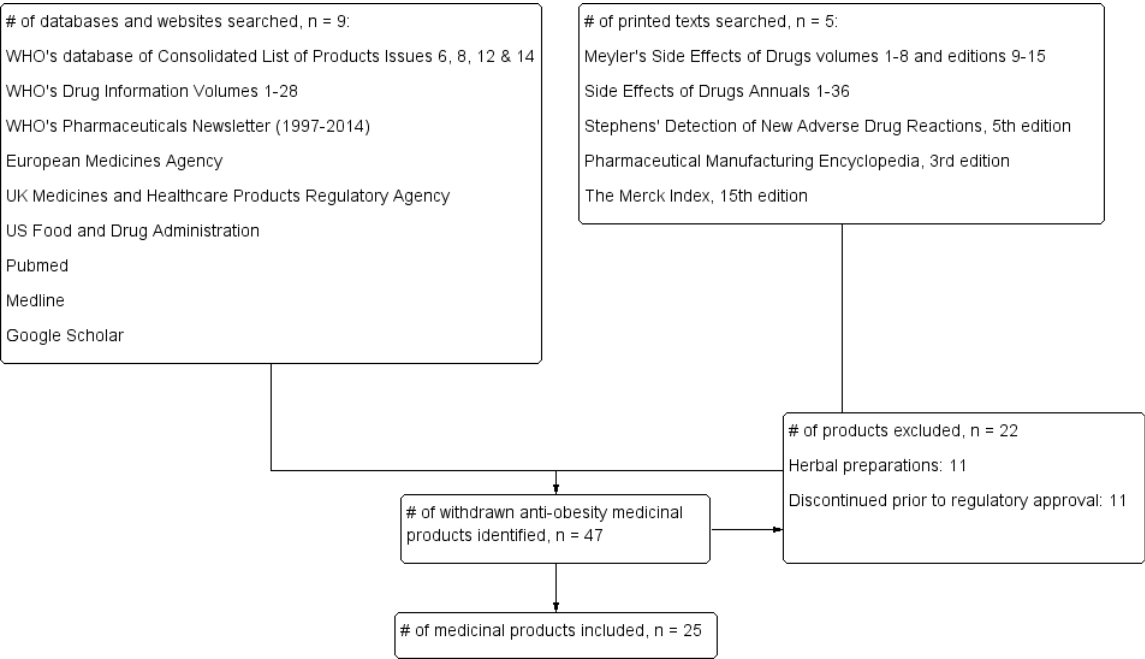
Summary tables were used to document the intervals between launch year and the year of first report of an adverse drug reaction, the interval between launch year and the year of first withdrawal, and the interval between the first report of an adverse drug reaction and the year of first withdrawal. Because these intervals were skewed, medians and interquartile ranges (IQR) were used as measures of central tendency and spread. The intervals to reports of adverse reactions and withdrawals between products based on their mechanistic actions were also compared. Fisher's exact test was used to test for differences in the proportions of withdrawals based on the pharmacological mechanisms of action; a P value of <0.05 was considered statistically significant.

7.3 RESULTS

A total of 47 withdrawn medicinal products used for treating obesity were identified (Figure 7.1). Eleven products were excluded because they were plant-based "herbal" products and another 11 because they were discontinued before being granted regulatory approval. This left 25 products for inclusion. Two of the products, fenfluramine and dexfenfluramine were withdrawn worldwide. Of the remaining 23 products, 19 were withdrawn in Europe, 11 in Asia, 9 in South America, 8 in North America, 4 in Africa, and 1 in Australasia (Table 7.1).

Of the 25 withdrawn products, 22 (92%) were appetite suppressants acting on monoamine neurotransmitters (Table 1). Their primary mechanisms of action were through central effects on adrenoceptors and dopamine receptors (8); adrenoceptors, dopamine receptors, and serotonin receptors (5); serotonin receptors only (6); adrenoceptors only (1); adrenoceptors and serotonin receptors (1); and serotonin and dopamine receptors (1). One drug acted on cannabinoid receptors, one by stimulating bile acid secretion, and one by attachment to thyroid hormone binding proteins. Eight products (32%) were approved for two or more indications.

Figure 7.1: Databases and selected texts used to identify withdrawn anti-obesity medications, their launch dates, dates of first adverse drug reaction reports and withdrawals



Case reports (Level 4 evidence) were cited as evidence for withdrawal in 20 instances (80%), and Level 3 evidence in two instances (8%) (Table 7.1). The withdrawal of one product, chlorphentermine, was based on evidence from animal studies. Cardiotoxicity accounted for 9 withdrawals (36%) and psychiatric adverse reactions for 8 (32%). Drug abuse or dependence was cited in more than half of the withdrawals (13 cases, 52%), and drug-attributed deaths were associated with the withdrawal of 7 products (28%).

Table 7.1: List of anti-obesity drugs withdrawn from the market because of adverse drug reactions

Medicinal Product	Primary mechanism of action	Therapeutic indication	Launch year	Year of first ADR report	Year first withdrawn	Countries withdrawn	Primary reason for withdrawal	LoE [†]
Amfepramone (diethylpropion) ‡	SNDRA	Obesity	1957	1974	1975	Turkey, Sweden, Oman, UAE, Norway, Venezuela, EU, France, UK, Brazil	Cardiotoxicity	4
Amphetamine	SNDRA	Obesity, narcolepsy	1939	1957	1973	USA, UAE, Turkey, Oman, Malaysia, Nigeria	Drug abuse and dependence	4
Aminorex fumarate*	SRI	Obesity	1962	1967	1967	Germany, Venezuela, Switzerland, Austria	Cardiotoxicity	4
Benfluorex*	SRI	Obesity, diabetes	1976	2003	2009	Europe	Cardiotoxicity	3
Chlorphentermine	SRI	Obesity	1962		1969	Germany, Venezuela	Cardiotoxicity	5
Clobenzorex	SNDRA	Obesity	1966	1986	2000	Mauritius, USA, Oman	Drug abuse, psychiatric	4
Cloforex	SRI	Obesity	1965	1967	1967	Germany, Sweden, Venezuela	Cardiotoxicity	4
Cycloalalone + retinol + tiratricol	Bile acid secretion	Hyperlipidemia, dyspepsia, obesity	1964	1984	1988	France	Liver toxicity	4
Dexfenfluramine	SRI	Obesity	1995	1995	1997	Worldwide	Cardiotoxicity	4
Fenbutrazate	NDRA	Obesity	1957	1963	1969	Europe	Drug abuse, psychiatric	2
Fenfluramine*	SRI	Obesity	1973	1981	1997	Worldwide	Cardiotoxicity	3
Fenproporex (perphoxene)	NRA	Obesity, ADHD, narcolepsy	1966	1997	1999	Europe, Brazil	Drug abuse, psychiatric	4
Iodinated casein strophanthin	Thyroxine analogue	Obesity	1944	1964	1964	USA	Endocrine, metabolism	4
Levamphetamine	SNDRA	Obesity	1944	1954	1973	USA, Oman, UAE	Drug abuse and dependence	4
Mazindol	NDRA	Obesity	1970	1980	1987	Oman, Brazil	Drug abuse, psychiatric (interaction with lithium)	4
Mefenorex methylphenethylamine)	SNDRA	Obesity	1966	1995	1999	Europe, Oman	Drug abuse, psychiatric	4
Methamphetamine (desoxyephedrine)*	SNDRA	Obesity, ADHD	1944	1971	1973	USA, Turkey, Oman, Nigeria	Drug abuse, drug dependence	4
Phendimetrazine	NDRA		1961	1979	1982	Turkey	Drug abuse	4
Phenmetrazine	NDRA	Obesity	1956	1959	1982	Turkey, Oman, Nigeria	Drug abuse	4
Phentermine*‡	NDRA	Obesity	1959	1964	1981	Sweden, UAE, Mauritius, Turkey, Oman, UK, Venezuela	Drug abuse	4
Phenylpropanolamine (norpseudoephedrine)	NDRA	Obesity, nasal decongestion	1947	1985	1987	Germany, Brazil, Malaysia, Singapore,	Haemorrhagic stroke	4

						USA, Oman, Canada, Cuba, India		
Pipradrol	NDRI	Obesity, ADHD, narcolepsy	1953	1968	1982	USA, Turkey, Denmark, Venezuela	Drug abuse	4
Pyrovalerone	NDRA	Obesity, chronic fatigue syndrome	1974	1975	1979	France	Drug abuse	4
Rimonabant*	CB ₁ antagonist/inverse agonist	Obesity	2006	2006	2007	Europe, India	Psychiatric	1
Sibutramine*	SNRI	Obesity	2001	2002	2002	European Union; 4 Asian countries; Australia; Canada; Mexico; New Zealand; USA	Cardiotoxicity, psychiatric	4

ABBREVIATIONS: ADHD: Attention deficit hyperactivity disorder; ADR: Adverse drug reaction; CB₁: Cannabinoid 1 [receptors]; LoE: Level of evidence; NRA: Norepinephrine releasing agent; NDRA: Norepinephrine-dopamine releasing agent; NDRI: Norepinephrine-dopamine reuptake inhibitor; SNDRA: Serotonin-norepinephrine-dopamine releasing agent; SNRI: Serotonin-norepinephrine reuptake inhibitor; SRI: Serotonin reuptake inhibitor

*Reported to have caused deaths

†Based on the Oxford Centre for Evidence-Based Medicine Levels of Evidence [14]. Level 1: Systematic review of randomized trials, systematic review of nested case-control studies, Level 2: Individual randomized trial or (exceptionally) observational study with dramatic effect; Level 3: Non-randomized controlled cohort/follow-up study (post-marketing surveillance); Level 4: Case-series, case-control, or historically controlled studies; Level 5: Mechanism-based reasoning

‡Re-introduced in the EU based on long-standing legal action unrelated to either new safety or new efficacy information

Table 7.2: Summary comparison of post-marketing withdrawal patterns of centrally acting anti-obesity medicinal products*

Primary mode of action at receptor ending	Primary reason for withdrawal	Median interval between launch and first ADR report	Median interval between first ADR report and withdrawal	†Statistical comparisons
Neurotransmitter re-uptake inhibition (n = 8)	Cardiotoxicity: n = 7 Drug misuse: n = 1	5.5 years (IQR = 1.3 to 13.3 years)	1 year (IQR = 0 to 12 years)	Withdrawal due to cardiotoxicity significantly more likely vs neurotransmitter releasers (P = 0.0004)
Neurotransmitter release (n = 14)	Cardiotoxicity: n = 1 Drug abuse or dependence: n = 12 Hemorrhagic stroke: n = 1	17.5 years (IQR = 5.8 to 28 years)	5 years (IQR = 2 to 16.3 years)	Withdrawal due to drug misuse significantly more likely vs neurotransmitter re-uptake inhibitors (P = 0.002)

ABBREVIATIONS: ADR: Adverse drug reaction; IQR: Interquartile range

*One centrally-acting product, rimonabant, has been excluded from the comparisons because it is an antagonist and inverse agonist at cannabinoid C1 receptors

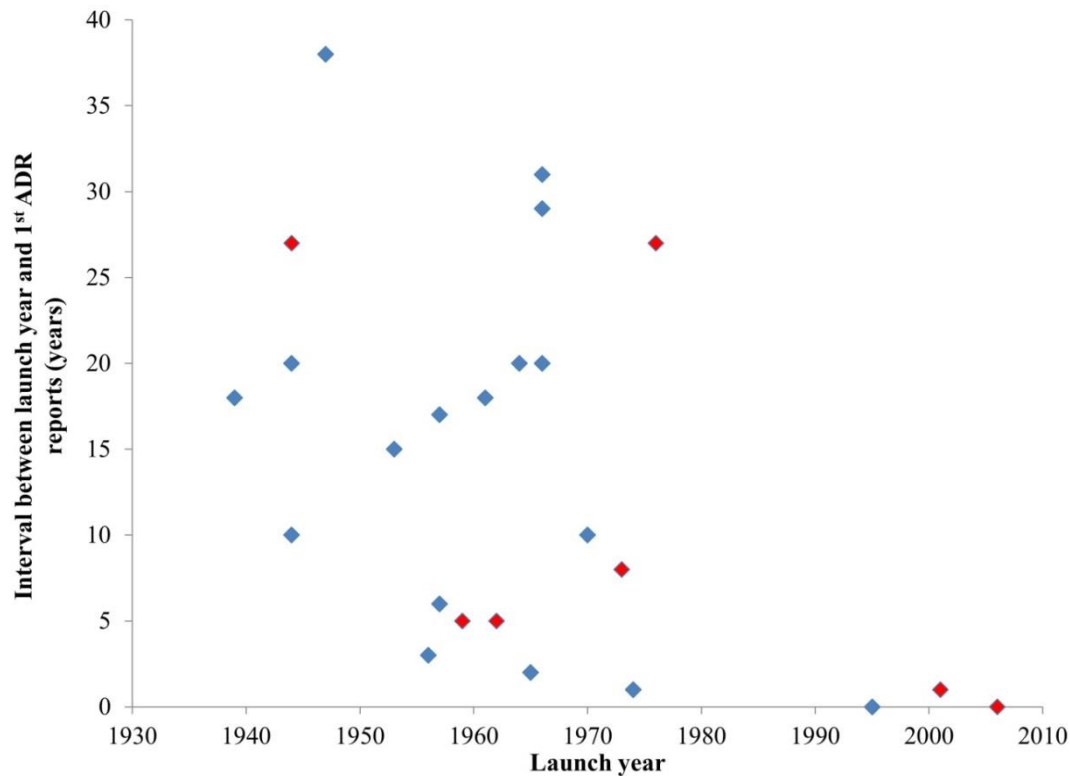
†Using Fisher's exact test; there was no significant difference between groups for proportion of psychiatric disturbances (P = 1.000)

Of the 23 withdrawn products acting via monoamine neurotransmitters, eight were re-uptake inhibitors and 14 were releasing agents (Table 7.1). One product, rimonabant was an antagonist and inverse agonist at cannabinoid receptors. The releasing agents were significantly more likely to be withdrawn because of drug abuse compared with the re-uptake inhibitors ($P = 0.002$); the re-uptake inhibitors were significantly more likely to be withdrawn because of cardiovascular adverse reactions compared with the releasing agents ($P = 0.0004$). Psychiatric adverse reactions were not significantly different between the two groups of agents.

7.3.1 Interval between launch year and first reported adverse drug reaction

The longest interval between launch and the first report of an adverse drug reaction was 38 years (norpseudoephedrine), while the shortest interval was less than 1 year (rimonabant). The median interval between launch and first report of an adverse drug reaction was 10 years (IQR = 3 to 20). In 24% of cases, first reports of the adverse drug reactions in the literature occurred within two years. Overall, there was a shortening in the interval between launch and first published reports of adverse drug reactions (Figure 7.2). The interval between launch and first reports of adverse reactions was considerably shorter with the re-uptake inhibitors than with the releasing agents: 5.5 years (IQR = 1 to 13) *versus* 18 years (IQR = 6 to 28); Table 7.2. The median interval to first reports of adverse reactions was considerably shorter when there was cardiotoxicity compared with drug abuse: 5.5 years (IQR = 1 to 15) *versus* 15 years (IQR = 6 to 24).

Figure 7.2: Interval between launch of anti-obesity medicinal products and first* ADR report. Red boxes indicate withdrawn products to which deaths were attributed.



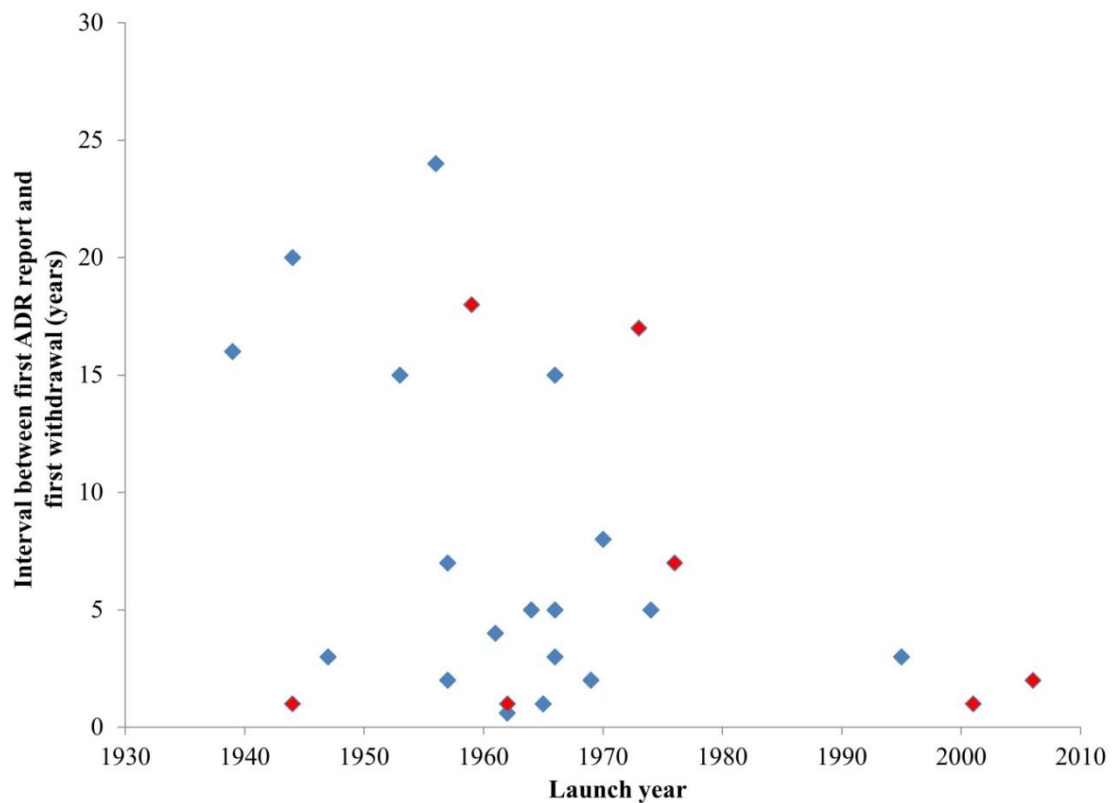
*Chlorphentermine was withdrawn from the market because the first ADR report appeared in the literature.

7.3.2 Interval between the first reported adverse drug reaction and the first withdrawal

The longest interval between first report and first withdrawal was 23 years (phenmetrazine), while the shortest interval was less than 1 year in 3 cases (aminorex fumarate, cloforex, and iodinated casein; Table 7.1). The median interval between first report and first withdrawal was 11 years (IQR = 0 to 23). Figure 7.3 shows that the more recent the launch year, the quicker the product was withdrawn from the market following adverse reaction reports. In 48% of cases, withdrawals occurred within two years of the first adverse drug reaction reports. When deaths were attributed to the products, the median

interval to withdrawal was 1 year. The median time to withdrawal following reports of adverse reactions was shorter with the re-uptake inhibitors than the releasing agents: 1 year (IQR = 0 to 12) *versus* 5 years (IQR = 2 to 16); Table 7.2. The median time to withdrawal following reports of adverse reactions was considerably longer with drugs that caused abuse or dependence than with drugs that caused cardiotoxicity: 7 years (IQR = 3.5 to 17) *versus* 1 year (IQR = 0 to 5).

Figure 7.3: Interval between first ADR reports and first withdrawal. The red boxes indicate withdrawn products to which deaths were attributed



7.4 DISCUSSION

7.4.1 Main findings

Twenty five anti-obesity medications withdrawn after marketing because of adverse reactions between 1964 and 2009 were identified; 23 of these had centrally-acting

mechanisms via monoamine neurotransmitters. The evidence for withdrawal in about 80% of cases was anecdotal reports. Cardiovascular and psychiatric adverse drug reactions and drug abuse and dependence together accounted for 83% of the withdrawals. In 28% of cases, deaths were attributed to the products. Among the centrally-acting agents, re-uptake inhibitors were more likely to be withdrawn because of cardiotoxicity, while the neurotransmitter releasers were more likely to be withdrawn because of drug abuse and dependence. When compared with our overall corpus of 462 medicinal products withdrawn from the market after 1950 (Chapter 2), there was no significant difference in the proportion of case reports being used as evidence for withdrawal. The median interval to first reports of adverse reactions and first withdrawals was longer with the anti-obesity products (11 *versus* 3 years), but this is likely due to the smaller proportion of anti-obesity products approvals after 1976 compared with the overall data (the median interval to withdrawal for the products withdrawn since 1995 was 3 years). Furthermore, the intervals to withdrawal with more recent product launch are also consistent with the trend observed in the overall corpus.

The use of case reports as evidence for making withdrawal decisions in a majority of instances corroborates our previous findings in chapters 1 to 6 that formal studies are seldom conducted when adverse drug reactions are suspected. In addition, the fact that most of the withdrawn products were centrally-acting anorectics suggests that use of this class of products in the treatment of obesity is associated with a negative benefit-to-harm balance over time [see box 7.1 and Appendix 4]. Furthermore, the discrepancy in withdrawal patterns across regulatory authorities indicates a lack of uniformity in harms assessment by different drug regulators, and also contributes to discrepancies in patterns of marketing authorizations of this class of products.

Box 7.1: Profile of centrally-acting anti-obesity products withdrawn because of associated deaths over the last 50 years*

Aminorex

- First introduced in 1962
- Became available within three years of introduction as an over-the-counter weight loss pill
- Between 1965 and 1972, there was an alarming increase in the incidence of primary pulmonary hypertension
- The pulmonary hypertension epidemic ended in 1972 following the withdrawal of aminorex from the market

Benfluorex

- Approved in 1976 as an add-on treatment in obese patients with diabetes mellitus
- Cases of valvulopathy attributed to its use began to appear from 2003
- Was withdrawn in 2009 following an epidemic of valvulopathy attributed to its use
- Several deaths reported
- Total, with over 3000 hospitalisations and at least 1300 deaths attributed to its use in France alone

Fenfluramine

- First approved in 1973
- Reports of pulmonary hypertension first appeared in 1981
- Several other case reports subsequently published
- Epidemiological studies showed an association between fenfluramine and pulmonary hypertension
- Withdrawn worldwide in 1997

Metamfetamine (desoxyephedrine)

- First introduced in 1944
- Within 10 years of its introduction, cases of its misuse had been reported
- By the early 1970s, reports of its abuse as an anorectic were reported
- Was withdrawn in the USA and other countries in 1973
- Several cases of cardiac abnormalities related to its abuse have subsequently been reported

Phentermine

- First approved in 1959
- Several cases of lung phospholipidosis in animals and humans reported thereafter
- Reports of death began to appear in 1974
- Withdrawn from most countries where it was marketed in 1981
- Still available for short-term management of obesity in the USA

Rimonabant

- Approved in Europe in 2006 for obesity treatment
- Within 1 year of approval, concerns were expressed about the risk of depression and suicide associated with its use
- 5 deaths attributed to its use in the UK
- Was withdrawn in 2007

Sibutramine

- Approved in 1997 in the USA and Europe in 2001
- Within a year of its European approval, serious cardiovascular adverse reactions were reported, resulting in temporary withdrawal in Italy
- Several cases of severe cardiovascular adverse reactions, including deaths were subsequently reported
- Withdrawn in Europe and USA in 2010

*See appendix 4 for full list of withdrawn products and their corresponding citations

That the delays to reports of adverse reactions with time were shortened, albeit inconsistently, suggests an influence of better methods for detection of adverse drug reactions, improved transparency in the report of adverse drug events by trials investigators, or a combination of the two. However, the speed with which withdrawals occurred following reports of suspected adverse reactions with more recently launched drugs arouses suspicion of selective reporting of harms in the pre-marketing phase. The shorter intervals to withdrawals when deaths are reported suggest that regulatory authorities are quicker at making withdrawal decisions in these circumstances.

7.4.2 Comparison with existing literature

The findings in this chapter are consistent with other published reports. A previous review reported that most anti-obesity treatments have been withdrawn from the market because of concerns about adverse reactions [16]. Two other reviews concluded that cardiovascular and psychiatric adverse reactions are major concerns with psychoactive anti-obesity drugs that have recently gained marketing approval from licensing authorities [17,18]. A recent analysis of serious adverse reactions reported to the EudraVigilance database also showed that cardiac and psychiatric disorders were the most common adverse reactions attributed to anti-obesity medicinal products [19]. The authors of another report concluded that lower doses of multiple chemical entities targeting different mechanistic pathways should be a priority in future drug development [1].

7.4.3 Strengths and limitations

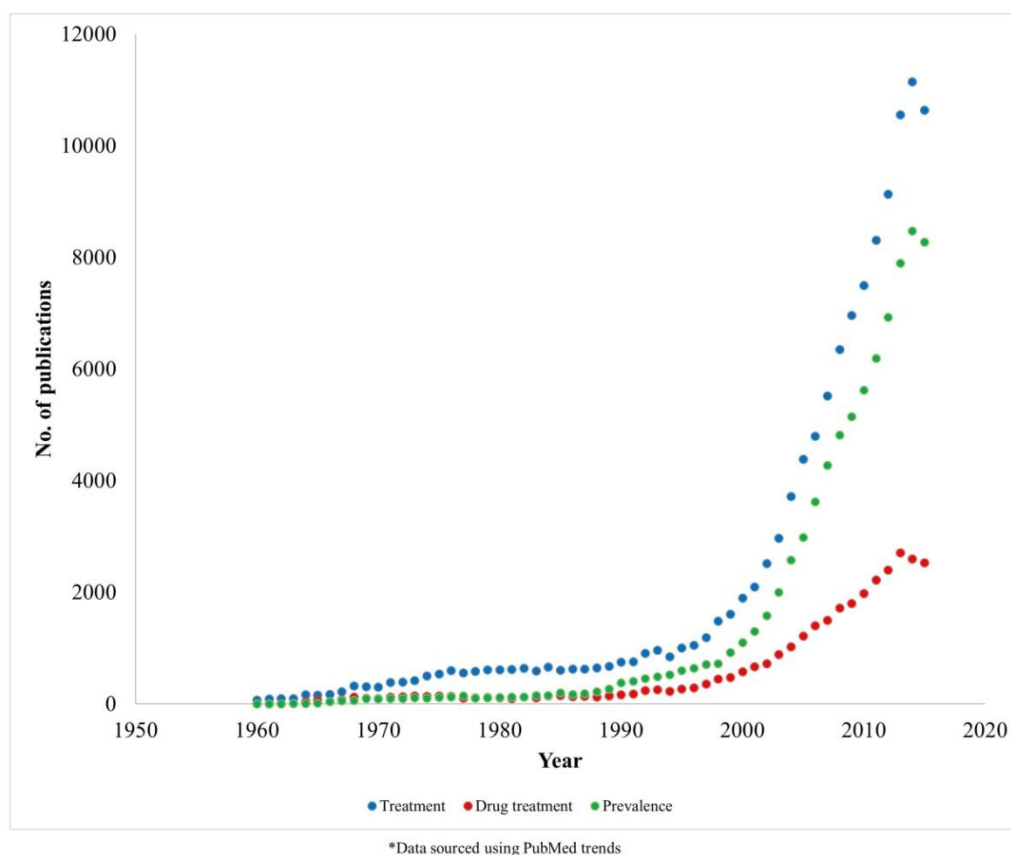
An extensive range of information sources was searched in order to identify anti-obesity medicinal products that have been withdrawn. The levels of evidence used in making withdrawal decisions were also accounted for, and the trends in between launch dates and dates of first adverse reaction reports and withdrawals over time were explored. Statistical tests were also used to compare the patterns of withdrawal. However, some limitations are recognized. Like in previous chapters, some countries in which products were withdrawn may not have been identified and the information about where all the products were marketed is incomplete; indeed it is possible that some products were withdrawn in a few countries because those were the only places where they were marketed. In addition, there was no information on the time lapse between the actual occurrence of an adverse reaction and the date the reaction appeared in the published literature; though it is unlikely that such delays would have significantly influenced our findings. Finally, the intervals between

launch, first adverse reaction reports and first withdrawals were computed irrespective of where products were first introduced, or where adverse reactions were first observed; however, some products were withdrawn in some countries because of adverse reactions reported in others irrespective of whether the product was first marketed in such countries.

7.4.4 Implications for drug therapy

Apart from two products (cyclovalone and iodinated casein), the products identified in the review had actions involving 5-hydroxytryptamine (5HT, serotonin). While agonist activity at 5HT_{2A} receptors can cause psychiatric dysfunction [20], stimulation of 5HT_{2B} receptors is associated with cardiac abnormalities, largely valvulopathies [21]. The unfavourable benefit-to-harm balance of this class of products therefore appears to have led to the development of new chemical entities that target other mechanistic pathways. These include leptin sensitizers, glucagon-like peptide 1 (GLP-1) receptor agonists, islet amyloid polypeptide (IAPP), and neuropeptide Y [22]. Of note, several medicinal products with similar mechanisms of action to the withdrawn psychotropic anti-obesity medications have been successfully used for treating other medical conditions, and these have not been withdrawn from the market. This may be because in those conditions their mechanisms of action are specifically targeted against abnormal pathways. For example, several analogues of amphetamine are available for treating attention deficit hyperactivity syndrome (ADHD) and narcolepsy [23,24].

Figure 7.4: Publication trends* for scientific articles related to obesity prevalence and treatments over time



There were no new approvals of anti-obesity medications during the 20 years from 1976 to 1995. It is unclear what caused this hiatus; however, we observed a steep increase in the number of scientific publications relating obesity prevalence and treatment after the hiatus (PubMed trend; Figure 7.4). The resurgence of new approval applications after the hiatus was not associated with a major shift in the development of drugs that affect neurotransmitters, but it is notable that no new drugs that cause neurotransmitter release have been marketed since 1974. This is consistent with the fact that of the nine medicinal products currently available for obesity management, all six (78%) that exert their weight reducing actions through centrally-acting mechanisms act via neurotransmitter release,

rather than inhibition of re-uptake (see Table 7.3). This suggests that drug developers have largely abandoned the use of chemical entities that inhibit reuptake in favour of releasing agents. However, the lack of long-term data on the safety of these products, especially with the more recent approvals is of great concern. Indeed, psychiatric and cardiovascular adverse events have been reported as major concerns of recently approved products with centrally-acting mechanisms [17].

Table 7.3: Anti-obesity drugs currently approved for use in at least one country

Brand name	Active ingredient	Mechanism of action	Year approved
Adipex-P; Ionamin	Phentermine	Precise mechanism unknown: norepinephrine-dopamine releasing agent	1959
*Alli or Xenical	Orlistat	Inhibits gastric and pancreatic lipases	1999
*Belviq	Lorcaserin	Selective 5-HT _{2C} receptor agonist	2012
*Contrave; Mysimba	Naltrexone + bupropion	Bupropion: reuptake inhibitor and releasing agent of norepinephrine and a nicotinic acetylcholine receptor antagonist; naltrexone augments bupropion's activation of proopiomelanocortin (POMC)	2014
Didrex	Benzphetamine	Precise mechanism unknown: norepinephrine-dopamine releasing agent	1960
Obezine	Phendimetrazine	Precise mechanism unknown: norepinephrine-dopamine releasing agent	1961
*Qsymia; Qnexa	Phentermine + topiramate	The precise mechanism of action for both drugs is unknown: phentermine is a norepinephrine-dopamine releasing agent; topiramate augments GABA, inhibits AMPA/kainate glutamate receptors, and inhibits carbonic anhydrase	2012
*Saxenda; Victoza	Liraglutide	Glucagon-like peptide-1 receptor agonist	2014
Tenuate Dospan	Diethylpropion	Precise mechanism unknown: norepinephrine-dopamine releasing agent	1959

*Approved for long-term treatment

Modest reduction in body weight has beneficial effects on short-term (≤ 1 year) cardiovascular profile [25]. However, whether the weight losses generated by anti-obesity medicinal products have beneficial effects on long-term cardiovascular outcome is unclear, largely because the follow-up duration of most of clinical trials are not long enough to assess these benefits beyond the weight losses achieved [26]; indeed, one large long-term study (n = 5145; median follow-up of 9.6 years) showed that weight reduction did not reduce the risk of adverse cardiovascular events in obese and overweight adults with type 2

diabetes [27]. In addition, the benefit of aggressive weight reduction in overweight and obese patients having cardiovascular decompensation (e.g. patients with heart failure) has been questioned because this group of patients survive for longer at higher body weights [28]. Furthermore, over one-third of the centrally acting products included in our review were withdrawn because their use was associated with adverse cardiovascular outcomes that are the health risks the use of the products were intended to reduce – an “obesity treatment paradox”.

7.4.5. Implications for future harms assessment and policy

Although there have been revisions to regulatory guidance for the assessment of harms in anti-obesity drug trials [29,30], there are uncertainties about the extent to which these guidelines are applied when assessing trial results for new weight loss products whose actions are through central mechanisms. For example, lorcaserin, a 5HT_{2C} receptor agonist was approved by the FDA based on the results of three pivotal trials [31,32,33], with discontinuation rates of 45%, 50%, and 34%, with mean differences in weight loss of only 3–3.6%. Although two of the three trials met the FDA guidance for effectiveness (“The proportion of subjects who lose greater than or equal to 5 percent of baseline body weight in the active-product group is at least 35%, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant”) [30], the analysis was based on the per-protocol population for completers. Furthermore, the trials failed to meet the FDA’s guidance for products for weight management, which sets clinical significance at 1 year as 5% weight loss with at least 80% power. Indeed, the FDA noted that baseline psychiatric history was limited in the clinical trials, discontinuations owing to nervous system and psychiatric disorders were higher with lorcaserin than with placebo, and the trials were not powered to detect cardiovascular

adverse events [34]; these same concerns influenced the decision of the EMA in declining the product's approval application [35]. In addition, transcripts from the FDA showed that although members of the voting panel approved the product many had concerns about cardiovascular harms [36]; it is of further concern that the post-marketing surveillance of the product is behind schedule [37].

Similarly, the approval of naltrexone plus bupropion (Contrave; Mysimba) by the FDA and EMA has been questioned by some authors, because of the potential for severe harms that appear to outweigh the benefits [38,39]. In a recent large randomized trial there was a significantly increased risk of psychiatric disorders, and the cardiovascular profile of the product is uncertain [40]. These questionable approvals by regulatory authorities lend credence to the argument that an independent group of experts should be given responsibility for assessing harms [41]. The re-introduction of amfepramone (diethylpropion) and phentermine in Europe, based on a long-standing legal action, unrelated to new information on benefits or harms, is another case in point [42,43].

The herbal weight loss medication, *Ephedra spp.*, which has agonist activity at 5HT and dopamine receptors and showed evidence of beneficial effects on body weight, was banned by the US FDA in 2004 because of an increased risk of cardiovascular and psychiatric adverse reactions [44,45]. That regulatory authorities removed this product from the market, yet granted its "conventional analogues" marketing licences arouses suspicion of regulatory bias [46].

In addition to the above, several of the products that have been withdrawn by regulatory authorities are now marketed as non-prescription formulations, alone, or in combination

over the counter or via the internet [47]. Indeed, there have been many reports of suspected adverse reactions attributed to such products [7,48,49]. There should be tougher legislative action against the promoting and marketing of such products.

7.5 CONCLUSIONS

A total of 25 anti-obesity medications have been withdrawn after marketing over the past 60 years because of adverse drug reactions, 23 of which were centrally-acting anorectics. Psychiatric disturbances, cardiotoxicity, or drug abuse and dependence accounted for over 80% of withdrawals. Centrally-acting products that caused release of monoamines were significantly more likely to be withdrawn because of adverse cardiovascular reactions, while monoamine reuptake inhibitors were more likely to be withdrawn because of drug abuse and dependence. Greater transparency in the reporting of the harms by trial investigators should be encouraged. Individuals with vested interests could be excluded from panels that consider new drug approval applications.

7.6 Chapter Summary

- 25 anti-obesity medicinal products have been withdrawn from the market because of adverse reactions
- 23 of these were centrally-acting, via monoamine neurotransmitters
- Case reports were cited as evidence for withdrawal in 80% of instances
- Psychiatric disturbances, cardiotoxicity, and drug abuse or dependence together accounted for 83% of withdrawals
- The reasons for withdrawal raise concerns about the wisdom of using pharmacological agents that target monoamine neurotransmitters in managing obesity

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Chapter 8 Post-marketing regulation of medicinal products withdrawn from the market because of drug-attributed deaths: an analysis of justification

8.1 INTRODUCTION

Regulatory authorities grant marketing licences when early-phase trials suggest a favourable benefit-to-harm balance. However, the harms may come to outweigh the benefits over time, and this could result in approved products being withdrawn from the market. When adverse reactions that result in death are suspected, one would expect faster regulatory action, with suspension or withdrawal of a product from the market.

It was previously thought that drug-attributed deaths usually occurred in very ill patients undergoing therapy with highly toxic medicinal products [1]. However, it is now recognized that adverse drug reactions are not only a major cause of deaths in hospital [2,3,4], but are also important in the general population [5,6].

The findings in chapter 3 showed that there are discrepancies in the patterns of withdrawal of medicines from the market when deaths are attributed to their use, and that formal confirmatory studies are rarely used in making withdrawal decisions. Although most withdrawal decisions are based on case reports, it is unclear whether other criteria are also used. Several signal detection algorithms are used to explore drug-adverse event relationships [7], but the extent to which confirmatory studies are used to investigate such relationships when deaths are reported is uncertain. Therefore, the objectives of this chapter were (i) to determine whether withdrawals of medicinal products because of drug-

attributed deaths were justified; (ii) to explore whether there is a relationship between the interval to first reports of deaths and time to first withdrawal of the product from the market; (iii) to examine how often confirmatory studies are performed to investigate associations between medicinal products and adverse reactions leading to deaths; and (iv) to document the levels of evidence of confirmatory studies and examine whether there is consistency across studies.

8.2 METHODS

8.2.1 Search methods

The first reviewer (IJO) documented medicinal products withdrawn after regulatory approval (after 1950) because of drug-attributed deaths using the data from Chapter 3. Products withdrawn because of deaths caused by overdose were excluded. The first reviewer (IJO) conducted searches in PubMed, Google Scholar (November 2016), and other non-electronic sources to compute the number of deaths attributed to the withdrawn product before the first withdrawal (or used any figures reported by the withdrawing regulatory authority). To assess whether any confirmatory studies were conducted, first reviewer (IJO) searched PubMed and Google Scholar (November 2016) to identify studies investigating the drug-adverse event relationships using the following order of priority: meta-analysis > observational studies > case series/reports [see appendix 5 for a comprehensive search strategy]. Animal studies were not included unless they directly investigated drug-death relationships.

8.2.2 Data extraction

The information from chapter 3 was used to document the data on launch year, the year any adverse reaction that was specifically related to death was first reported (e.g. if the

death was due to liver failure, the first reviewer (IJO) searched for, and documented the first report of a hepatic abnormality attributed to the product after regulatory approval), the year in which deaths were first reported, the first year of withdrawal in any country, and the reported mechanism through which death occurred for each included product. For each documented first report of death attributed to a product, there had to be sufficient suspicion of a cause and effect relationship to warrant reporting it. Data on the total number of reported deaths before the first withdrawal based on the results of electronic and non-electronic searches were also extracted.

8.2.2 Assessing the justification for withdrawals

A previously published framework [8] was used to determine whether the first withdrawal decisions were justified. This framework comprises an algorithm for regulatory action when a new serious adverse drug reaction is suspected, and examines the following domains: (i) an identifiable susceptible population; (ii) the availability of an adequate monitoring strategy; (iii) the availability of an adequate preventive strategy; and (iv) a favourable benefit-to-harm balance in the population. The information from case reports, case series, or confirmatory studies was used to determine whether each withdrawn product fulfilled the criteria in each domain. Depending on how many of the domains were fulfilled in the algorithm, a decision that the algorithm suggested was appropriate was assigned, as follows; decision A implies empowering the patient, B implies adding a caution, C implies adding a contraindication, and D implies licence revocation. [See appendix 6 for the schematic diagram]. The first reviewer (IJO) applied the framework methodology to make overall judgements on the justification for withdrawals; a second reviewer (JKA) independently verified them. Disagreements were resolved through discussion.

8.2.3 Rating the level of evidence

The first reviewer (IJO) used the Oxford Centre for Evidence-based Medicine (OCEBM) criteria [9] to determine the highest levels of evidence for confirmatory studies. Where confirmatory studies investigating drug-adverse events relationships were identified, the first reviewer (IJO) examined whether the studies confirmed the relationships using “Yes”, “No” or “Unclear” variables. When two or more studies were identified, the first reviewer (IJO) assessed whether the evidence regarding the drug-adverse event relationship was consistent across the studies. When the deaths occurred primarily in children ($n = 7$), the confirmatory studies must have been conducted in children. The first reviewer (IJO) applied the overall rating for each product and a second reviewer (JKA) independently verified them. Disagreements were resolved through discussion.

8.2.4 Statistical analysis

The proportions for each domain fulfilling the criteria for assessing withdrawal decisions were computed. Because the intervals to the first reports of deaths or confirmatory studies were skewed, medians and interquartile ranges (IQR) were used to express measures of central tendency and spread. Box and whisker plots were used to display the numbers of reported deaths by system, while scatter plots were used to explore relationships between the interval to the first reports of deaths and the time to the first withdrawal. Scatter plots were used to explore relationships between the first withdrawal and the interval to the first confirmatory study.

8.3 RESULTS

Of the 114 medicinal products withdrawn because of drug-attributed deaths, 99 were withdrawn after 1950 (as in Chapter 3, the 1950 cut-off was chosen because this was the

year the WHO initiated the use of INN for active pharmaceutical ingredients). Of the 99 products, nine were excluded because they caused deaths through overdose. Therefore, a total of 90 products were included in the analysis. The products were launched between 1951 and 2007, and the first withdrawals occurred between 1957 and 2011 (Table 8.1). Excluding the products withdrawn worldwide (n= 25), the first withdrawals following reports of deaths by geographical region were in Europe (n = 45), North America (n = 17), Australasia (n = 2), and Asia (n = 1).

In 56 instances (62%), the first reports of deaths occurred within a year of the initial adverse reaction reports, and reports of deaths with 9 products (10%) occurred within 2 years (Table 8.1); when deaths primarily occurred in children, all initial reports of deaths occurred within 1 year of the first adverse reaction report (with the exception of pemoline – 16 years). The median interval between the first reported adverse reaction and the first reported death was 1 year (IQR = 1 to 3). The number of reported deaths before initial withdrawal ranged from as low as 1 to as high as 1300 (benfluorex). The median number of reported deaths before initial withdrawal was 9 (IQR = 2 to 11). There was no relationship between the number of deaths and the interval to the first withdrawal (data not shown).

When analysed by system, the median number of deaths before the initial withdrawal was highest with gastrointestinal toxicity (n = 13), followed by cardiotoxicity (n = 7) (see Figure 8.1). The median interval between the first report of a death and the first withdrawal was shortest when the adverse reactions involved the gastrointestinal system: median 0.5 years (IQR = 0 to 5); and longest when the causes of death were related to the metabolic system: median 3 years (IQR = 1 to 6) (Table 8.2).

Table 8.1: Details of launch to withdrawal profile of 90 medicinal products withdrawn from the market because of drug-attributed deaths

Medicinal product	Launch year	First ADR report†	First report of death	First withdrawal	No of deaths	First country of withdrawal	Year re-introduced	Examined in studies?	Consistent?‡	Highest level study ^Δ	Association confirmed?
Alosetron	2000	2000	2000	2000	5	USA	2002	Yes	No	1	No
Alpidem	1991	1993	1993	1994	2	France	Nil	No	-	-	-
Azaribine	1975	1976	1976	1976	1	USA	Nil	No	-	-	-
Beclobrate	1985	1990	1990	1990	2	Switzerland	Nil	No	Yes	-	-
Benfluorex	1976	2003	2003	2009	1300	Europe	Nil	Yes	-	2	Yes
Benoxaprofen	1980	1982	1982	1982	57	Worldwide	Nil	Yes	-	1	Unclear**
Benzarone	1964	1987	1992	1992	5	Germany	Nil	No	Yes	-	-
Benzyl alcohol	1972	1981	1981	1982	15	Israel	Nil	Yes	-	3	Yes
Bicalutamide (150 mg)	1995	2001	2001	2003	5	Canada	Nil	Yes	-	2	Yes
Bromfenac Na	1997	1998	1998	1998	5	USA	Nil	Yes	-	1	Yes
Bromocriptine mesylate [for suppression of lactation]	1976	1983	1989	1994	3	USA	Nil	No	-	-	-
Buflomedil	1970	1981	1981	2006	11***	France	Nil	Yes	Yes	1	Yes
Buformin	1957	1976	1976	1978	15	Germany	Nil	No	-	-	-
Bunamiodyl	1958	1960	1962	1964	3	USA	Nil	No	Yes	-	-
Celecoxib	1999	2002	2005	2011	?	Europe	Nil	Yes	Yes	1	Yes
Cerivastatin	1990	1999	2001	2001	52	Worldwide	Nil	Yes	-	1	Yes
Cianidanol	1976	1980	1985	1988	4	Worldwide	Nil	No	Yes		-
Cisapride monohydrate	1993	1993	1998	2000	70	Ireland	Nil	Yes	Yes	1	Yes
Clofibrate	1967	1969	1973	1978	?	Germany	Nil	Yes	Yes	1	Yes
Clometacin	1977	1981	1981	1987	3	France	Nil	Yes	Yes	3	Yes
Clozapine	1972	1975	1975	1975	10	Finland	Nil	Yes	-	2	Yes
Coumarin (synthetic)	1996	1996	1996	1996	2	France	Nil	Yes	-	3	Yes
Diiododiethyltin & isolinoleic ester	1954	1955	1955	1957	2	France	Nil	No	-	-	-
Dithiazanine iodide	1959	1960	1960	1964	1	USA	Nil	No	Yes	-	-
Domperidone (Inj)	1979	1982	1982	1985	4	Worldwide	Nil	Yes	-	3	Yes
Doxycycline	1959	1984	1984	1989	?	France	Nil	No	-	-	-
Ebrotidine	1997	1997	1997	1998	4	Spain	Nil	Yes	-	4	Yes

Encainide	1980	1981	1991	1991	8	UK	Nil	Yes	Yes	2	Yes
Felbamate	1993	1993	1993	1994	10	USA	Nil	Yes	-	3	Yes
Fenclofenac	1978	1984	1984	1985	7	Worldwide	Nil	No	No	-	-
Fenoterol	1971	1987	1987	1990	?	New Zealand	Nil	Yes	-	2	?
Fipexide	1973	1990	1990	1991	1	France	Nil	No	-	-	-
Flosequinan	1992	1992	1992	1993	?	UK	Nil	Yes	-	2	Yes
Gemtuzumab ozogamicin	2000	2001	2002	2010	?	USA	Nil	Yes	-	2	Yes
Grepafloxacin	1997	1999	1999	1999	7	Worldwide	Nil	No	-	-	-
Indoprofen	1976	1982	1982	1983	46	Worldwide	Nil	No	-	-	-
Interferon-gamma-1b	2002	2002	2007	2007		USA	Nil	Yes	-	2	Yes
Isaxonine phosphate	1981	1983	1983	1984	5	France	Nil	No	-	-	-
Isoxicam	1983	1985	1985	1985	1	Worldwide	Nil	No	Yes	-	-
Ketoconazole	1976	1981	1981	2013	?	Europe, Australia	Nil	Yes	Yes	1	Yes
Ketorolac injection	1990	1992	1993	1993	80	Germany	Nil	Yes	-	1	Yes
Levamisole [as antihelminthic]	1966	1976	1978	1999	2	USA	Nil	Yes	-	2	Yes
Loperamide (syrups & drops)	1975	1980	1990	1990	6	Worldwide	Nil	No	Yes	-	-
Loxoprofen	1983	1993	1993	2000	1	Singapore	Nil	Yes	Yes	2	Yes
L-tryptophan	1963	1989	1989	1989	30	Worldwide	2005	Yes	-	3	Yes
Lumiracoxib	2007	2007	2007	2007	2	Australia	Nil	Yes	-	3	Yes
Mibefradil	1997	1998	1998	1998	1	USA	Nil	Yes	Yes	3	Yes
Muzolimine	1985	1985	1987	1987	7	Worldwide	Nil	Yes	-	3	Yes
Naftidrofuryl oxalate IV	1974	1976	1994	1995	2	France	Nil	No	-	-	-
Nebacumab	1991	1993	1993	1993	?	Worldwide	Nil	Yes	-	2	Yes
Nefazodone	1994	1999	2002	2003	1	Europe	Nil	Yes	Yes	3	Yes
Nimesulide	1986	1998	2000	2002	5	Portugal	Nil	Yes	-	2	Yes
Nitrefazole	1980	1984	1984	1984	?	Germany	Nil	No	-	-	-
Nomifensine	1976	1980	1985	1986	4	Worldwide	Nil	Yes	-	3	Yes
Orgotein	1968	1985	1985	1990	1	Switzerland	Nil	No	-	-	-
Osmosin (indomethacin)	1975	1978	1979	1983	20?	UK		Yes	Yes	3	Yes
Oxyphen-butazone	1955	1964	1965	1984	11	Worldwide	Nil	Yes	Yes	3	Yes
Oxyphenisatine acetate	1955	1970	1970	1970	1	Worldwide	Nil	Yes	Yes	3	Yes

Pemoline	1975	1975	1989	2005	9	Worldwide	Nil	Yes	Yes	2	Yes
Phenformin HCl	1957	1959	1963	1970	36	Europe	Nil	Yes	-	3	Yes
Pirprofen	1982	1984	1986	1990	7	Worldwide	Nil	No	Yes	-	-
Practolol	1970	1972	1976	1994	12	Greece	Nil	Yes	-	3	Yes
Prenylamine	1960	1971	1973	1989	4	Worldwide	Nil	Yes	Yes	1	Yes
Propofol	1987	1987	1987	1992	20	Israel	Nil	Yes	-	2	Yes
Propy-phenazone	1951	1980	1986	1989	5	Turkey	Nil	Yes	-	2	Yes
Pumactant	1992	2000	2000	2000	?	UK	Nil	No	-	-	-
Rapacuronium bromide	1999	2000	2000	2001	5	USA	Nil	Yes	Yes	2	Yes
Rimonabant	2006	2006	2006	2007	5	Europe	Nil	Yes	Yes	1	Yes
Rofecoxib	1999	2002	2002	2004	?	Worldwide	Nil	Yes	Yes	1	Yes
Rosiglitazone	1999	2001	2007	2011	?	UK	Nil	Yes	Yes	1	Yes
Sertindole	1994	1996	1996	1998	35	UK	2001	Yes	No*	2	No*
Sibutramine	2001	2002	2002	2010	33	Europe	Nil	Yes	-	2	Yes
Sitaxentan sodium	2006	2009	2009	2010	2	Worldwide	Nil	Yes	Yes	1	Yes
Somatropin (pituitary-derived)	1973	1984	1984	1985	4	Europe	1992	Yes	Yes	2	Yes
Sorivudine	1993	1993	1993	1993	18	Germany	Nil	Yes	-	5	Yes
Sulfadi-methoxine	1958	1961	1962	1966	3	USA	Nil	No	-	-	-
Suloctidil	1975	1982	1983	1985	3	Worldwide	Nil	No	-	-	-
Technetium (99mTc) fanolesomab	2004	2005	2005	2005	2	USA	Nil	No	-	-	-
Temafloxacin	1991	1992	1992	1992	3	Worldwide	Nil	Yes	Yes	4	Yes
Terfenadine	1985	1991	1991	1997	21	Europe	Nil	Yes	Yes	3	Yes
Terodiline	1965	1989	1989	1991	14	Worldwide	Nil	Yes	Yes	3	Yes
Thenalidine	1953	1958	1958	1958	2	USA	Nil	Yes	-	3	Yes
Tienilic acid	1976	1979	1980	1980	2	Greece	Nil	Yes	-	3	Yes
Tocainide	1981	1985	1985	1986	1	USA	Nil	Yes	Yes	2	Yes
Tolcapone	1998	1998	1998	1998	3	UK	2006	Yes	-	2	No
Tolrestat	1982	1995	1995	1996	3	Worldwide	Nil	Yes	-	1	Yes
Troglitazone	1997	1997	1997	1997	7	UK	Nil	Yes	Yes	2	Yes
Trovafloxacin	1997	1997	1998	1999	6	Europe	Nil	No	-	-	-
Vitamin E (IV)	1983	1984	1984	1984	38	USA	Nil	Yes	-	3	Yes

Zomepirac Na	1979	1981	1983	1983	5	Worldwide	Nil	Yes	-	3	Yes

ABBREVIATION: ADR: Adverse drug reaction

*Cochrane review with “insufficient data” suggested increased risk of cardiovascular events; however, other studies were largely consistent and reported no increased risk of deaths

**No studies identified exploring association with hepatotoxicity

***at least 65 deaths because of overdose have been reported

†First adverse reaction related to the suspected deaths

‡Where two or more studies were identified

§Refers to number of deaths before first withdrawal

^Based on the OCEBM Levels of evidence [9]: Level 1: systematic review (highest); Level 2: randomized clinical trial; Level 3: non-randomized, cohort or follow-up studies; Level 4: case-series or case-control studies; and Level 5: mechanism-based reasoning (lowest)

Confirmatory studies exploring the drug-adverse event relationships were conducted for 63 products (70%; Table 8.1). The first reviewer (IJO) identified two or more confirmatory studies for 40 of the 63. In 58 cases (79%), confirmatory studies showed evidence of an association between the withdrawn product and the adverse reaction; in one of these (an interaction of sorivudine with 5-fluorouracil leading to bone marrow suppression), the authors investigated the relationship between the interaction and deaths in animals. Level 1 evidence was identified for 16 products (25%), Level 2 evidence for 22 products (35%), and Level 3 evidence for 22 products (35%). In 13 instances (14%), confirmatory studies were published before the year of the first withdrawal following reports of deaths. The median interval between the first withdrawal and the first confirmatory study was 3 years (IQR = 1 to 6). Figure 8.2 shows an inconsistent shortening in the interval to the first confirmatory study with more recent launch dates. Of the four products re-introduced after initial withdrawal, one death has since been attributed to one (L-tryptophan) [10].

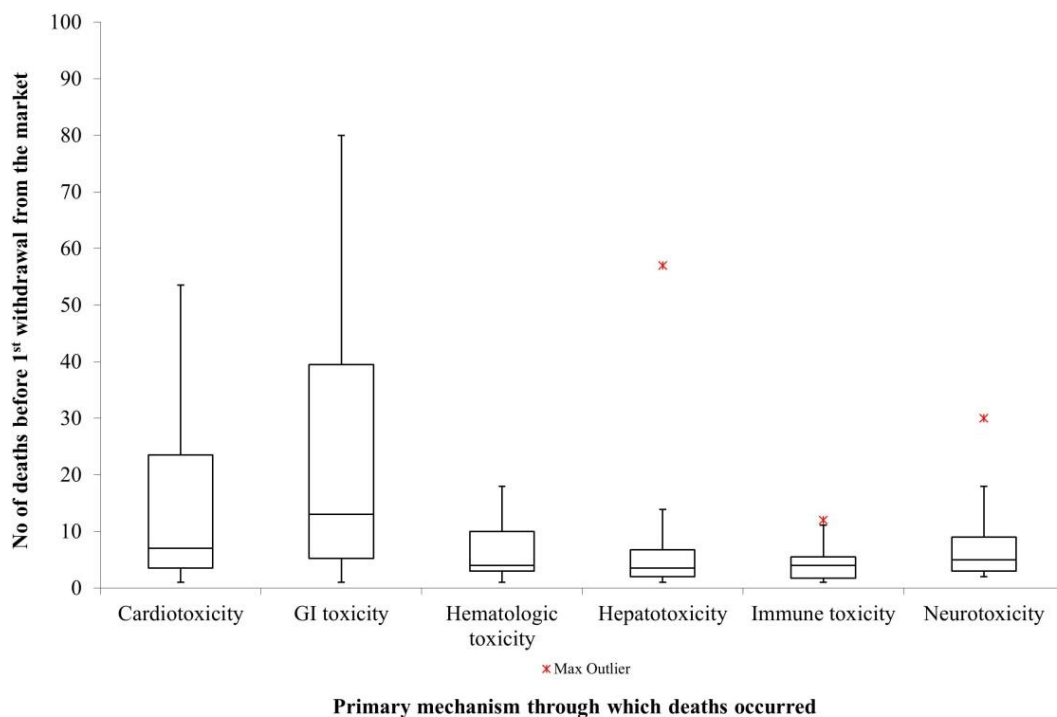
Table 8.2: Median interval to withdrawal based on primary organ-system classification for medicinal products withdrawn from the market because of drug-attributed deaths

Organ/system	Median interval to withdrawal (years)	Interquartile range (years)	Number of products
Cardiovascular	2.5	0.25-6	23
Gastrointestinal	0.5	0-4.75	6
Haematologic	1	0-3	9
Hepatotoxic	1	0-1	28
Immune	1	0.25 to 4.75	9
Metabolic	3	1.25 to 6.25	4
Neurotoxic	1	0 to 11.5	6
Nephrotoxic	N/A	11.5	3
Respiratory	N/A	11.5	2

Susceptible populations were identified in 23 (26%) instances (Table 8.3); four of these were attributed to interactions with other medications. In 11 instances (12%), there was an adequate monitoring strategy, and in 4 cases (4%) there was an adequate preventive

strategy or evidence of a favourable benefit-to-harm balance in the population for which the medicine was primarily intended. Based on analysis of the individual domains, outright revocation of the licence was the appropriate decision in 67 cases (74%). Either revocation or empowering the patient was appropriate in 11 instances (12%), and revocation or adding a caution was appropriate in 7 instances (8%; Table 8.3). In 3 cases (3%), adding a contraindication would have been the most appropriate decision, and adding a caution should have been the most appropriate decision in 2 cases (2%). Overall, the reason for first withdrawal appeared to be justified in 86 cases (96%). In 4 instances (4%), the withdrawn products were re-introduced in the countries of initial withdrawal.

Figure 8.1: Box and whisker plots* showing the number of reported suspected deaths attributed to medicinal products by system before the first withdrawal from the market



*The ends of the whiskers are set at 1.5*IQR above the third quartile (Q3) and 1.5*IQR below the first quartile (Q1).

Figure 8.2: Scatter plot showing the interval to the first confirmatory study after withdrawal of 90 medicinal products to which deaths were attributed*

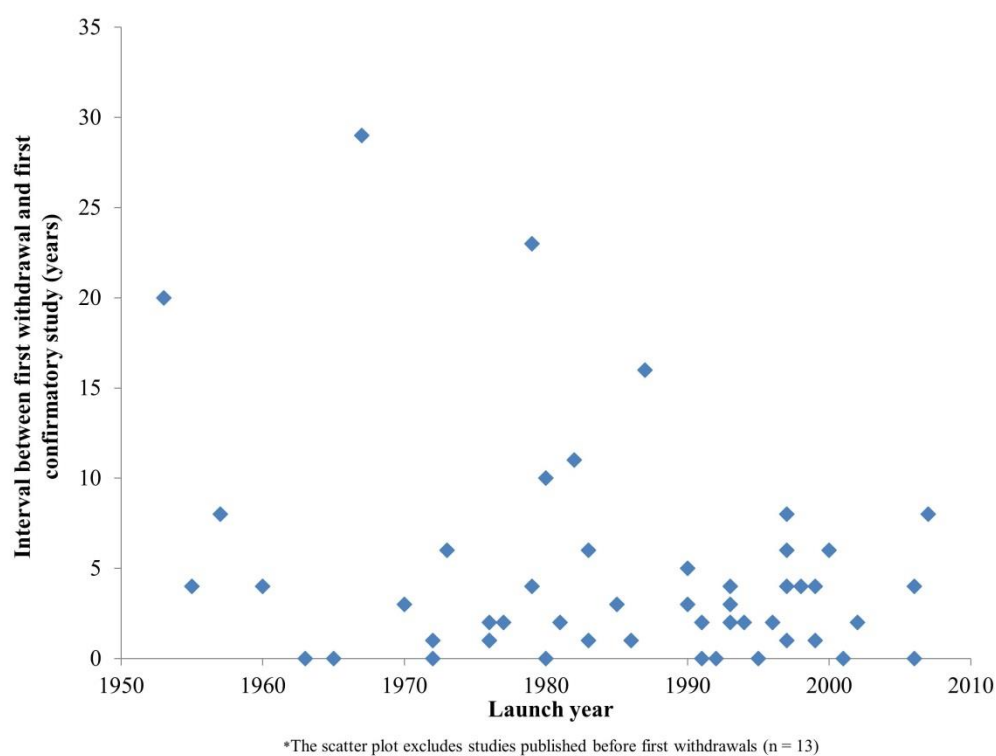


Table 8.3: Determination of justification for withdrawal of 90 medicinal products to which deaths were attributed¹

Medicinal product	Adverse reaction	Susceptible population	Monitoring strategy	Preventive strategy	Population benefit to harm balance ²	Overall rating	Withdrawal justified?
Alosetron ³	Ischaemic colitis	Men > women	No	No	Poor	A/D	Yes
Alpidem	Hepatotoxicity	No	No	No	Poor	D	Yes
Azaribine	Thromboembolism	Hereditary homocystinuria	No	No	Poor	A/D	Yes
Beclobrate	Hepatotoxicity	No	Unclear	No	Poor	D	Yes
Benfluorex	Cardiotoxicity	No	No	No	Poor	D	Yes
Benoxaprofen	Hepatotoxicity	Elderly	No	No	Poor	A/D	Yes
Benzarone	Hepatotoxicity	No	LFT	No	Poor	B/D	Yes
Benzyl alcohol	Metabolic acidosis	No	No	No	Poor	D	Yes
Bicalutamide (150 mg)	“Accelerated deaths”	No	No	No	Poor	D	Yes
Bromfenac Na	Hepatotoxicity	No	LFT	Restrict duration of therapy	Poor	B/D	Yes
Bromocriptine mesylate [for suppression of lactation]	Cardiotoxicity, neurotoxicity	No	No	No	Poor	D	Yes
Buflomedil ⁴	Cardiotoxicity, neurotoxicity	Elderly; renal impairment	No	No	No	D	Yes
Buformin	Metabolic acidosis	Impaired renal function	Plasma concentration measurement predictive, but not practicable	No	Poor	A/D	Yes
Bunamiodyl	Nephrotoxicity	No	No	No	Poor	D	Yes
Celecoxib (for familial adenomatous polyposis)	Cardiotoxicity	No	No	No	Poor	D	Yes
Cerivastatin	Rhabdomyolysis; renal failure	Patients using other medicines; high-doses	No	No	Poor	A/D	Yes
Cianidanol	Haemolytic anaemia	No	No	No	Poor	D	Yes
Cisapride monohydrate	Cardiotoxicity (QT interval prolongation)	No	ECG	No	Poor	B/D	Yes
Clofibrate	“Accelerated deaths”	No	No	No	Poor	D	Yes
Clometacin	Hepatotoxicity	No	No	No	Poor	D	Yes
Clozapine	Agranulocytosis	No	WBC	No	Good	B	No
Coumarin (synthetic)	Hepatotoxicity	No	No	No	Poor	D	Yes
Diiododihytltin & isolinoleic ester	Cerebral oedema	No	No	No	Poor	D	Yes
Dithiazanine iodide	Metabolic acidosis	No	No	No	Poor	D	Yes
Domperidone (Inj)	Cardiotoxicity	No (high dose ⁵)	No	No	Good	C	No
Doxycycline	Anaphylaxis; oesophagitis	Female, elderly	No	Patch test; take with fluids	Good	B	No
Ebrotidine	Hepatotoxicity	No	No	No	Poor	D	Yes
Encainide	Cardiotoxicity	No	No	No	Poor	D	Yes

Felbamate ³	Hepatotoxicity; aplastic anaemia	Pre-existing blood dyscrasias or pre-existing immune disorders	Yes, but not helpful	No	Poor	A/D	Yes
Fenclofenac	Toxic epidermal necrolysis	No	No	No	Poor	D	Yes
Fenoterol	Increased mortality due to asthma	Children	No	No	Poor	A/D	Yes
Fipexide	Hepatotoxicity	No	No	No	Poor	D	Yes
Flosequinan	Cardiotoxicity	No	No	No	Poor	D	Yes
Gemtuzumab ozogamicin	“Accelerated deaths”	No	No	No	Poor	D	Yes
Grepafloxacin	Cardiotoxicity	No	No	No	Poor	D	Yes
Indoprofen	Gastrointestinal haemorrhage	No	No	No	Poor	D	Yes
Interferon-gamma-1b	Accelerated deaths	No	No	No	Poor	D	Yes
Isaxonine phosphate	Hepatotoxicity	No	No	No	Poor	D	Yes
Isoxicam	Fatal skin reactions	No	No	No	Poor	D	Yes
Ketoconazole	Hepatotoxicity	No	LFT	No	Poor	B/D	Yes
Ketorolac injection	Gastrointestinal; renal	No	No	No	Poor	D	Yes
Levamisole [as antihelminthic]	Neurotoxicity	No	No	No	Poor	D	Yes
Loperamide (syrops & drops for paediatric use)	Paralytic ileus	Children	No	No	Poor	D	Yes
Loxoprofen	Gastrointestinal haemorrhage	No	No	No	Poor	D	Yes
L-tryptophan ³	Eosinophilia-myalgia syndrome (EMS)	No	No	No	Poor	D	Yes
Lumiracoxib	Hepatotoxicity	No	No	No	Poor	D	Yes
Mibefradil	Drug interactions	Patients using other medicines	No	No	Poor	D	Yes
Muzolimine	Neurotoxicity; renotoxicity	No	No	No	Poor	D	Yes
Naftidrofuryl oxalate IV	Anaphylaxis	No	No	No	Poor	D	Yes
Nebacumab	Accelerated deaths	No	No	No	Poor	D	Yes
Nefazodone	Hepatotoxicity	Women > men	No	No	Poor	D	Yes
Nimesulide	Hepatotoxicity	No	LFT	No	Poor	D	Yes
Nitrefazole	Hepatotoxicity	No	No	No	Poor	D	Yes
Nomifensine	Haemolytic anaemia	Coombs'-positive patients?	Blood count	No	Poor	C	No
Orgotein	Anaphylaxis	No	No	No	Poor	D	Yes
Osmosin [®] (indometacin)	Intestinal ulceration	No	No	Short-term use	Poor	B/D	Yes
Oxyphenbutazone	Bone marrow suppression	No	No	No	Poor	D	Yes
Oxyphenisatine acetate	Hepatotoxicity	No	No	No	Poor	D	Yes
Pemoline	Hepatotoxicity	No	No	No	Poor	D	Yes
Phenformin HCl	Metabolic acidosis	Impaired renal function	Phenotyping ⁸ for PMs, but not widely available	No	Poor	B/D	Yes

Pirprofen	Hepatotoxicity	No	No	No	Poor	D	Yes
Practolol	Oculomucocutaneous syndrome	No	No	No	Poor	D	Yes
Prenylamine	Cardiotoxicity	No	No	No	Poor	D	Yes
Propofol (children)	Hepatotoxicity, metabolic	Children	No	No	Good	C	Yes
Propyphenazone	Haematologic	No	No	No	Poor	D	Yes
Pumactant	“Accelerated deaths”	Neonates	No	No	Poor	D	Yes
Rapacuronium bromide	Bronchospasm	Children	No	No ⁶	Poor	D	Yes
Rimonabant	Psychiatric	No	No	No	Poor	D	Yes
Rofecoxib	Cardiotoxicity	No	No	No	Poor	D	Yes
Rosiglitazone	Cardiotoxicity	No	No	No	Poor	D	Yes
Sertindole ³	Cardiotoxicity	Patients at risk of cardiac dysrhythmias	ECG	No	Poor	A/D	Yes
Sibutramine	Cardiotoxicity	No (CVD history ⁷)	No	No	Poor	D	Yes
Sitaxentan sodium	Hepatotoxicity	No	No	No	Poor	D	Yes
Somatropin (pituitary-derived)	Creutzfeldt-Jakob disease	No	No	No	Poor	D	Yes
Sorivudine	Bone marrow suppression	Patients taking fluorouracil	No	No	Poor	A/D	Yes
Sulfadimethoxine	Immunologic	Children	No	No	Poor	D	Yes
Suloctidil	Hepatotoxicity	No	No	No	Poor	D	Yes
Technetium (99mTc) fanolesomab	Cardiotoxicity	No	No	No	Poor	D	Yes
Temafloxacin	Haemolytic anaemia	No	No	No	Poor	D	Yes
Terfenadine	Cardiotoxicity	Patients on other medications	No	No	Poor	B/D	Yes
Terodiline	Cardiotoxicity	No	No	No	Poor	D	Yes
Thenalidine	Neutropenia	No	No	No	Poor	D	Yes
Tienilic acid	Hepatotoxicity	No	No	No	Poor	D	Yes
Tocainide	Haematologic	No	No	No	Poor	D	Yes
Tolcapone	Hepatotoxicity	No	LFT	No	Poor	B/D	Yes
Tolrestat	Hepatotoxicity	No	No	No	Poor	D	Yes
Troglitazone	Hepatotoxicity	No	No	No	Poor	D	Yes
Trovafloxacin	Hepatotoxicity	Children	No	No	Poor	D	Yes
Vitamin E (intravenous)	Hepatotoxicity	Children	No	No	Poor	A/D	Yes
Zomepirac Na	Anaphylaxis	No	No	No	Poor	D	Yes

ABBREVIATIONS: CVD: Cardiovascular disease; ECG: Electrocardiography; LFT: Liver function test; PM: Poor metabolizers

¹Based on the Aronson et al criteria [8]: A Empower patient; B = Add caution; C = Add contraindication; D = Revoke licence

²Judgement at the time of first withdrawal

³Re-introduced after initial withdrawal

⁴withdrawn because of toxicity at therapeutic doses and reports of fatal overdose

⁵Possible overdose caused by physician administration of product in doses above that recommended by the manufacturer (the patient had failed to respond to therapeutic doses (<https://www.ncbi.nlm.nih.gov/pubmed/6122831>))

⁶Sugammadex, an agent for reversal of neuromuscular blockade was not available at the time of initial withdrawal

⁷Recent studies have shown a low absolute risk of cardiovascular events in people without pre-existing CVD (<https://www.ncbi.nlm.nih.gov/pubmed/25971925>; <https://www.ncbi.nlm.nih.gov/pubmed/20553061>)

⁸Phenotype testing was unavailable at the time of first withdrawal

8.4 DISCUSSION

8.4.1 Main findings

The withdrawal of medicinal products from the market by regulatory agencies because of drug-attributed deaths over the last 60 years has been largely justified, based on the information available at the time of initial withdrawal. Initial withdrawals following reports of deaths almost always occurred in either Europe or North America. The sooner deaths occurred following initial reports of the relevant adverse reactions, the sooner such products were withdrawn; this is consistent with the findings in chapters 2 and 3, which showed that the shortened intervals between launch and withdrawal was largely due to quicker reports of deaths following product launch. Regulatory authorities were also more likely to withdraw products from the market very quickly if the deaths involved children. The more recent the launch year, the quicker confirmatory studies were conducted after a product was removed from the market until 1980; although the interval to the first confirmatory study does not appear to have shortened afterwards, twice as many confirmatory studies were published when products were withdrawn, and the median interval was shorter (3 years *versus* 4 years). In most cases, the results of confirmatory studies investigating the association between the withdrawn products and adverse reactions suggested a true association.

Withdrawals were justified in the overwhelming majority of cases. When the decision algorithm suggested more than one possible course of action (17 cases), e.g., adding a contraindication or revoking the licence, the regulatory authorities revoked the licence, which suggests that they applied the precautionary principle [11]. The failure of initial withdrawals in Africa or South America suggests that concerted regulatory actions to

withdraw products in those regions are taken only after actions have been taken in other regions.

8.4.2 Strengths and limitations

This is the first review to examine whether post-marketing withdrawals of medicinal products because of drug-attributed deaths were justified, and also the first to examine the trends in the conduct of confirmatory studies when suspected drug-associated deaths are reported. A risk management algorithm was used to determine whether the initial withdrawals of products because of suspected drug-attributed deaths were justified. Comprehensive literature searches were conducted to identify confirmatory studies exploring the drug-adverse event (or death) relationships; the quality of the studies was accounted for, and great efforts were used to check for consistency across the studies. However, several limitations in this research are noted. It is possible that some medicinal products withdrawn from the market because of drug attributed deaths may not have been identified. There was no data on the exact number of deaths attributed to each withdrawn product before withdrawal; indeed the number of deaths included in this research is probably an underestimation of the total number. Although products that caused deaths due to overdose were excluded, some of the reported deaths may have included patients who took overdoses, either deliberately or accidentally.

The algorithm used for assessing regulatory actions when deaths are detected invokes population data and assumes causality. The final regulatory decision in any country will also depend on the capacity of the pharmacovigilance systems to account appropriately for the different domains of the algorithm; it is plausible that a lack of monitoring or

preventive capacity could result in faster regulatory actions when new serious adverse drug reactions emerge.

8.4.3 Implications for future decision making when deaths are suspected

Although it appears that regulatory authorities have appropriately revoked the marketing authorizations of medicinal products because of drug-attributed deaths, it is possible that effective compounds may have been hitherto removed from the market because of a lack of well-developed methods for risk assessment, monitoring, or minimization. Improved adverse event monitoring and reporting strategies in clinical trials could identify the important feature of susceptibility, i.e. those who are at higher risk of adverse events, and therefore reduce the need to withdraw such products after approval, or lead to re-introduction after initial suspension. For instance, a clinical trial of felbamate, conducted in the context of a “black box” warning, showed that it was relatively safe in epilepsy [12], and alosetron was re-introduced for use restricted to women, who were thought to be less susceptible to the adverse outcome of ischaemic colitis [13]. Similarly, newer confirmatory evidence from public and industry funding has suggested that the risk of cardiovascular-related death with sibutramine is only significantly increased in patients with a prior history of cardiovascular disease [14,15].

Greater co-ordination of drug post-marketing surveillance across regulatory authorities should lead to consistency in the patterns of withdrawal across geographical regions when deaths are suspected; this will also minimize unnecessary exposure of the public to potentially fatal hazards, especially in settings with weak pharmacovigilance systems. The use of an algorithm such as we have used in this study could help to expedite the process of decision making. Because regulatory actions could be influenced by vested interests, drug

regulatory bodies should have independent advisors in their panels when determining what regulatory actions to take when adverse reactions are attributed to medicinal products.

In two cases (domperidone and loperamide) withdrawal was occasioned by deaths when the products were either administered inappropriately by physicians in doses above those recommended by the manufacturers [16,17] or used indiscriminately in children [18]. It is therefore suggested that training of physicians in appropriate prescribing [19] should be a priority for undergraduate medical training, as should promotion of the rational use of medicines [20].

8.4.4 Implications for future monitoring of adverse drug reactions

Signal detection (e.g. from pharmacovigilance databases) does not prove a drug-adverse event association. Integrated evidence synthesis and algorithms that combine data from spontaneous adverse reaction databases and systematic reviews or observational studies (teleoanalysis) could be used to investigate drug-adverse event relationships, especially when deaths are suspected.

Drug manufacturers and regulatory authorities should ensure that there is consistency in how medications are used, irrespective of settings. For instance, there were discrepancies in the lower age limit for the use of loperamide in children [21]; the minimum age at which the product could be prescribed was two years in the USA and four years in the UK, but one year in developing countries. All the reported deaths associated with this product occurred in children aged less than six and a half months.

8.4.5 Implications for the future conduct of confirmatory studies

Confirmatory studies were identified for a majority of the products studied, and the results across the studies were largely consistent. In the very few instances where the direction of the effect estimate for a risk of adverse reactions was inconsistent ($n = 3$), the sources of funding for the studies differed. For example, publicly funded confirmatory studies showed that fenoterol was associated with an increased risk of asthma deaths in New Zealand and Japan [22,23,24] and in women aged over 35 years in Italy [25]. However, a similar study funded by a drug manufacturer did not find an association between fenoterol and an increased risk of asthma deaths [26]. Similarly, sertindole (used in the management of schizophrenia) was initially withdrawn because signals detected in adverse reactions databases suggested that its use was associated with a 10-fold increase in the risk of death, and publicly funded research showed that the product significantly increased the risk of adverse cardiovascular events [27]; however, confirmatory studies funded by the manufacturer did not suggest an increased risk [28,29] and the product was re-introduced. Furthermore, the number of deaths estimated to have been caused by the weight loss product benfluorex (1300) was based on the results of a publicly funded study [30], but another group of authors with financial ties to the manufacturer has described the number of reported deaths as an overestimate [31]. In the case of buflomedil, there was discrepancy in the number of drug-attributed deaths when data from the WHO database and the database of the marketing authorization holder were compared [32,33]. While public-industry partnerships in drug development are being fostered [34,35], similar partnerships appear not to have been considered for monitoring serious adverse reactions. Collaborative research between public and independently funded entities when deaths are suspected could be considered for future confirmatory studies on harms, especially when the product has a favourable population benefit-to-harm balance.

8.5 CONCLUSIONS

Regulatory authorities have been largely justified in making withdrawal decisions when suspected deaths have been attributed to medicinal products. Medicinal products suspected of causing drug-attributed deaths are more likely to be withdrawn from the market quickly when there is a short interval between the first adverse reaction reports and the first reported deaths. New methods for regulatory courses of action when deaths are suspected should be developed, and research aimed at determining whether specific susceptibilities predispose particular patient groups to severe reactions should be instigated. Collaborative research involving both publicly and independently funded institutions should be encouraged, to help strengthen monitoring and evaluation processes when drug-related deaths (and other serious adverse drug reactions) are suspected.

8.6 Chapter Summary

- Regulatory authorities have been justified in making withdrawal decisions when deaths have been attributed to medicinal products, using the precautionary principle when alternative decisions could have been made
- Medicinal products are likely to be quickly withdrawn from the market when there is a short interval to the first reported deaths
- The use of algorithms could help to expedite the process of decision making when adverse reactions are attributed to approved medicinal products
- Collaborative research involving both publicly and independently funded institutions could help obviate inconsistencies in the direction of effects in evaluation processes when adverse reactions are suspected

8.7 REFERENCES

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Chapter 9 Benefits and harms of centrally-acting anti-obesity medicinal products: a systematic review and meta-analysis of pivotal clinical trials

9.1 INTRODUCTION

Overweight and obesity remain major a public health challenge [1], and obesity is associated with significantly increased risks of mortality [2]. Based on World Health Organisation figures, the worldwide prevalence of obesity has more than doubled since 1980, and there were over 600 million obese individuals worldwide in 2014 [3]. Current management strategies include dietary and lifestyle adjustments, as well as pharmacotherapy [4].

About 30 medicinal products have been approved for treatment of obesity over the last few decades. However, the results in Chapter 7 showed that 25 of these have been withdrawn from the market because of concerns about harms; 23 of these had centrally-acting mechanisms of action. Despite evidence of post-marketing withdrawals of this class of products because of adverse reactions, they are still being developed for obesity management, and some new products, such as lorcaserin and phentermine plus topiramate (P-T), have recently gained approval from regulatory authorities. One reason for this could be the pattern of outcomes reporting, which can skew trial results in favour of effectiveness over harms.

Adverse events and discontinuation rates in clinical trials can influence the benefit-to-harm balance of a new medicinal product [5], and the balance becomes more difficult to assess as the number of drop-outs increases. Assessing discontinuation can also provide valuable information about the uptake of a new product by the study participants [6].

Pivotal trials are large Phase III trials used by drug manufacturers to gain marketing licences from regulatory authorities [7]. Since 1995, pivotal trials have been used by drug sponsors to gain the marketing approvals for centrally-acting anti-obesity medicinal products. Following discussions with my supervisors, we decided that the next logical step was to compare the benefit-harm profile of withdrawn products with currently approved ones, using the evidence that was available at the time of authorization. However, there were no systematic reviews of pivotal studies of such products.

9.1.1 Objective

- To critically appraise the evidence for benefits and harms in pivotal clinical trials used to gain marketing licences for centrally-acting anti-obesity products since 1995, using evidence from regulatory documents, journal publications, and a clinical trial registry

9.1.2 Research questions

- How effective are centrally-acting anti-obesity medicinal products at generating weight losses, as reported in pivotal trials?
- Are there differences in the risk of adverse events between centrally-acting anti-obesity products and placebo, as reported in pivotal trials?
- Are there differences in the risk of treatment discontinuation between centrally-acting anti-obesity products and placebo, as reported in pivotal trials?
- Are adverse event and discontinuation rates in pivotal clinical trials of centrally-acting anti-obesity products consistently reported when regulatory documents and journal publications are compared?
- What is the quality of the evidence in pivotal clinical trials of centrally-acting anti-obesity medicinal products?

9.2 METHODS

9.2.1 Search strategy

The first reviewer (IJO) searched the EMA and FDA websites to identify anti-obesity medicinal products approved between January 1995 and June 2016. Before searching the FDA website, we accessed CenterWatch (<https://www.centerwatch.com/>) to identify anti-obesity products approved by the FDA [See Figure 9.1 for detailed search methods].

Products were included irrespective of current regulatory approval status. Products for which the reported mechanisms of actions were not via centrally-acting pathways were excluded. For each approved product identified, data on the trade name, active ingredient, and year of approval were documented. Products for which the first reviewer (IJO) was unable to identify regulatory documents relating to their approval history or their corresponding documents in journal publications (or trial registry) were also excluded. The review protocol was registered at the PROSPERO International prospective register of systematic reviews: CRD42016047109.

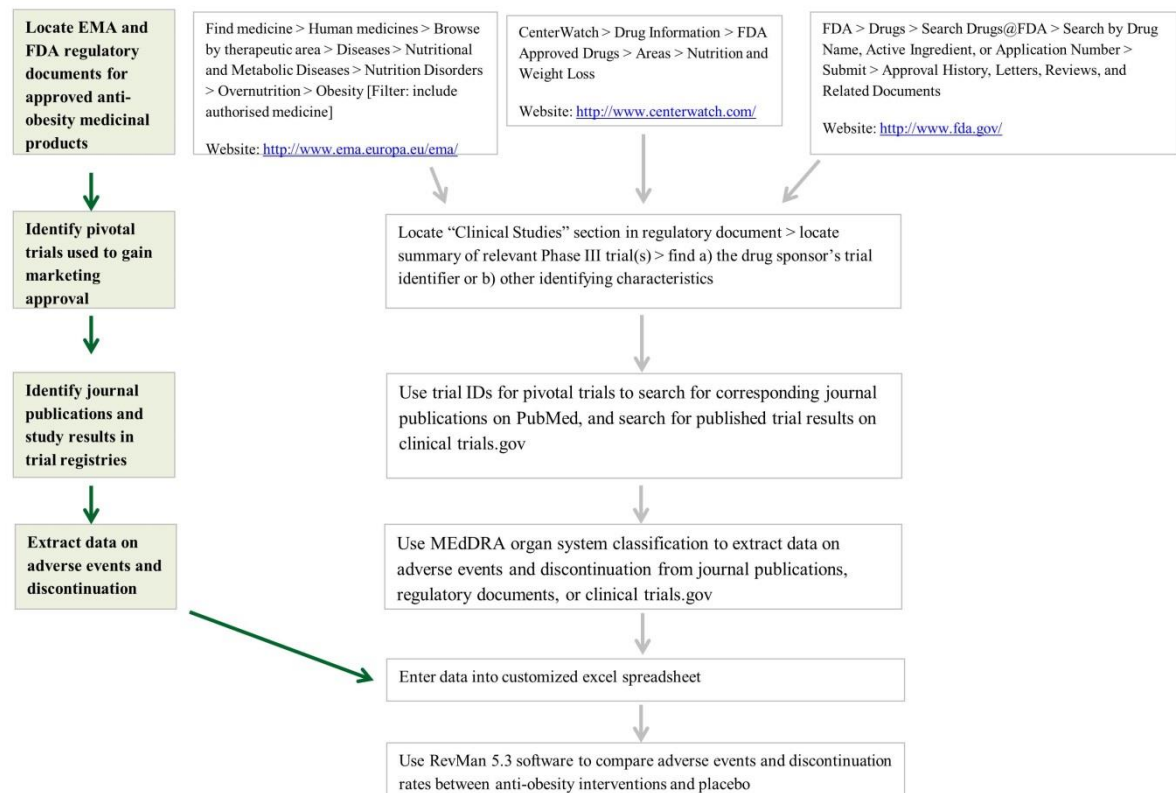
Using approval regulatory documents from both regulatory websites (FDA Briefing Document and/or EMA Assessment Report), the first reviewer (IJO) searched for the pivotal trials used by drug sponsors to gain marketing approvals. The trial IDs of pivotal trials in the regulatory documents were then mapped to corresponding journal publications (via PubMed searches) and trial results on clinical trials.gov [see appendix 7; and appendix 8]. Where necessary, contact was made with the corresponding authors of journal publications to request additional data.

9.2.2 Inclusion and exclusion criteria for pivotal trials

Pivotal phase III trials on which marketing authorizations were based were included.

Pivotal trials were included irrespective of study design and duration. Extension phases of pivotal trials were excluded. Where pivotal trials contained active comparator arms, such arms were excluded from the review.

Figure 9.1: Flow chart showing the process for identification of pivotal clinical trials of anti-obesity medicinal products with centrally-acting mechanisms of action



9.2.3 Outcomes

9.2.3.1 Primary outcomes

Body weight

Overall adverse events

Overall discontinuation due to adverse events

9.2.3.2 Secondary outcomes

Serious adverse events

Overall discontinuations

Discontinuation due to adverse events by system

Discontinuation due to individual adverse events

Discontinuation due to other events

Because cardiovascular and neuropsychiatric adverse reactions have been reported as the major reasons for post-marketing withdrawal of centrally-acting anti-obesity products (see chapter 7), further assessment of individual adverse events and discontinuations within this sub-category was carried out. In addition, individual adverse events and discontinuations within the gastrointestinal system were also evaluated because they have been reported as one of the commonest adverse events of anti-obesity medicinal products [8,9].

9.2.4 Risk of bias assessment

The risk of bias in the journal publications of pivotal trials was assessed using the Cochrane criteria [10] which examines the following domains:

- method of randomisation;
- concealment of allocation;
- blinding of participants and personnel;
- blinding of outcome assessment;
- incomplete outcome data;
- selective reporting;
- other bias (e.g. industry funding, conflicts of interest, etc.).

The first reviewer (IJO) assessed the risk of bias in included pivotal trials; these were independently verified by other reviewers (DJC, NJHB). Disagreements were resolved through consensus. If an agreement could not be reached, a third reviewer (JKA or CJH) arbitrated.

To assess whether there was consistency in the reporting of adverse event rates, the data on participant flow (including reporting of adverse events) across journal publications, regulatory documents, and clinical trials.gov were cross-checked.

9.2.5 Data extraction

The first reviewer (IJO) extracted data on study ID, year of journal publication, study design and setting, participant characteristics, study duration, body weight, adverse events, serious adverse events, overall discontinuation, discontinuation due to adverse events, description of placebo and lifestyle adjustments. The medical dictionary for regulatory activities (MedDRA) organ system classification was used to compute the number of adverse events, because it distinguishes an adverse event by anatomy, physiology, aetiology, or function [11]. The information from journal publications, regulatory documents and clinical trials.gov was used to report the number of adverse events.

9.2.6 Data synthesis

Randomized participants who received at least one dose of medication were included in the meta-analysis. Where two or more intervention arms were present, the arms were combined to create single pair-wise comparisons [12]. The number of adverse events per intervention group was used primarily unit of analysis. However, where studies did not

report the number of adverse events, we used the number of adverse events per patient as analysis unit. The Mantel-Haenszel method with random-effect model of the RevMan 5.3 software [13] was used for meta-analysis. Risk ratios (RR) with their 95% CI were used to compare the rates of adverse events and discontinuation rates between centrally-acting anti-obesity products and controls. Body weight was reported as a dichotomous outcome because updated EMA and FDA guidance for development of weight loss products also recommends dichotomous outcomes for assessing efficacy [14,15]. The first reviewer (IJO) entered data for meta-analysis onto RevMan software, and these were independently verified by a second review author (DJC). Using the control group event rates, the first reviewer (IJO) computed the number needed to treat to benefit (NNTB), the number needed to treat to harm (NNTH) and the number need to treat to discontinue treatment (NNTD) with their respective 95% CI.

The intention-to-treat (ITT) population (all randomized) was primarily used to report changes in body weight in both intervention and comparator groups; for harms assessment. The data on modified intention-to-treat (mITT) population were excluded because such analyses are more likely to be associated with post-randomization exclusions [16,17].

9.2.7 Subgroup analyses and assessment of heterogeneity

Sensitivity and subgroup analyses based on regulatory approval status were used to test the robustness of overall analyses. I-square (I^2) statistic were used to assess heterogeneity; values of 25%, 50%, and 75% represented mild, moderate and substantial heterogeneity respectively. Because only evidence from pivotal trials using trial IDs from regulatory documents was evaluated, funnel plots were not used to test for publication bias.

9.2.8 Assessing the quality of the body of evidence

The quality of the evidence for each outcome was rated using the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) [18] criterion which examines the following domains:

- Study design
- Risk of bias
- Inconsistency
- Indirectness
- Imprecision

Using the GRADEpro software (version 3.6) [19], the overall quality of the body of the evidence was rated from high to very low as follows:

- High - Further research is very unlikely to change our confidence in the estimate of effect
- Moderate - Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
- Low - Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
- Very low - We are very uncertain about the estimate

The publication bias domain was not used in rating the quality of the evidence. The quality of the evidence was not rated with GRADEpro when meta-analysis included pooled FDA data for individual products. The quality of the evidence was upgraded when the overall effect estimate was dramatic, i.e., large ($RR > 2$) or very large ($RR > 5$). Summary of findings (SOF) tables were used to present these results.

9.3 RESULTS

Eight anti-obesity medicinal products approved between 1995 and 2014 were identified; three of these (dexfenfluramine, rimonabant, and sibutramine) are amongst the list of 23 centrally-acting products that were withdrawn because of adverse reactions in chapter 7, while the remaining five are still on the market (i.e. they have never been withdrawn). One product, orlistat, was excluded because they did not exert their anti-obesity effects through centrally-acting mechanisms, and a second, liraglutide, excluded because it exerts its effects through both central and peripheral pathways. One centrally-acting product, dexfenfluramine, was excluded because the first reviewer (IJO) could not access regulatory documents relating to its approval. Therefore, five products, lorcaserin, naltrexone-bupropion (N-B), phentermine-topiramate (P-T), rimonabant and sibutramine were included in the review. The first reviewer (IJO) considered inclusion of a phase II N-B trial (NB-201) because the sponsors presented it as a pivotal trial; however, that trial was excluded because there was no related journal publication, the trial results were not posted onto the clinical trial database, and the tablet formulation and doses used were not identical to the ones used in corresponding pivotal Phase III trials. In total, the five included products comprised of 16 pivotal trials (3 trials for lorcaserin [20,21,22]; 4 for N-B [23,24,25,26]; 3 for P-T [27,28,29]; 4 for rimonabant [30,31,32,33]; and 2 for sibutramine [34,35]) with a total of 24,555 participants. All five products were approved by the FDA, while three were approved by the EMA (Table 9.1). Two of the included products, rimonabant and sibutramine, have been withdrawn from the market after regulatory approval because of serious adverse reactions.

9.3.1 Mechanisms of action

The mechanisms of action of the products were: 1) selective 5-HT_{2c} receptor agonist activity (lorcaserin) [36]; 2) stimulation hypothalamic neurons plus acetylcholine receptor antagonist activity (N-B) [37]; 3) stimulation of hypothalamic neurons in the hypothalamus with blockade of auto-inhibitory feedback (P-T) [38]; 4) inverse agonist activity at the cannabinoid receptor (CB1) (rimonabant) [39]; and 5) activation of hypothalamic neurons and inhibition of orexigenic peptides-associated neurons (sibutramine) [40] (Table 9.2).

9.3.2 Approval indications

All five products were approved as add-on to reduced caloric intake in conjunction with exercise for chronic weight management, either in adults with body mass index (BMI) at ≥ 30 kg/m², or with BMI ≥ 27 kg/m² having at least one weight-related comorbidity such as hypertension, type 2 diabetes, or dyslipidemia (Table 9.2).

9.3.3 Study designs and participants' characteristics

All the included studies were multi-centred, placebo-controlled, and conducted in the USA (Table 9.1). The duration of intervention ranged from 28 to 104 weeks. Participants' ages ranged from 18 to 70 years, with BMI between 27 and 45 kg/m². Thirteen trials (81.3%) included subjects with comorbidities (largely hypertension and dyslipidemia). Only four studies (25%) included subjects with diabetes (one each for lorcaserin [21], N-B [25], P-T [29], and rimonabant [32]). All the included studies incorporated lifestyle adjustments into their trial regimen (Table 9.1); these included reduced caloric intake, physical activity, counselling and behavioural modification.

Table 9.1: Key characteristics of pivotal clinical trials of recently approved centrally-acting anti-obesity medicinal products

Study ID Country	Study duration	Age (years)	BMI (kg/m ²)	Comorbidities	Intervention	Placebo	Lifestyle adjustments	Drop- out rates**
Lorcaserin pivotal trials								
Fidler 2011* USA [20]	52 weeks	18-65	27-45	±HT ^a , CVD, IGT, sleep apnea, dyslipidemia	Lorcaserin 10 mg BID (n = 1602) Lorcaserin 10 mg QID (n = 801)	Not described (n = 1601)	Patients were instructed to reduce daily caloric intake to 600 kcal below individual estimated energy requirements, using WHO equations and a fixed activity factor of 1.3 (1.4 for any subject who reported 1h of aerobic exercise per day), and were encouraged to exercise moderately for 30 min per day.	44.6%
O'Neil 2012* USA [21]	52 weeks	18-65	27-45‡	T2DM	Lorcaserin 10 mg BID (n = 256) Lorcaserin 10 mg QID (n = 95)	Not described (n = 252)	Exercise moderately for 30 min each day, reduce daily caloric intake by 600 kcal below estimated daily energy requirements.	33.7%
Smith 2010* USA [22]	104 weeks	18-65	27-45	±HT ^a , CVD, IGT, sleep apnea, dyslipidemia	Lorcaserin 10 mg BID (n = 1593)	Not described (n = 1584)	Standardized nutritional and exercise counselling during individual sessions (lasting 15 minutes to 1 hour, depending on the study week). instructed to exercise moderately for 30 minutes daily and to reduce the daily calorie intake to 600 kcal below the individual estimate for daily energy requirements based on WHO criteria and a fixed activity factor of 1.3 (1.4 for any subject who reported 1h of aerobic exercise per day), and were encouraged to exercise moderately for 30 min per day.	49.8%
Naltrexone-bupropion pivotal trials								
Apovian 2013 USA [23]	28 weeks	18-65	27-45	Controlled HT and/or dyslipidemia	NLX SR 32 mg/BUP SR 360 mg/day (n = 1000)	Not described (n = 493)	Ancillary therapy consisting of diet instruction, advice on behaviour modification, and exercise counselling.	46%
Greenway 2010 USA [24]	56 weeks	18-65	27-45	Controlled HT and/or dyslipidemia	NLX SR 16 mg/BUP SR 360 mg/day (n = 578) NLX SR 32 mg/BUP SR 360 mg/day (n = 583)	Not described (n = 581)	Diet instruction, advice on behaviour modification, and exercise counselling	50%
Hollander 2013 USA [25]	56 weeks	18-70	27-45‡	T2DM, controlled HT and/or dyslipidemia	NLX SR 32 mg/BUP SR 360 mg/day (n = 335)	Not described (n = 170)	Hypocaloric diet (500 kcal deficit/day, based on the WHO algorithm for calculating resting metabolic rate), dietary counselling, advice on behavioural modification, including written instructions, to increase physical activity (to walking for at least 30 min most days of the week)	40.8%
Wadden 2011* USA [26]	56 weeks	18-65	27-45	±HT ^a , CVD, IGT, sleep apnea, dyslipidemia	NLX SR 32 mg/BUP SR 360 mg/day (n = 591)	Not described (n = 202)	Daily caloric intake reduced according to body weight. Keeping detailed daily records of their food intake. Gradual increase up to 180 min/week of moderate physical activity (typically brisk walking) for the first 6 months, then up to 360 min/week for months 7-12.	42%
Phentermine-topiramate pivotal trials								
Allison	56	≤70	35	Controlled HT	3.75 mg	Not	500-kcal daily reduction in dietary	46.3%

2011* USA [27]	weeks			and/or dyslipidemia	PHEN/23 mg TPM (n = 241) 15 mg PHEN /92 mg TPM (n = 512)	described (n = 214)	intake, increased water consumption, and increased physical activity.	
Aronne 2013 USA [28]	28 weeks	≤70	30-45	None	15 mg PHEN/92 mg TPM (n = 108) 7.5 mg PHEN /46 mg TPM (n = 107)	Not described (n = 109)	LEARN® Manual (Lifestyle, Exercise, Attitude, Relationships, Nutrition) and included counselling to reduce energy intake by 500 kcal/day, to monitor calorie intake with a food diary, and to increase physical activity as tolerated	35.2%
Gadde 2011 USA [29]	56 weeks	≤70	27†	HT, T2DM, dyslipidemia	15 mg PHEN/92 mg TPM (n = 995) 7.5 mg PHEN /46 mg TPM (n = 498)	Not described (n = 994)	Standardised counselling for diet and lifestyle modification	37.9%
Rimonabant pivotal trials								
Despres 2005 8 countries [30]	52 weeks	18-70	27-40	Mild HT	Rimonabant 5 mg/day (n = 345) Rimonabant 20 mg/day (n = 346)	Not described (n = 342)	Hypocaloric diet (a deficit of 600 kcal per day in relation to the calculated daily intake to maintain body weight)	40%
Pi- Sunyer 2006 USA & Canada [31]	52 weeks	≥18	≥27	HT and/or dyslipidemia controlled or uncontrolled	Rimonabant 5 mg/d (n = 1214) Rimonabant 20 mg/d (n = 1219)	Not described (n = 617)	Hypocaloric diet (approximately 600 kcal/d deficit)	49%
Scheen 2006 11 countries [32]	52 weeks	18-70	27-40	T2DM	5 mg/day rimonabant (n = 358) 20 mg/day rimonabant (n = 339)	Not described (n = 348)	All patients were put on a mild hypocaloric diet and were advised on increased physical activity during the run-in period and until the end of the study	33.8%
Van Gaal 2005 Europe & USA [33]	52 weeks	≥18	≥27	±HT ^a , CVD, IGT, sleep apnea, dyslipidemia	5 mg/day rimonabant (n = 599) 20 mg/day rimonabant (n = 603)	Not described (n = 305)	600 kcal were subtracted by a dietician to calculate a recommended daily energy intake for each patient	39%
Sibutramine pivotal trials								
Bray 1999 USA [34]	24 weeks	18-65	30-40	None	Sibutramine 1 mg/day (n = 149) Sibutramine 5 mg/day (n = 151) Sibutramine 10 mg/day (n = 150) Sibutramine 15 mg/day (n = 152) Sibutramine 20 mg/day (n = 146) Sibutramine 30 mg/day (n	Not described (n = 148)	Standardized care was provided to all patients that included one counselling visit by a registered dietitian during run-in, an exercise program of walking 20 to 30 minutes/day to utilize 3 to 5 kcal/minute, and instructions in behavioral change techniques. Women and men received instructions for 1200 kcal/day or 1500 kcal/day diets, respectively.	34.8%

					= 151)			
Smith 2001* USA [35]	52 weeks	18-65	27-40	±HT ^a	Sibutramine 10 mg/day (n = 161) Sibutramine 15 mg/day (n = 160)	Not described (n = 163)	Added certain food to diet: 12 oz of vegetables and fruit, 6 oz of bread, cereal, potatoes or rice, 10 oz of skimmed milk; substitute low-calorie foods for sugary and fried foods	53.4%

ABBREVIATIONS: HT: Hypertension; CVD: Cardiovascular disease; IGT: Impaired glucose tolerance; ITT: Intention-to-treat; Mitt: Modified intention-to-treat; LOCF: Last observation carried forward; T2DM: Type 2 diabetes mellitus; NLX/BP: Naltrexone/bupropion; PHEN/TPM: Phentermine/topiramate

*Study did not include all randomized subjects in ITT population; prespecified ITT-LOCF

**Based on total number of participants who received at least one dose of medication

†Included both diabetic and non-diabetic subjects

‡Included only diabetic subjects

^acontrolled hypertension

The intervention and placebo groups refer to randomized subjects who received at least one dose of intervention

Apovian 2013: mITT-LOCF which excluded 17.5% of randomized subjects who received at least one dose of medication; at 28 and 44 weeks, participants in placebo who achieved <5% weight loss were re-randomized to N-B

Aronne 2013: mITT-LOCF which excluded 35% of randomized subjects who received at least one dose of medication

Table 9.2: Approval details of centrally-acting anti-obesity products marketed since 1995

Generic name	Brand name	Approval authority	Approval date	Mechanism of action	Indications	Population group approved for*
Lorcaserin	Belviq	FDA	27/06/2012	Selective 5-HT _{2c} receptor agonist [36]	As add-on to a reduced-calorie diet and exercise, for chronic weight management	Adults with a BMI ≥ 30 kg/m ² , or adults with a BMI of ≥ 27 kg/m ² and who have at least one weight-related condition such as hypertension, type 2 diabetes, or dyslipidemia
Naltrexone plus bupropion	Contrave; Mysimba	EMA; FDA	10/09/2014; 19/12/2014	Stimulation of POMC neurons in the hypothalamus plus nicotinic acetylcholine receptor antagonist activity [37]	Add-on treatment option for chronic weight management in addition to a reduced-calorie diet and physical activity	Adults with a BMI ≥ 30 kg/m ² , or adults with a BMI of ≥ 27 kg/m ² and who have at least one weight-related condition such as hypertension, type 2 diabetes, or dyslipidemia
Phentermine plus topiramate	Qsymia; Qnexa	FDA	17/07/2012	Stimulation of POMC neurons in the hypothalamus with blockade of auto-inhibitory feedback [38]	As add-on to a reduced-calorie diet and exercise, for chronic weight management	Adults with a BMI ≥ 30 kg/m ² , or adults with a BMI of ≥ 27 kg/m ² and who have at least one weight-related condition such as hypertension, type 2 diabetes, or dyslipidemia
Rimonabant*	Acomplia; Zimulti	EMA	19/06/2006	Inverse agonist and antagonist activity at the cannabinoid 1 receptor† [39]	As add-on to a reduced-calorie diet and exercise, for chronic weight management	Adults with a BMI ≥ 30 kg/m ² , or adults with a BMI of ≥ 27 kg/m ² and who have at least one weight-related condition such as hypertension, type 2 diabetes, or dyslipidemia
Sibutramine*	Meridia; Reductil	EMA; FDA	11/1997; 1999	Activation of POMC/CART neurons and inhibition of NPY/AgRP neurons [40]	As add-on to a reduced-calorie diet and exercise, for chronic weight management	Adults with a BMI ≥ 30 kg/m ² , or adults with a BMI of ≥ 27 kg/m ² and who have at least one weight-related condition such as hypertension, type 2 diabetes, or dyslipidemia

ABBREVIATIONS: EMA: European Medicines Agency; FDA: United States Food and Drug Administration; POMC:

Proopiomelanocortin; CART: Cocaine amphetamine regulating transcript; NPY: neuropeptide Y; AgRP: Agouti related peptide

*Information as reported in documents from regulatory authorities

**Withdrawn after initial regulatory approval

†Also found in the liver and intestines

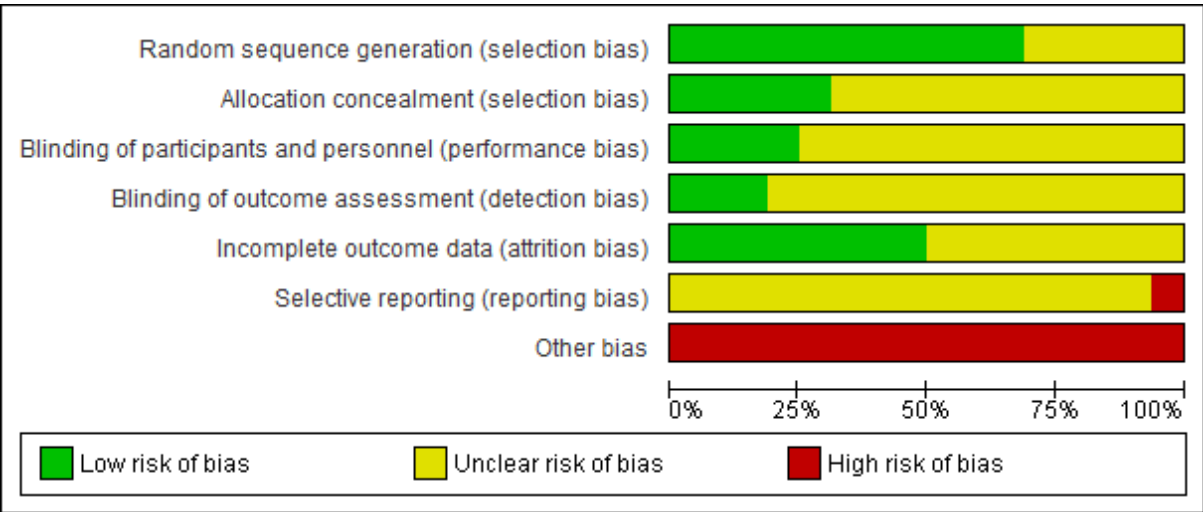
9.3.4 Risk of bias in journal publications

There were some variations in the quality of reporting across the included trials (Figure

9.2). Eleven studies adequately reported the methods used for random sequence generation,

and five reported adequate allocation concealment techniques. Four studies adequately reported the methods used to blind study personnel and participants, and three adequately reported the blinding of outcome assessments. Nine studies adequately reported drop-out details of participants, and there was unclear risk of selective reporting bias across all studies. All the included trials had high risk of other bias [see appendix 9 for reasons used to justify the ratings for each domain]. None of the included studies described the contents of the placebo used in their trial. All studies were funded by pharmaceutical companies, and most of the authors of journal publications of the trials had financial ties with the drug sponsor. The overall risk of bias across the trials was moderate.

Figure 9.2: Risk of bias graph for pivotal trials of centrally-acting anti-obesity medicinal products



9.3.5 Consistency in reporting across sources of information

The results of pivotal trials for three products, lorcaserin, N-B, and P-T were posted on clinicaltrials.gov. Though the protocol for trials of rimonabant and sibutramine were

registered with the clinical trials registry, their trial results were not posted; of note however, mandatory requirement for posting of clinical trials results came into force in 2007 – after the conduct of the trials for the two products.

The extent of reporting on the occurrence of adverse events experienced by trial participants was not always consistent across journal publications and regulatory documents for individual products [Appendix 10]; for instance, while regulatory documents for pivotal trials of lorcaserin reported adverse events when they occurred with a frequency of >1 , journal publications only reported adverse events data when the frequency was either $\geq 3\%$ or $\geq 5\%$ (i.e. rare and very adverse events were scarcely reported); similar findings were observed across the other four products. For the series of pivotal trials for each approved product, there were inconsistencies in the reporting of the frequency of adverse events across journal publications for four products [Appendix 10]; for the one product, rimonabant, where there were no discrepancies, the authors of one of the journal publications [31] did not specify whether they reported adverse event data based on frequency.

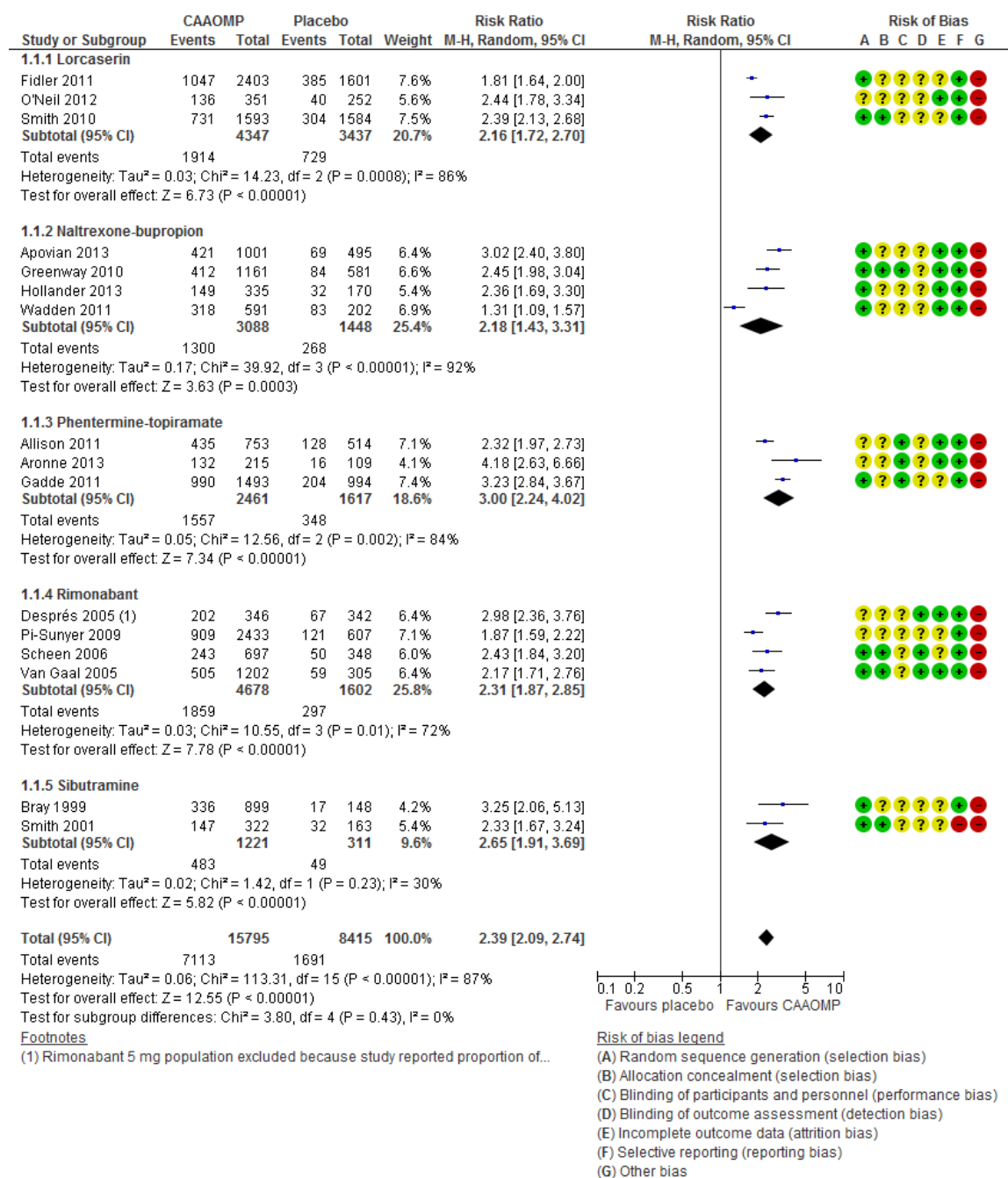
9.3.6 Primary outcomes

9.3.6.1 Effect of centrally-acting products on body weight

There was a significant increase in the rates of participants who achieved at least 5% reduction in body weight from baseline with the centrally-acting obesity products compared with placebo: RR 2.39 (95% CI: 2.09 to 2.74), $P < 0.00001$, $I^2=87\%$ (Figure 9.3), $NNT_B = 4$ (3 to 5). The quality of the evidence was low (SoF Table 9.1). Similar effects were seen when only the per-protocol population were analysed; however, the

quality of the evidence was very poor. Sensitivity analyses based on approval status revealed similar results without a reduction in heterogeneity (Table 9.3).

Figure 9.3: Effect of CAAOMP on proportion of subjects with weight loss of at least 5% from baseline



Summary of Findings Table 9.1: GRADE summary of effects of centrally-acting anti-obesity products on body weight reduction in overweight and obesity

Patient or population: Overweight and/or obese subjects with or without comorbidities Settings: Private or institutional practices; research centres; academic and primary care centres Intervention: Centrally-acting anti-obesity medicinal products						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	NNT _B (95% CI)
	Assumed risk	Corresponding risk				
	Control	Effect of centrally-acting anti-obesity products on body weight				
ITT Proportion of participants who achieved at least 5% weight loss	Study population		RR 2.39 (2.09 to 2.74)	24210 (16 studies)	⊕⊕⊕⊖ low ¹	4 (3 to 5)
	198 per 1000	485 per 1000 (421 to 558)				
	Moderate					
	193 per 1000	473 per 1000 (411 to 544)				
Per-protocol proportion of participants who achieved at least 5% weight loss	Study population		RR 2.28 (1.87 to 2.79)	8659 (12 studies)	⊕⊕⊕⊖ very low ²	3 (2 to 4)
	276 per 1000	647 per 1000 (520 to 807)				
	Moderate					
	240 per 1000	562 per 1000 (451 to 701)				
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; NNT _B : Number needed to treat to benefit; RR: Risk ratio.						
GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.						
¹ Moderate risk bias; substantial heterogeneity; RR >2 ² Moderate risk of bias; substantial heterogeneity; wide confidence interval; RR >2						

Table 9.3: Effect of centrally-acting anti-obesity products on body weight and rates of adverse events*

Outcome	Overall analysis	Comparison of currently approved and withdrawn products		Test for subgroup differences
		Approved products	Withdrawn products	
Body weight reduction of at least 5% from baseline	ITT (n = 24,210): RR 2.39 (2.09 to 2.74), P < 0.00001, I ² =87%	RR 2.39 (1.97 to 2.89), P < 0.0001, I ² =92% (3 products, n = 16,398)	RR 2.39 (2.01 to 2.84), P < 0.0001, I ² =62% (2 products, n = 8,157)	P = 0.99, I ² =0%
	PP (n = 9579): RR 2.28 (1.87 to 2.79), P < 0.00001, I ² =91%	RR 2.34 (1.88 to 2.92), P < 0.00001, I ² =92% (3 products, n = 8,432)	RR 1.83 (1.46 to 2.31), P < 0.00001, (1 product: 1 RCT, n = 920)	P = 0.13, I ² =55.8%
Overall adverse events	(n = 23,023): RR 1.12 (1.07 to 1.17), P < 0.00001, I ² =90%	RR 1.17 (1.10 to 1.24), P < 0.00001, I ² =92% (3 products, n = 16,398)	RR 1.03 (1.00 to 1.06), P < 0.00001, I ² =0% (1 product, n = 6625)	P = 0.0002, I ² =92.9%
Serious adverse events	(n = 23,023): RR 1.18, (1.00 to 1.39), P = 0.05, I ² =15%	RR 1.10 (0.90 to 1.35), P = 0.33, I ² =16% (3 products, n = 16,398)	RR 1.34 (1.02 to 1.77), P = 0.04, I ² =10% (1 product, n = 6625)	P = 0.26, I ² =20.7%
Deaths	(n = 13,825): RR 0.70, (0.20 to 2.42), P = 0.62, I ² =0%	RR 0.42 (0.07 to 2.66), P = 0.36, I ² =0% (3 products, n = 8,233)	RR 1.07(0.19 to 5.94), P = 0.94, I ² =5% (1 product, n = 5592)	P = 0.47, I ² =0%
Nervous system: Headache	(n = 23,023): RR 1.34 (1.12 to 1.60), P = 0.002, I ² =79%	RR 1.53 (1.31 to 1.80), P < 0.00001, I ² =68% (3 products, n = 16,398)	RR 0.86 (0.71 to 1.77), P = 0.14, I ² =0% (1 product, n = 6625)	P < 0.00001, I ² =95%
Nervous system: Dizziness	(n = 24,555): RR 2.03 (1.72 to 2.41), P < 0.00001, I ² =41%	RR 2.18 (1.78 to 2.68), P < 0.00001, I ² =49% (3 products, n = 16,398)	RR 1.65 (1.28 to 2.13), P = 0.0001, I ² =0% (2 products, n = 8157)	P = 0.10, I ² =63.9%
Psychiatric adverse events	(n = 17,905): RR 1.76 (1.49 to 2.06), P < 0.00001, I ² =0%	RR 1.75 (1.49 to 2.06), P < 0.00001, I ² =0% (3 products, n = 16,398)	RR 2.79 (0.36 to 21.54), P = 0.32 (1 product: 1 RCT, n = 1507)	P = 0.66, I ² =0%
Psychiatric: Anxiety	(n = 10,656): RR 1.32, 95% CI 1.03 to 1.69, P = 0.03, I ² =0%	RR 1.11 (0.77 to 1.60), P = 0.57, I ² =0% (2 products, n = 4031)	RR 1.53 (1.07 to 2.20), P = 0.02, I ² =9% (1 product, n = 6625)	P = 0.22, I ² =33%
Psychiatric: Insomnia	(n = 14,219): RR 1.59 (1.38 to 1.84), P < 0.00001, I ² =0%	RR 1.60 (1.35 to 1.90), P < 0.00001, I ² =0% (2 products, n = 8614)	RR 1.34 (0.71 to 2.54), P = 0.37, I ² =57% (1 product, n = 4073)	P = 0.59, I ² =0%
Psychiatric: Depression	(n = 19,966): RR 1.25 (0.89 to 1.75), P = 0.20, I ² =52%	RR 1.12 (0.77 to 1.64), P = 0.54, I ² =52% (3 products (n = 15893)	RR 1.93 (0.93 to 4.01), P = 0.08, I ² =24% (1 product, n = 4073)	P = 0.20, I ² =40.2%
Cardiac	(n = 17,581): RR 1.04 (0.59 to 1.84), P = 0.89, I ² =0%	RR 1.02 (0.55 to 1.88), P = 0.96, I ² =6% (3 products, n = 16,074)	RR 2.29 (0.12 to 42.41), P = 0.58 (1 product: 1 RCT, n = 1507)	P = 0.59, I ² =0%
Vascular: Hypertension	(n = 9,086): RR 1.78 (1.10 to 2.88), P =	RR 1.86 (1.10 to 3.14), P = 0.02, I ² =0% (3	RR 1.43 (0.44 to 4.65), P = 0.56 (1 product: 1	P = 0.69, I ² =0%

	0.02, $I^2=0\%$	products, n = 8039)	RCT, n = 1037)	
General disorders	(n = 17,905): RR 1.20 (0.86 to 1.68), P = 0.28, $I^2=69\%$	RR 1.20 (0.86 to 1.69), P = 0.28, $I^2=72\%$ (3 products, n = 16,398)	RR 0.76 (0.03 to 18.69), P = 0.87 (1 product: 1 RCT, n = 1507)	P = 0.78, $I^2=0\%$
Musculoskeletal	(n = 16,163): RR 1.01 (0.92 to 1.12), P = 0.79, $I^2=0\%$	RR 1.01 (0.92 to 1.12), P = 0.78, $I^2=0\%$ (3 products, n = 14,656)	RR 0.97 (0.40 to 2.37), P = 0.95 (1 product: 1 RCT, n = 1507)	P = 0.93, $I^2=0\%$
Gastrointestinal	(n = 17,905): RR 2.04 (1.59 to 2.62), P < 0.00001, $I^2=95\%$	RR 2.12 (1.65 to 2.73), P < 0.00001, $I^2=95\%$ (3 products, n = 16,398)	RR 0.42 (0.10 to 1.76), P = 0.24 (1 product: 1 RCT, n = 1507)	P = 0.03, $I^2=79\%$
Gastrointestinal: Nausea	(n = 24,069): RR 2.18 (1.59 to 2.98), P < 0.00001, $I^2=89\%$	RR 2.36 (1.55 to 3.60), P < 0.0001, $I^2=92\%$ (3 products, n = 16,398)	RR 1.80 (1.38 to 2.34), P < 0.0001, $I^2=62\%$ (2 products, n = 7671)	P = 0.28, $I^2=13.6\%$
Gastrointestinal: Diarrhoea	(n = 23,023): RR 1.18 (1.06 to 1.32), P = 0.003, $I^2=0\%$	RR 1.15 (1.02 to 1.29), P = 0.01, $I^2=0\%$ (3 products, n = 16,398)	RR 1.39 (1.03 to 1.88), P = 0.03, $I^2=25\%$ (1 product, n = 6625)	P = 0.24, $I^2=26.6\%$
Gastrointestinal: Dry mouth	(n = 16,832): RR 3.39 (2.40 to 4.80), P < 0.00001, $I^2=72\%$	RR 3.35 (2.29 to 4.91), P < 0.0001, $I^2=75\%$ (3 products, n = 15,795)	RR 3.87 (1.95 to 7.69), P = 0.00001 (1 product: 1 RCT, n = 1037)	P = 0.72, $I^2=0\%$

ITT: Intention-to-treat; PP: Per-protocol; RR: Risk ratio

Summary of Findings Table 9.2: GRADE summary of effects of centrally-acting anti-obesity products on rates of adverse events in overweight and obesity

Patient or population: Overweight and/or obese subjects with or without comorbidities Settings: Private or institutional practices; research centres; academic and primary care centres Intervention: Centrally-acting anti-obesity medicinal products						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	NNT _H (95% CI)
	Assumed risk	Corresponding risk				
	Control	Adverse events of centrally-acting anti-obesity medications				
Overall adverse events	Study population		RR 1.12 (1.07 to 1.17)	23023 (14 studies)	⊕⊕⊕⊕ very low ¹	11 (8 to 19)
	734 per 1000	844 per 1000 (800 to 896)				
	Moderate					
	779 per 1000	896 per 1000 (849 to 950)				
Nervous	Study population		RR 2.09 (1.85 to 2.37)	16398 (10 studies)	⊕⊕⊕⊖ low ²	6 (5 to 7)
	163 per 1000	353 per 1000 (309 to 403)				
	Moderate					
	165 per 1000	356 per 1000 (312 to 408)				
Headache - Nervous	Study population		RR 1.34 (1.12 to 1.60)	23023 (14 studies)	⊕⊕⊕⊖ very low ³	26 (15 to 67)
	105 per 1000	144 per 1000 (119 to 173)				
	Moderate					
	101 per 1000	138 per 1000 (115 to 167)				
Dizziness - Nervous	Study population		RR 2.03 (1.72 to 2.41)	24555 (16 studies)	⊕⊕⊕⊖ moderate ⁴	24 (18 to 34)
	40 per 1000	83 per 1000 (70 to 100)				
	Moderate					
	43 per 1000	89 per 1000 (75 to 107)				
Tremors - Nervous	Study population		RR 4.30 (2.48 to 13.24)	1298 (3 studies)	⊕⊕⊕⊖ moderate ⁵	13 (5 to 42)
	13 per 1000	74 per 1000 (32 to 170)				
	Moderate					
	13 per 1000	74 per 1000 (32 to 172)				
Para/hypoaesthesia - Nervous	Study population		RR 7.50 (5.38 to 10.47)	5610 (5 studies)	⊕⊕⊕⊕ high ⁶	8 (6 to 12)
	19 per 1000	140 per 1000 (100 to 195)				
	Moderate					
	20 per 1000	150 per 1000 (108 to 209)				
Psychiatric	Study population		RR 1.76 (1.49 to 2.06)	17905 (11 studies)	⊕⊕⊕⊖ moderate ⁷	50 (36 to 77)
	27 per 1000	50 per 1000 (41 to 61)				
	Moderate					
	33 per 1000	61 per 1000 (50 to 74)				
Anxiety - Psychiatric	Study population		RR 1.29 (1.03 to 1.62)	12188 (8 studies)	⊕⊕⊕⊖ moderate ⁸	66 (36 to 171)
	30 per 1000	39 per 1000 (31 to 49)				

	Moderate				
	23 per 1000	30 per 1000 (24 to 37)			
Insomnia - Psychiatric	Study population		RR 1.59	14219	⊕⊕⊕⊖
	50 per 1000	82 per 1000 (69 to 98)	(1.38 to 1.84)	(11 studies)	moderate ⁹
	Moderate				33 (23 to 52)
Depression - Psychiatric	Study population		RR 1.25	19966	⊕⊕⊕⊖
	19 per 1000	23 per 1000 (17 to 32)	(0.89 to 1.75)	(8 studies)	very low ¹⁰
	Moderate				-208 (-60 to 473)
Cardiac	Study population		RR 1.04	17581	⊕⊕⊕⊖
	4 per 1000	4 per 1000 (2 to 7)	(0.59 to 1.84)	(10 studies)	low ¹¹
	Moderate				8813 (-419 to 860)
Vascular	Study population		RR 2.55	10608	⊕⊕⊕⊖
	5 per 1000	15 per 1000 (7 to 31)	(1.23 to 5.29)	(6 studies)	moderate ¹²
	Moderate				126 (46 to 851)
Hypertension - vascular	Study population		RR 1.78	9086	⊕⊕⊕⊖
	6 per 1000	12 per 1000 (7 to 19)	(1.10 to 2.88)	(6 studies)	low ¹³
	Moderate				224 (93 to 1744)
General disorders	Study population		RR 1.20	17905	⊕⊕⊕⊖
	37 per 1000	48 per 1000 (35 to 64)	(0.86 to 1.68)	(11 studies)	low ¹⁴
	Moderate				138 (-41 to 466)
Musculoskeletal	Study population		RR 1.01	16163	⊕⊕⊕⊖
	70 per 1000	72 per 1000 (65 to 80)	(0.92 to 1.12)	(10 studies)	moderate ¹⁵
	Moderate				1089 (-91 to 136)
Gastrointestinal	Study population		RR 2.04	17905	⊕⊕⊕⊖
	197 per 1000	418 per 1000 (317 to 548)	(1.59 to 2.62)	(11 studies)	very low ¹⁶
	Moderate				5 (3 to 9)
Nausea - GI	Study population		RR 2.18	24069	⊕⊕⊕⊖
	57 per 1000	127 per 1000 (90 to 177)	(1.59 to 2.98)	(15 studies)	very low ¹⁷
	Moderate				15 (9 to 30)
Vomiting - GI	Study population		RR 3.74	4536	⊕⊕⊕⊖
	54 per 1000	121 per 1000 (86 to 169)			
	Moderate				12

	25 per 1000	60 per 1000 (38 to 97)	(2.36 to 5.94) (4 studies)	low ¹⁸	(7 to 24)
	Moderate				
	24 per 1000	58 per 1000 (36 to 92)			
Diarrhoea - GI	Study population		RR 1.18 23023 (1.06 to 1.32) (14 studies)	⊕⊕⊕⊖ moderate ¹⁹	96 (54 to 288)
	57 per 1000	70 per 1000 (62 to 78)			
	Moderate				
	53 per 1000	65 per 1000 (57 to 73)			
Constipation - GI	Study population		RR 1.96 17445 (1.61 to 2.39) (11 studies)	⊕⊕⊕⊖ low ²⁰	19 (13 to 29)
	56 per 1000	112 per 1000 (90 to 139)			
	Moderate				
	49 per 1000	98 per 1000 (79 to 123)			
Dry mouth - GI	Study population		RR 3.39 16832 (2.40 to 4.80) (10 studies)	⊕⊕⊕⊖ low ²¹	17 (11 to 28)
	26 per 1000	92 per 1000 (69 to 124)			
	Moderate				
	24 per 1000	84 per 1000 (63 to 113)			
Infections and infestations	Study population		RR 1.00 16398 (0.90 to 1.12) (10 studies)	⊕⊖⊖⊖ very low ²²	24 (-20 to 24)
	414 per 1000	435 per 1000 (397 to 476)			
	Moderate				
	352 per 1000	370 per 1000 (338 to 405)			
Overall serious adverse events	Study population		RR 1.18 23023 (1.00 to 1.39) (14 studies)	⊕⊕⊕⊖ moderate ²³	78 (77 to 79)
	33 per 1000	39 per 1000 (34 to 46)			
	Moderate				
	32 per 1000	38 per 1000 (33 to 44)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **NNT_H:** Number needed to treat to harm; **RR:** Risk ratio.

GI: gastrointestinal

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Moderate risk of bias; substantial heterogeneity

² Moderate risk of bias; substantial heterogeneity; RR >2

³ Moderate risk of bias; substantial heterogeneity; RR >2

⁴ Moderate risk bias; moderate heterogeneity; RR >2

⁵ Moderate risk of bias; low heterogeneity; RR >2

⁶ Moderate risk bias; RR >5

⁷ Moderate risk of bias

⁸ Moderate risk of bias

⁹ Moderate risk of bias

¹⁰ Moderate risk of bias; moderate heterogeneity; wide confidence interval

¹¹ Moderate risk of bias; wide confidence interval

¹² Moderate risk of bias; wide confidence interval; RR >2

¹³ Moderate risk of bias; wide confidence interval

¹⁴ Moderate risk of bias; moderate heterogeneity

¹⁵ Moderate risk of bias

¹⁶ Moderate risk of bias; substantial heterogeneity; wide confidence interval; RR >2

¹⁷ Moderate risk of bias; wide confidence interval; substantial heterogeneity; RR >2

¹⁸ Moderate risk of bias; wide confidence interval; moderate to high heterogeneity; RR >2
¹⁹ Moderate risk of bias
²⁰ Moderate risk of bias; moderate to high heterogeneity
²¹ Moderate risk of bias; wide confidence interval; moderate to high heterogeneity; RR >2
²² Moderate risk of bias; substantial heterogeneity
²³ Moderate risk of bias

Table 9.4: Discontinuations due to adverse events in pivotal clinical trials of centrally-acting anti-obesity medicinal products

Outcome	Overall analysis	Sensitivity analysis		Test for subgroup differences
		<i>Approved products</i>	<i>Withdrawn products</i>	
Overall adverse events	(n = 24,555): RR 1.52 (1.33 to 1.74), P < 0.00001, I ² =56%	RR 1.61 (1.36 to 1.92), P < 0.00001; I ² =62% (3 products, n = 16,398)	RR 1.36 (1.10 to 1.69), P = 0.004; I ² =37% (2 products (n = 8,157))	P = 0.23, I ² =30.6%
Nervous system	(n = 22,699): RR 1.91 (1.52 to 2.40), P < 0.00001, I ² =0%	RR 2.05 (1.43 to 2.94), P = 0.0001; I ² =29% (3 products, n = 16,074)	RR 1.83 (0.99 to 3.38), I ² =0%, P = 0.05 (1 product, n = 6625)	P = 0.75, I ² =0%
Headache - Nervous	(n = 22,699): RR 1.56 (0.97 to 2.51), P = 0.06, I ² =21%	RR 1.76 (1.02 to 3.02), P = 0.04; I ² =29% (3 products, n = 16,074)	RR 0.96 (0.32 to 2.87), I ² =9%, P = 0.94 (1 product, n = 6625)	P = 0.33, I ² =0%
Dizziness - Nervous	(n = 17783): RR 3.68 (2.09 to 6.49), P < 0.00001, I ² =0%	RR 3.70 (2.03 to 6.75), P < 0.0001; I ² =0% (3 products, n = 14,198)	RR 3.53 (0.65 to 19.10), P = 0.14, I ² =0% (1 product, n = 3585)	P = 0.96, I ² =0%
Psychiatric system	(n = 22,709): RR 1.66 (1.14 to 2.40), P = 0.008, I ² =64%	RR 1.54 (0.89 to 2.65), P = 0.12; I ² =70% (3 products, n = 16,074)	RR 1.73 (1.04 to 2.89), I ² =53%, P = 0.04 (1 product, n = 6625)	P = 0.75, I ² =0%
Depression disorders - Psychiatric	(n = 22,824): RR 1.49 (0.93 to 2.41), P = 0.10, I ² =47%	RR 1.26 (0.55 to 2.86), P = 0.58; I ² =60% (3 products, n = 16,199)	RR 1.65 (0.92 to 2.97), I ² =33%, P = 0.09 (1 product, n = 6625)	P = 0.60, I ² =0%
Anxiety - Psychiatric	(n = 20,823): RR 1.30 (0.87 to 1.95), P = 0.20, I ² =0%	RR 1.21 (0.71 to 2.06), P = 0.49; I ² =25% (3 products, n = 14,198)	RR 1.98 (0.80 to 4.90), P = 0.14, I ² =0% (1 product, n = 6625)	P = 0.36, I ² =0%
Gastrointestinal	(n = 16,656): RR 3.75 (1.72 to 8.15), P = 0.0009, I ² =59%	RR 4.28 (1.19 to 15.39), P = 0.03; I ² =82% (2 products, n = 10,031)	RR 3.13 (1.17 to 8.37), P = 0.02, I ² =64% (1 product, n = 6625)	P = 0.70, I ² =0%
Nausea - Gastrointestinal	(n = 18,945): RR 4.59 (2.09 to 10.11), P = 0.0002, I ² =57%	RR 5.48 (1.76 to 17.07), P = 0.003; I ² =78% (2 products, n = 12,320)	RR 3.94 (1.20 to 11.08), P = 0.02, I ² =0% (1 product, n = 6625)	P = 0.70, I ² =0%
Vomiting - Gastrointestinal	(n = 3,847): RR = 3.79 (0.88 to 16.33), P = 0.07, I ² =0%	RR 5.85 (0.77 to 44.63), P = 0.09; I ² =0% (1 product, n = 1,393)	RR 2.38 (0.29 to 19.47), P = 0.42, I ² =0% (1 product, n = 2,549)	P = 0.55, I ² =0%

Summary of Findings Table 9.3: GRADE summary of effects of centrally-acting anti-obesity products on rates of discontinuation due to adverse events in overweight and obesity

Patient or population: Overweight and/or obese subjects with or without comorbidities Settings: Private or institutional practices; research centres; academic and primary care centres Intervention: Centrally acting anti-obesity medicinal products						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	NNT _D (95% CI)
	Assumed risk	Corresponding risk				
	Control	Discontinuations due to adverse events				
Overall discontinuation	Study population		RR 1.52 (1.33 to 1.74)	24555 (16 studies)	⊕⊕⊕⊖ low ¹	25 (17 to 39)
	78 per 1000	122 per 1000 (106 to 140)				
	Moderate					
	85 per 1000	133 per 1000 (116 to 153)				
Nervous system	Study population		RR 1.91 (1.52 to 2.40)	22699 (13 studies)	⊕⊕⊕⊕ moderate ²	87 (56 to 157)
	12 per 1000	24 per 1000 (18 to 30)				
	Moderate					
	8 per 1000	16 per 1000 (12 to 20)				
Headache - Nervous system	Study population		RR 1.56 (0.97 to 2.51)	22699 (13 studies)	⊕⊕⊕⊕ moderate ³	310 (-115 to 5794)
	5 per 1000	9 per 1000 (5 to 15)				
	Moderate					
	4 per 1000	7 per 1000 (4 to 11)				
Dizziness - Nervous system	Study population		RR 3.68 (2.09 to 6.49)	17783 (12 studies)	⊕⊕⊕⊕ moderate ⁴	211 (103 to 518)
	2 per 1000	7 per 1000 (4 to 11)				
	Moderate					
	0 per 1000	0 per 1000 (0 to 0)				
Psychiatric system	Study population		RR 1.66 (1.14 to 2.40)	22709 (13 studies)	⊕⊕⊕⊖ very low ⁵	94 (46 to 343)
	15 per 1000	26 per 1000 (18 to 37)				
	Moderate					
	12 per 1000	20 per 1000 (14 to 29)				
Gastrointestinal	Study population		RR 3.75 (1.72 to 8.15)	16656 (9 studies)	⊕⊕⊕⊖ low ⁶	70 (27 to 268)
	5 per 1000	20 per 1000 (9 to 47)				
	Moderate					
	3 per 1000	12 per 1000 (5 to 28)				
Nausea - GI	Study population		RR 4.59 (2.09 to 10.11)	18945 (11 studies)	⊕⊕⊕⊖ low ⁷	65 (25 to 213)
	4 per 1000	21 per 1000 (9 to 47)				
	Moderate					
	2 per 1000	10 per 1000 (4 to 22)				
Vomiting - GI	Study population		RR 3.79 (0.88 to	3847 (4 studies)	⊕⊕⊕⊖ low ⁸	367 (-66 to
	0 per	0 per 1000				

	1000	(0 to 0)	16.33)	8517)
	Moderate			
	0 per 1000	0 per 1000 (0 to 0)		
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; NNT_D: Number needed to treat to discontinue; RR: Risk ratio.				
GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.				
¹ Moderate risk of bias; moderate heterogeneity ² Moderate risk of bias ³ Moderate risk of bias ⁴ Moderate risk of bias; wide confidence interval; RR >2 ⁵ Moderate risk of bias; wide confidence interval; moderate to high heterogeneity ⁶ Moderate risk of bias; moderate heterogeneity; wide confidence interval; RR >2 ⁷ Moderate risk of bias; moderate heterogeneity; wide confidence interval; RR >2 ⁸ Moderate risk of bias; substantial heterogeneity; RR >2				

9.3.6.2 Overall adverse events

The data on overall adverse event rates for sibutramine trials could not be pooled because of inadequate data. For one study of lorcaserin that lasted 104 weeks [21], we used the data at the 52-week time point for meta-analysis because less than 50% of participants were followed up for the second year following re-randomization. There was a significantly increased risk of adverse events with the anti-obesity products: RR 1.12 (1.07 to 1.17), $P < 0.00001$, $I^2=90\%$ (Figure 9.4), $NNT_H = 11$ (8 to 19); the quality of the evidence was very low (SoF Table 9.2). Sensitivity analyses based on approval status revealed similar results; however, heterogeneity was significantly reduced with the withdrawn product ($I^2=0\%$; Table 9.3).

9.3.6.3 Overall discontinuations due to adverse events

There was a significantly increased risk of discontinuation due to adverse events with the centrally-acting anti-obesity products compared with placebo: RR 1.52 (1.33 to 1.74), $P < 0.00001$, $I^2=56\%$ (Figure 5), $NNT_D = 25$ (17 to 39). The quality of the evidence was low (SoF Table 9.3). Sensitivity analysis showed the same direction of effect for presently approved or withdrawn products (Table 9.4).

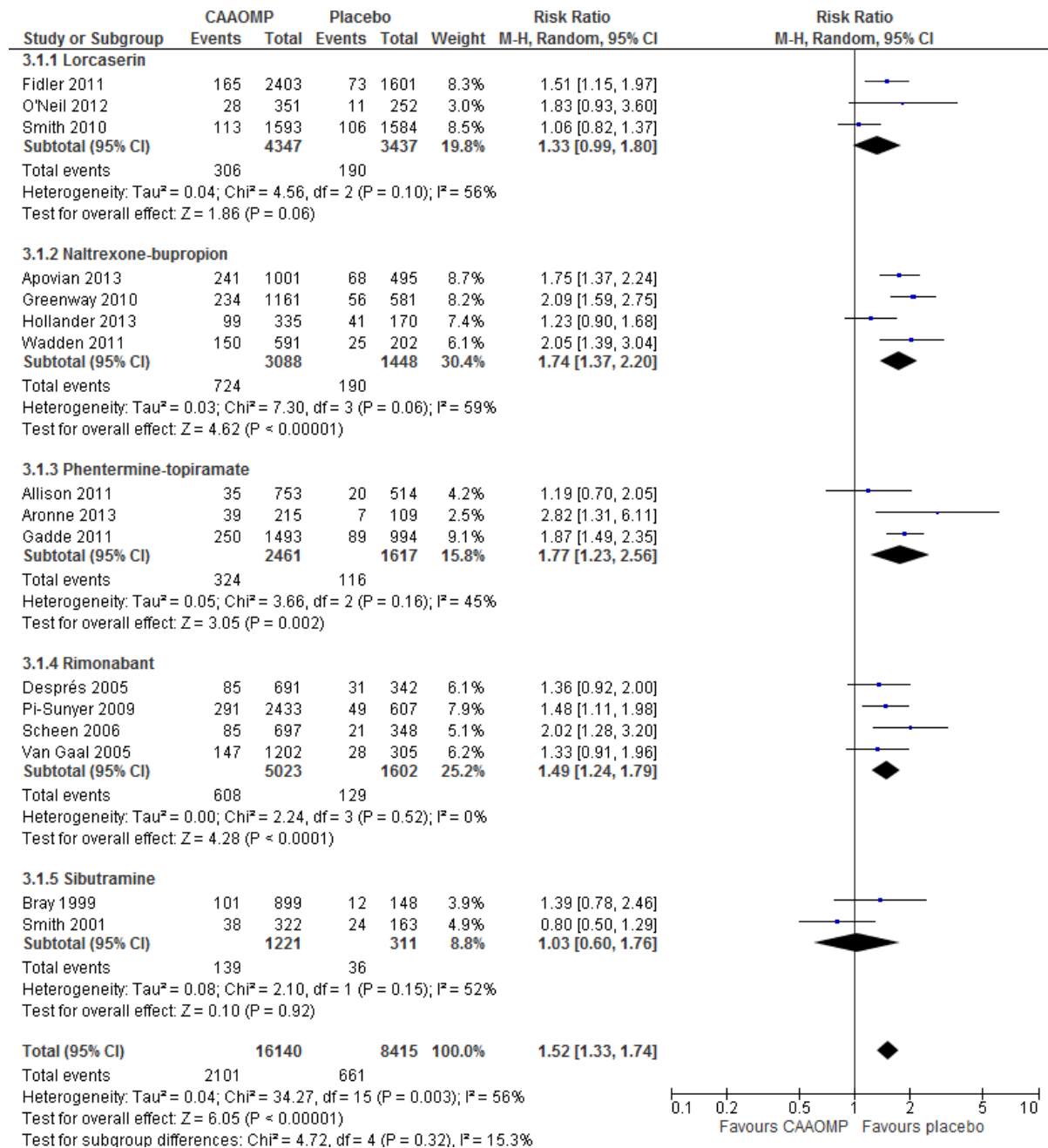
9.3.7 Secondary outcomes

9.3.7.1 Serious adverse events

The risk of serious adverse events was significantly increased with use of anti-obesity products compared with placebo: RR 1.18, (1.00 to 1.39), $P = 0.05$, $I^2=15\%$ (Figure 6), $NNT_H = 78$ (77 to 79); the quality of the evidence was moderate (SoF Table 9.2).

Sensitivity analyses showed that rimonabant trials had similar direction of effect, but there were no significant differences with the currently approved products (Table 9.3).

Figure 9.4: Effect of CAAOMP* on risk of discontinuation due to adverse events



In total, 11 deaths were reported across six trials for four products: eight with the centrally-acting anti-obesity products and three in the placebo group. Four of the deaths in the active intervention groups and two in the placebo groups were due to cardiovascular-related events (see appendix 11 for description of the individual cases). There was no significant

difference in mortality rates between the centrally-acting anti-obesity products and placebo (Table 9.3).

9.3.7.2 Nervous system adverse events

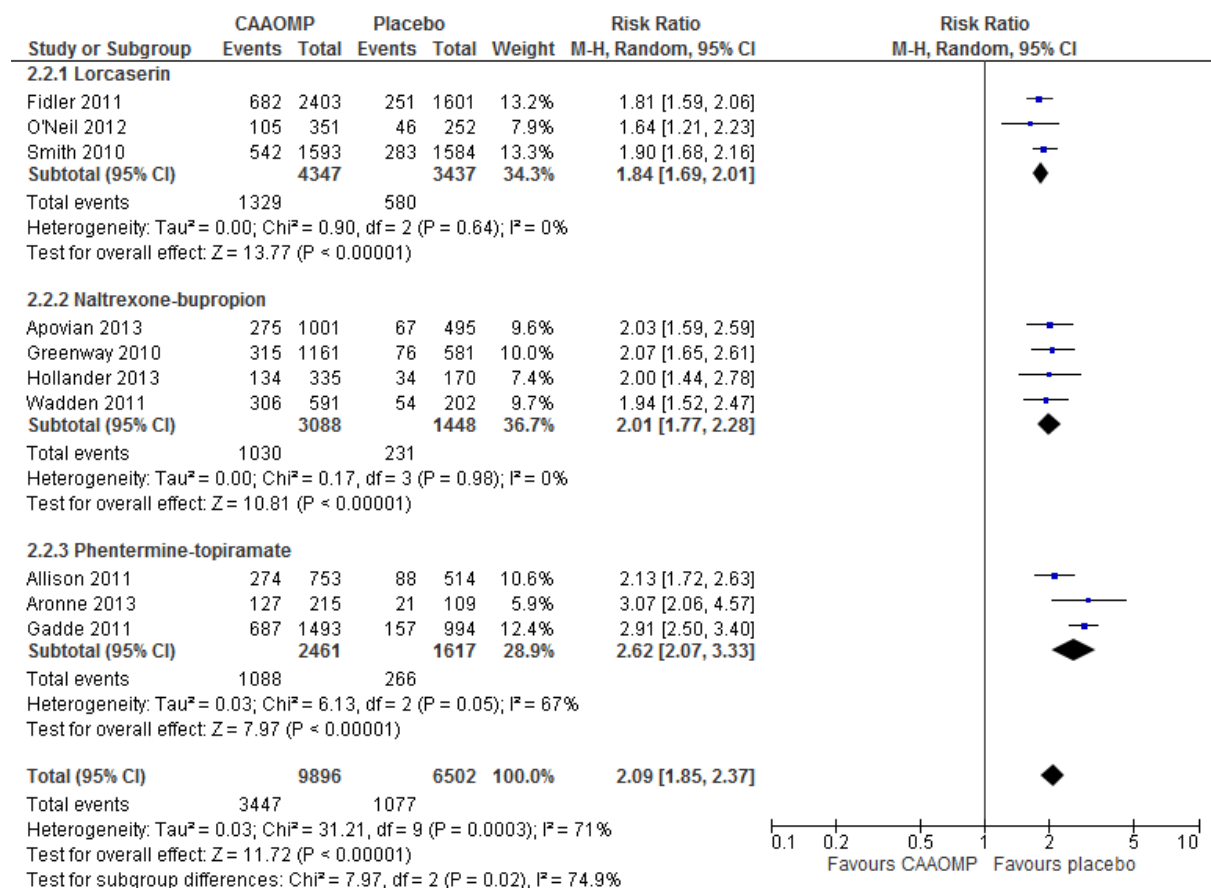
The results for the two withdrawn products, rimonabant and sibutramine, could not be included due to lack of adequate data – no records on journal publications, regulatory documents or clinical trials database. However, FDA data for sibutramine included eight trials (2 pivotal plus 6 supportive placebo-controlled studies, $n = 2952$). Analysis of the data showed a significantly increased risk of nervous system adverse events with sibutramine compared with placebo: 1146/2068 vs 207/884, $RR = 2.37$ (2.09 to 2.68), $P < 0.0001$, $NNT_H = 3$ (3 to 4). Similar results (only rates for dizziness reported) were observed with phase III studies of rimonabant based on FDA regulatory documents: 347/5262 vs 101/2474, $RR = 1.62$ (1.30 to 2.01), $P < 0.0001$, $NNT_H = 40$ (24 to 82).

There was a significantly increased risk of nervous system adverse events with the centrally-acting products compared with placebo: $RR 2.09$ (1.85 to 2.37), $P < 0.00001$, $I^2 = 71\%$ (Figure 9.5), $NNT_H = 6$ (5 to 7); the quality of the evidence was low (SoF Table 9.2).

The risk of headache was significantly increased with the centrally-acting products compared with placebo: $RR 1.34$ (1.12 to 1.60), $P = 0.002$, $I^2 = 79\%$, $NNT_H = 26$ (15 to 67). The quality of the evidence was very low (SoF Table 9.2). The analyses with presently approved products showed similar results; but there was no significant difference with the one withdrawn product (rimonabant) that had adequate data for this outcome (Table 9.3); subgroup analyses showed that presently approved products significantly increased the risk of headache compared to their withdrawn counterparts.

Dizziness was also significantly increased with the products compared with placebo: RR 2.03 (1.72 to 2.41), $P < 0.00001$, $I^2=41\%$, $NNT_H = 24$ (18 to 34). The quality of the evidence was moderate (SoF Table 9.2). Sensitivity analyses with either presently approved or withdrawn products revealed same direction of effect (Table 9.3).

Figure 9.5: Effect of CAAOMP* on overall risk of nervous system adverse events



Pooled analysis from the sibutramine trials (FDA data) showed a trend towards significantly increased risk of tremors: RR 14.22(0.86 to 235.34), $P = 0.06$. FDA pooled analysis from rimonabant trials also showed a trend towards a significantly increased risk of tremors: RR 2.85 (0.74 to 10.96), $P = 0.06$. Meta-analysis of N-B trials showed a significantly increased risk of tremors compared with placebo: RR 4.30 (1.86 to 9.90), $P =$

0.0006, $I^2=0\%$, $NNT_H = 13$ (5 to 42); the quality of the evidence was moderate (SoF Table 9.2). There was insufficient data to compute tremor frequency with the other products.

There was a significantly increased risk of paraesthesia or hypoesthesia with the centrally-acting products compared with placebo: RR 7.50 (5.38 to 10.47), $P < 0.00001$, $I^2=0\%$, $NNT_H = 8$ (6 to 12) – this analysis included only presently approved products. The quality of the evidence was high (SoF Table 9.2). FDA pooled data for rimonabant showed a trend towards a significantly increased risk of hypo/paraesthesia compared with placebo: 123/4396 vs 31/1602, $P = 0.06$.

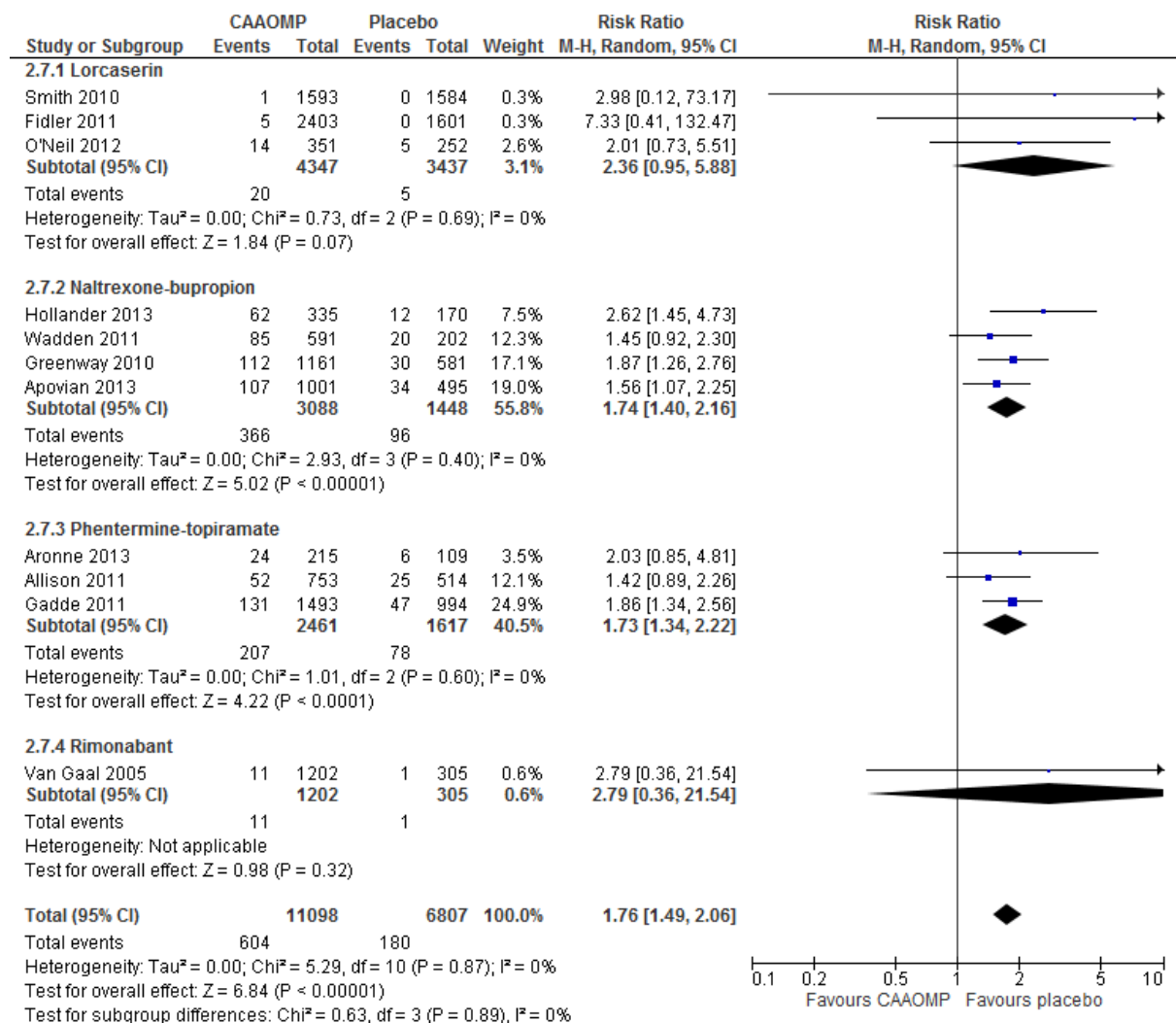
9.3.7.3 Psychiatric system adverse events

There was a significantly increased risk of psychiatric adverse events with the centrally-acting products compared with placebo: RR 1.76 (1.49 to 2.06), $P < 0.00001$, $I^2=0\%$, $NNT_H = 50$ (36 to 77) (Figure 9.6). The quality of the evidence was moderate (SoF Table 9.2). Sensitivity analyses revealed similar directions for the effect for products presently approved (Table 9.3); however, there was no significant difference with the one RCT for the withdrawn product, rimonabant. Test for subgroups for diabetic *versus* non-diabetic participants was not significant: $P = 0.23$, $I^2=31.1\%$

Pivotal trials of two products, N-B and rimonabant that reported sufficient data revealed a significantly increased risk of anxiety compared with placebo: RR 1.32 (1.03 to 1.69), $P = 0.03$, $I^2=0\%$, $NNT_H = 66$ (36 to 171). The quality of the evidence was moderate (SoF Table 9.2). Pooled FDA data for sibutramine did not reveal a significant difference in risk: 75/1221 vs 16/311, $P = 0.51$. Meta-analysis of the seven pivotal clinical trials for the same two products showed a significantly increased risk of insomnia compared with placebo:

RR 1.59 (1.38 to 1.84), $P < 0.00001$, $I^2=0\%$, $I^2=22\%$, $NNT_H = 33$ (23 to 52). The quality of the evidence was moderate (SoF Table 9.2); sensitivity analyses revealed similar effect with presently approved products, but not with the one withdrawn product, rimonabant. There was a trend towards significantly increased risk in diabetic *versus* non-diabetic participants: $P = 0.09$, $I^2=66.2\%$.

Figure 9.6: Effect of CAAOMP* on overall risk of psychiatric adverse events



There was no significant difference in the risk of depression between anti-obesity products and placebo: RR 1.25 (0.89 to 1.75), $P = 0.20$, $I^2=52\%$; the quality of the evidence was very low (SoF Table 9.2). The effect was similar when presently approved products or the one withdrawn product were analysed separately (Table 9.3); and being diabetic did not result in a difference in risk: $P = 0.79$, $I^2=0\%$. Pooled FDA data for withdrawn products showed a non-significant difference in the risk of depression between sibutramine and placebo: 79/1221 vs 16/311, $P = 0.39$.

9.3.7.4 Cardiac system adverse events

There was no significant difference in the risk of cardiac adverse events between the anti-obesity products and placebo, RR 1.04 (0.59 to 1.84), $P = 0.89$, $I^2=0\%$. The quality of the evidence was low (SoF Table 9.2). Sensitivity analyses for either three presently available products or for the one RCT of a withdrawn product showed similar results (Table 9.3). Subgroup analysis including diabetic participants also showed that the risk was significantly reduced in diabetic participants: $P = 0.02$, $I^2=82.7\%$.

FDA briefing document showed no significant difference in the risk of palpitation between lorcaserin and placebo: RR 1.06 (0.66 to 1.71). Pooled FDA data revealed that the risk of palpitation was significantly increased with P-T: 41/2318 vs 12/1561, RR 2.30 (1.21 to 4.36), $P = 0.01$, $NNT_H = 100$ (38 to 619). The FDA data for rimonabant included eight trials (2 pivotal plus 6 supportive placebo-controlled studies, $n = 2952$); analysis of the data showed a significantly increased risk of cardiovascular adverse events with rimonabant compared with placebo: 239/2068 vs 46/884, $RR = 2.22$ (1.64 to 3.01), $P < 0.0001$, $NNT_H = 16$ (10 to 30). Because the data were FDA pooled data, we did not use GRADE to rate the quality of the body of the evidence.

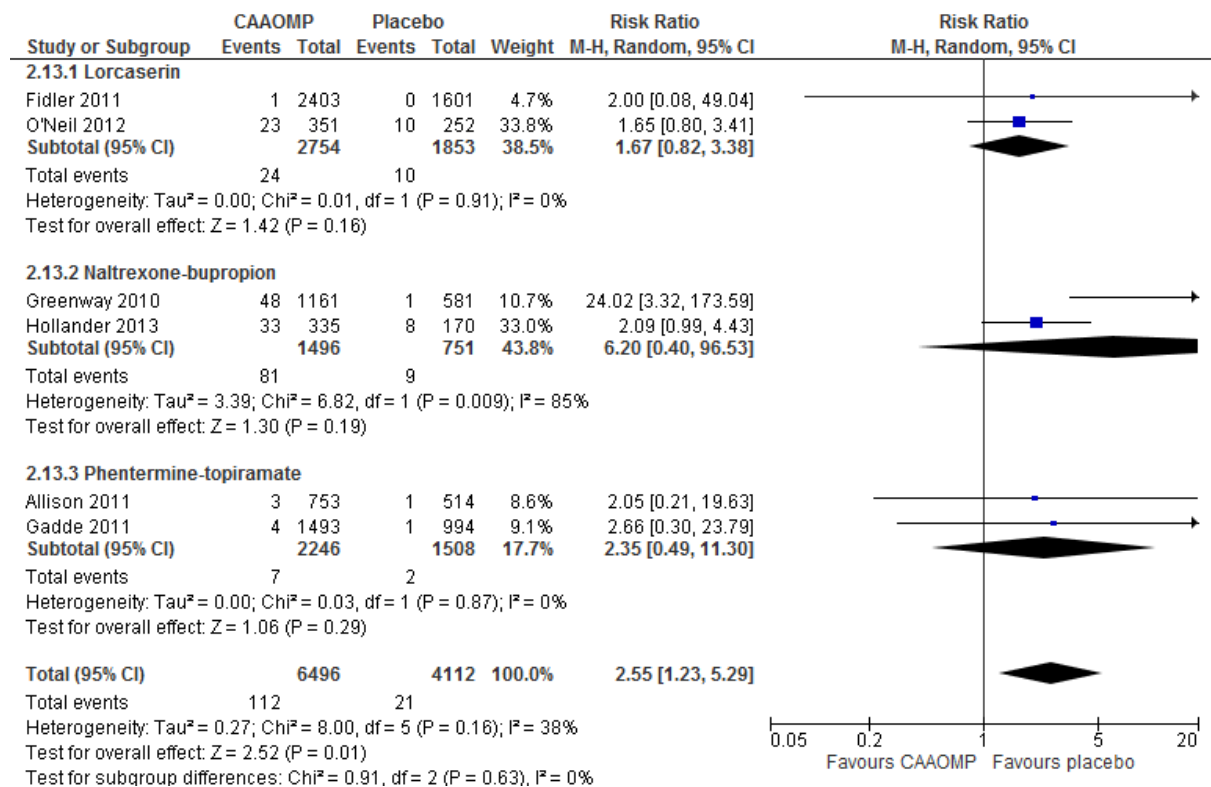
One trial of sibutramine [34] reported the frequency of palpitations, and there was no significant difference: 30/899 *versus* 1/148 ($P = 0.11$). FDA documents showed that there was a significantly increased risk of palpitations with sibutramine compared with placebo: 41/2068 vs 7/884, RR 2.50 (1.13 to 5.56), $P = 0.02$, $NNT_H = 84$ (28 to 971).

9.3.7.5 Vascular system adverse events

Treatment with centrally-acting products was associated with a significantly increased risk of vascular adverse events compared with placebo: RR 2.55 (1.23 to 5.29), $P = 0.01$, $I^2=38\%$, $NNT_H = 126$ (46 to 851) (Figure 9.7). The quality of the evidence was moderate (SoF Table 9.2). The risk of vascular events was also significantly increased in participants with diabetes ($P = 0.001$), but not significantly increased with non-diabetics ($P = 0.09$); however, the test for subgroup differences was not significant ($P = 0.30$; $I^2=6.9\%$).

There was a significant increase in the risk of hypertension with the centrally-acting products compared with placebo: RR 1.78 (1.10 to 2.88), $P = 0.02$, $I^2=0\%$, $NNT_H = 224$ (93 to 1744); the quality of the evidence was low (SoF Table 9.2). In diabetic participants, the risk of hypertension was also significantly increased with the products: RR 1.95 (1.14 to 3.34), $P = 0.01$, $I^2=0\%$, $NNT_H = 66$ (25 to 468), but not significantly different compared with non-diabetics ($P = 0.40$; $I^2=0\%$).

Figure 9.7: Effect of CAAOMP* on overall risk of vascular system adverse events



9.3.7.6 Gastrointestinal system adverse events

There was a significant increase in the risk of gastrointestinal adverse events with centrally-acting products compared with placebo: RR 2.04 (1.59 to 2.62), $P < 0.00001$, $I^2=95\%$, $NNT_H = 5$ (3 to 9) (Figure 9.8); however, the quality of the evidence was very low (SoF Table 9.2). Sensitivity analyses showed similar effect with presently available products (Table 9.3); however, there was no significant effect with the one trial ($n = 1507$) of a withdrawn product (rimonabant) that reported this outcome.

The risk of nausea was significantly increased with the anti-obesity products: RR 2.18 (1.59 to 2.98), $P < 0.00001$, $I^2=89\%$, $NNT_H = 15$ (9 to 30). The quality of the evidence was very low (SoF Table 9.2). Sensitivity analyses with the presently available or withdrawn products revealed similar results (Table 9.3).

Data on vomiting from individual trials were only available for one product, N-B. Meta-analysis of the four trials showed a significantly increased risk of vomiting with N-B: RR 3.74 (2.36 to 5.94), $P < 0.00001$, $I^2=55\%$, $NNT_H = 12$ (7 to 24). The quality of the evidence was low (SoF Table 9.2). Pooled FDA data was available for three products: lorcaserin, P-T and rimonabant. Meta-analysis of the pooled data also revealed a significantly increased risk of vomiting with the products: RR 1.35 (1.03 to 1.76), $P = 0.03$, $I^2=53\%$, $NNT_H = 117$ (54 to 1361).

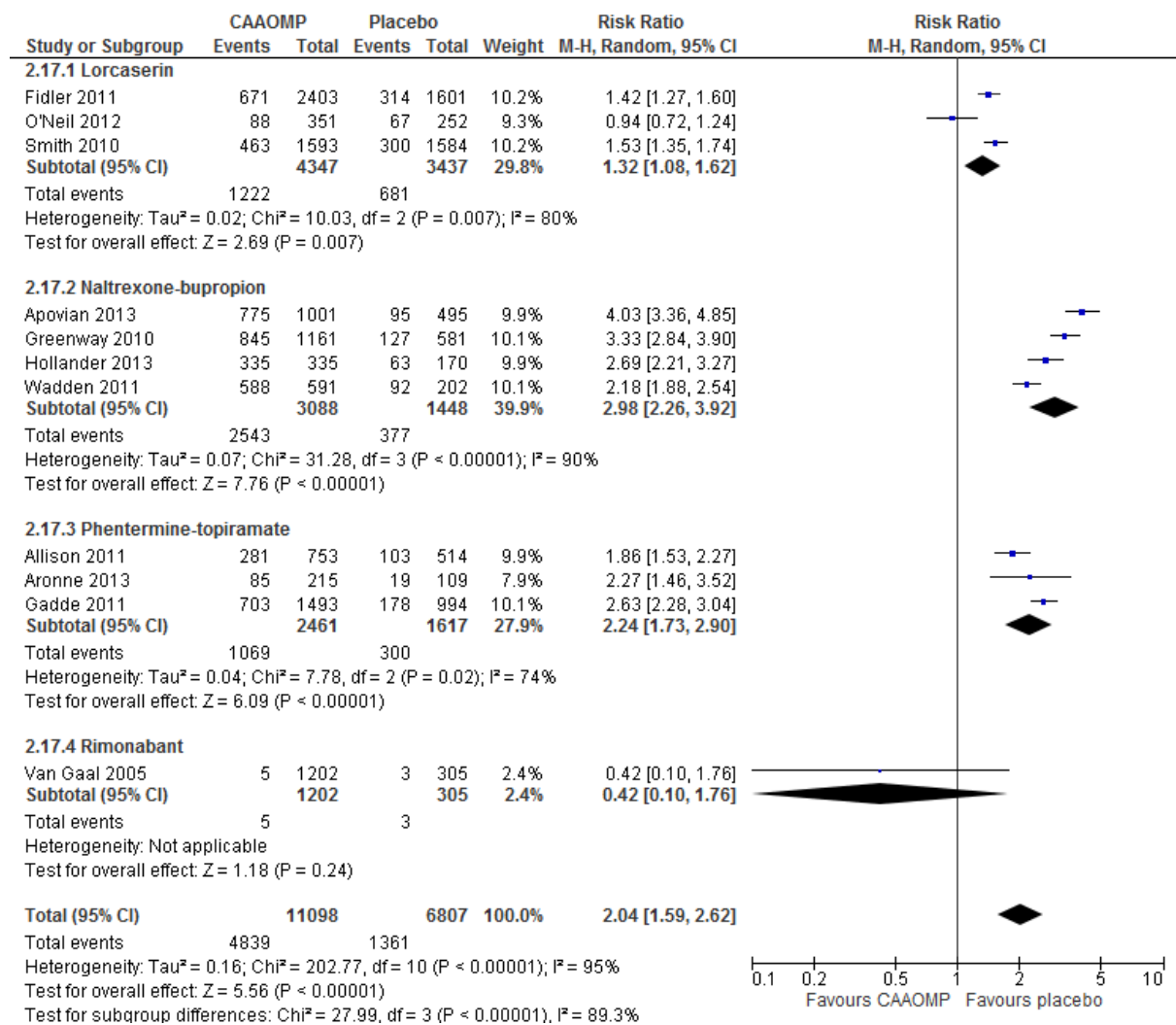
The anti-obesity products significantly increased the risk of diarrhoea compared with placebo: RR 1.18 (1.06 to 1.32), $P = 0.003$, $I^2=0\%$, $NNT_H = 96$ (54 to 288). The quality of the evidence was moderate (SoF Table 9.2); regulatory approval status did not change the direction of the effect (Table 9.3). The anti-obesity products also significantly increased the risk of constipation: RR 1.96 (1.61 to 2.39), $P < 0.00001$, $I^2=64\%$, $NNT_H = 19$ (13 to 29). The quality of the evidence was low (SoF Table 9.2). There was a significantly increased risk of dry mouth with centrally-acting products compared with placebo: RR 3.39 (2.40 to 4.80), $P < 0.00001$, $I^2=72\%$, $NNT_H = 17$ (11 to 28). The quality of the evidence was low (SoF Table 9.2). The effect was similar when presently approved or withdrawn products were analysed separately (Table 9.3).

9.3.7.7 General disorders

Only presently approved products reported adequate data for statistical pooling. There was no significant difference in the frequency of general disorders between interventions and placebo, RR 1.20 (0.86 to 1.68), $P = 0.28$, $I^2=69\%$. The quality of the evidence was low (SoF Table 9.2). Sensitivity and subgroup analyses did not reveal any significant

differences; but heterogeneity was significantly reduced in subgroup analyses ($I^2=0\%$; Table 9.3).

Figure 9.8: Effect of CAAOMP on overall risk of gastrointestinal system adverse events



9.3.7.8 Musculoskeletal disorders

Only presently approved products reported adequate data for statistical pooling. There was no significant difference in the frequency of musculoskeletal disorders between the interventions and placebo, RR 1.01 (0.92 to 1.12), $P = 0.79$, $I^2=0\%$. The quality of the

evidence was moderate (SoF Table 9.2); this result was consistent when each presently approved product was analysed separately.

9.3.7.9 Infections and infestations

Only presently approved products reported adequate data for statistical pooling. There was no significant difference in the risk of infections and infestations between the anti-obesity products and placebo, RR 1.00 (0.90 to 1.12), $P = 0.95$, $I^2=87\%$. The quality of the evidence was very low (SoF Table 9.2). Sensitivity analyses revealed an inconsistency across the three products; there was a significantly increased risk with lorcaserin, a significantly decreased risk with N-B, and no significant difference in risk with P-T.

9.3.7.10 Overall discontinuations

All included studies had high drop-out rates; these ranged from 34% to 50% (Table 9.1). There was no significant difference in overall discontinuation rates between centrally-acting products and placebo, RR 0.94 (0.87 to 1.01), $P = 0.09$, $I^2=80\%$. The quality of the evidence was very low (SoF Table 9.2); sensitivity analysis with either presently approved or withdrawn products showed similar results (Table 9.4).

Participants in placebo groups were significantly more likely to withdraw consent to continued participation in the trials compared with those receiving centrally-acting products, RR 0.72 (0.66 to 0.79), $P < 0.00001$, $I^2=66\%$, $I^2=68\%$, $NNT_D = 13$ (10 to 17). The quality of the evidence was low (SoF Table 9.3). Sensitivity analysis of either presently approved or withdrawn products showed similar results (Table 9.4).

9.3.7.11 Discontinuations due to nervous system adverse events

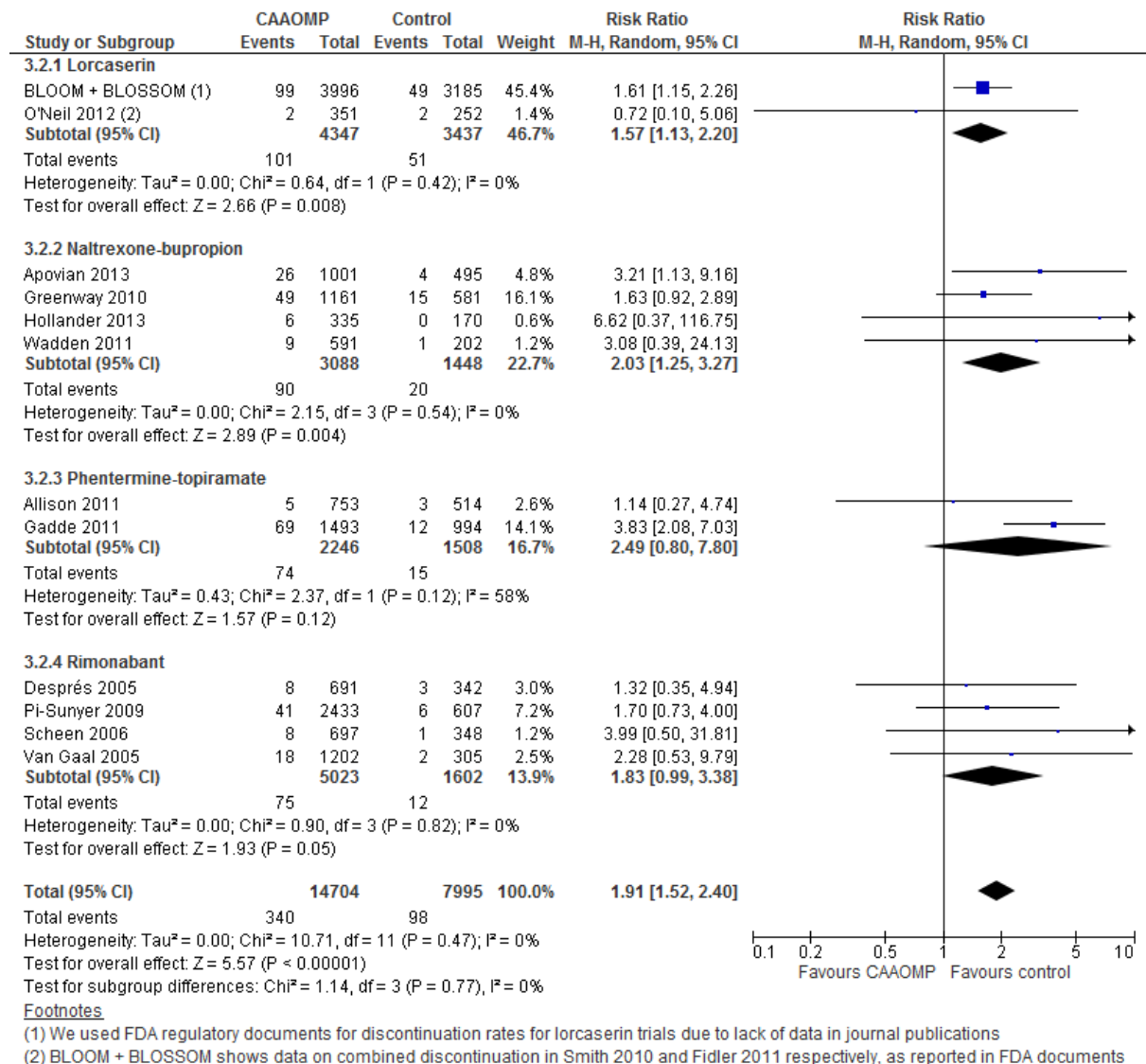
There was a significant increase in the risk of discontinuation due to nervous system adverse events with the centrally-acting products compared with placebo, RR 1.91 (1.52 to 2.40), $P < 0.00001$, $I^2=0\%$ (Figure 9.9), $NNT_D = 87$ (56 to 157). The quality of the evidence was moderate (SoF Table 9.3). Sensitivity analyses revealed a similar effect with presently available products, with a trend towards a similar effect with the one withdrawn product (rimonabant) that reported adequate data (Table 9.4).

Discontinuation because of headache was not significantly increased by the centrally-acting products compared with placebo: RR 1.56 (0.97 to 2.51), $P = 0.06$, $I^2=21\%$, $NNT_D = 307$ (-115 to 2115). The quality of the evidence was moderate (SoF Table 9.3). Sensitivity analysis revealed a significant effect with presently approved products: RR 1.76 (1.02 to 3.02), $P = 0.04$; $I^2=29\%$, $NNT_D = 241$ (91 to 9166); however, there was no significant difference with the one withdrawn product (rimonabant) that reported this outcome (Table 9.4).

The information from both journal publications and regulatory documents was used to pool the data on discontinuations because of dizziness. There was a significantly increased risk of discontinuation because of dizziness with the centrally-acting products compared with placebo: RR 3.68 (2.09 to 6.49), $P < 0.00001$, $I^2=0\%$, $NNT_D = 211$ (103 to 518). The quality of the evidence was low (SoF Table 9.3). Sensitivity analyses with presently available products showed similar results; however, analyses of trials of the one withdrawn product (rimonabant) that reported adequate data did not reveal a significant difference (Table 9.4). Pooled FDA data also showed a significantly increased risk of discontinuation due to hypo/paraesthesia with P-T compared with placebo: RR 2.01 (2.01 to 542.32), $P =$

0.01, NNT_D = 49 (3 to 1546); there was no data on this outcome for trials of the other four products.

Figure 9.9: Effect of CAAOMP* on risk of discontinuation due to nervous system adverse events

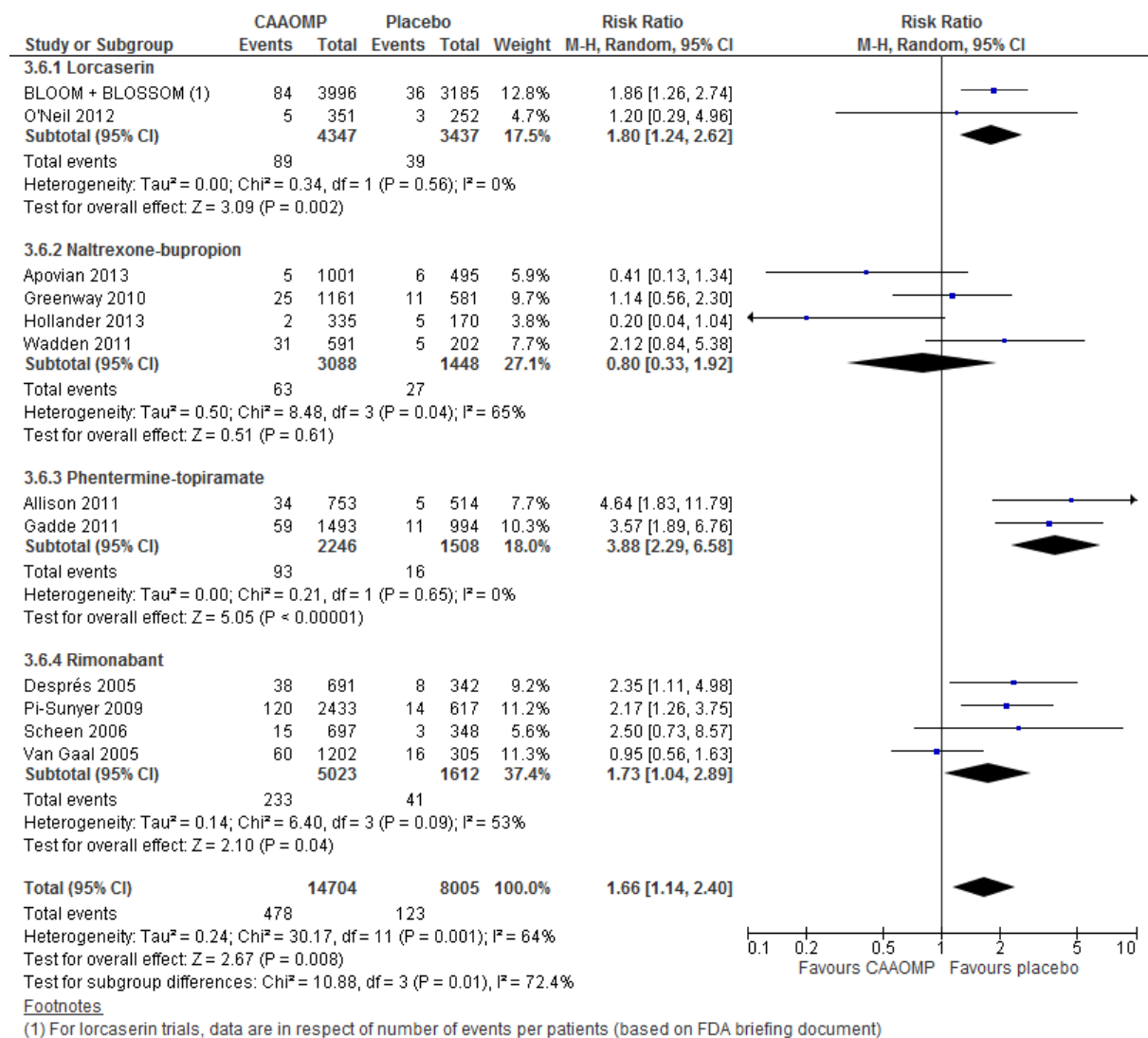


9.3.7.12 Discontinuations due to psychiatric system adverse events

There was a significant increase in discontinuation rates due to psychiatric adverse events between centrally-acting products and placebo, RR 1.66 (1.14 to 2.40), P = 0.008, I²=64%

(Figure 9.10), $NNT_D = 94$ (46 to 343). The quality of the evidence was very low (SoF Table 9.3). This effect was largely influenced by the results of one withdrawn product that reported the outcome (Table 9.4).

Figure 9.10: Effect of CAAOMP* on risk of discontinuation due to psychiatric system adverse events



Meta-analysis of pooled FDA data for the individual products (sibutramine excluded)

showed no significantly increased risk of discontinuation because of insomnia: RR 1.67

(0.66 to 4.20), $P = 0.28$, $I^2=59\%$. There was also no significant difference in the risk of discontinuation due to anxiety: RR 1.30 (0.87 to 1.95), $P = 0.20$, $I^2=0\%$.

There was no significant difference in the risk of discontinuation because of depression: RR 1.49 (0.93 to 2.41), $P = 0.10$, $I^2=47\%$; this analysis included pooled FDA data for lorcaserin and P-T combined with individual trials results for N-B and rimonabant.

9.3.7.13 Discontinuations due to cardiac adverse events

There was inadequate data to allow for statistical pooling. However, pooled FDA data on lorcaserin did not show a significant difference in the risk of discontinuation because of cardiac adverse events: 18/4347 vs 13/3437, $P = 0.80$; there was also no significant difference in the risk of discontinuation because of palpitations: 10/3239 vs 0/1515, $P = 0.11$. The authors of one sibutramine study noted the withdrawal of a patient on sibutramine intervention from the trial “because of palpitations due to frequent ventricular ectopic beats” [35].

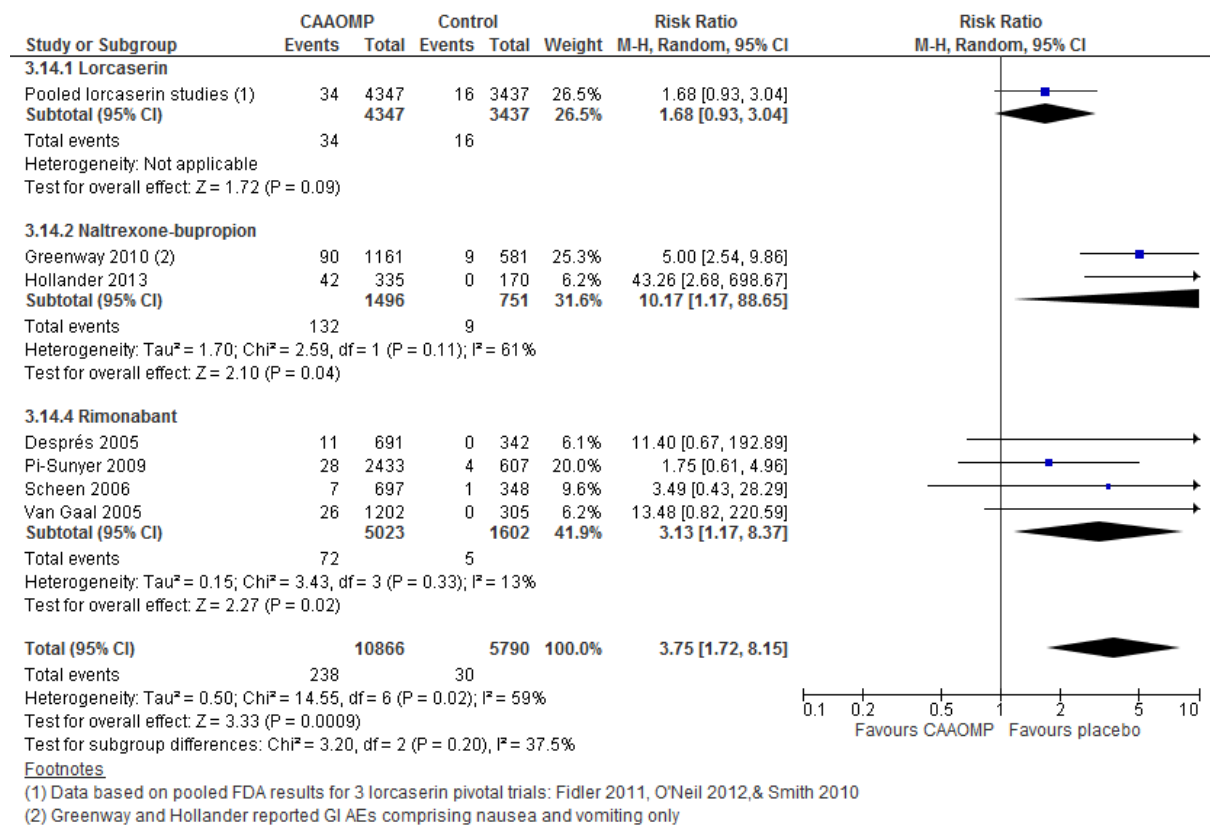
9.3.7.14 Discontinuations due to vascular system adverse events

There was inadequate data to allow for statistical pooling. However, pooled FDA data on lorcaserin did not show a significant difference in the risk of discontinuation because of vascular adverse events: 14/4347 vs 10/3437, $P = 0.81$. Meta-analysis of pooled FDA data for lorcaserin and N-B, and one trial report for P-T showed no significant difference in the risk of discontinuation because of hypertension: RR 1.26 (0.41 to 3.90), $P = 0.69$, $I^2=44\%$.

9.3.7.15 Discontinuations due to gastrointestinal system adverse events

There was a significantly increased risk of discontinuation because of gastrointestinal adverse events with the centrally-acting products: RR 3.75 (1.72 to 8.15), $P = 0.0009$, $I^2=59\%$ (Figure 9.11), $NNT_D = 70$ (27 to 268). The quality of the evidence was low (SoF Table 9.3), and the effects were similar for either presently approved or withdrawn products (Table 9.4). The risk of discontinuation because of nausea was significantly increased with the centrally-acting products: RR 4.59 (2.09 to 10.11), $P = 0.0002$, $I^2=57\%$, $NNT_D = 65$ (25 to 213); the quality of the evidence was low (SoF Table 9.3); sensitivity analysis based on approval status of the products did not result in a change in the direction of the results (Table 9.4). The risk of discontinuation due to vomiting was nearly significantly increased: RR = 3.79 (0.88 to 16.33), $P = 0.07$, $I^2=0\%$ (this analysis comprised lorcaserin and rimonabant trials); sensitivity analysis showed that the near significant increase was due to the lorcaserin (Table 9.4). Meta-analysis of pooled FDA data for two individual products (lorcaserin and N-B) revealed a significantly increased risk of discontinuation because of constipation with the centrally-acting products: RR 4.02 (1.17 to 13.78), $P = 0.03$, $I^2=0\%$.

Figure 9.11: Effect of CAAOMP* on risk of discontinuation due to gastrointestinal system adverse events



9.4 DISCUSSION

9.4.1 Summary of main results

The evidence from pivotal clinical trials indicates that centrally-acting anti-obesity products are significantly more likely to cause at least a 5% reduction in baseline body weight compared with placebo; the effects are similar when presently approved products are compared with their withdrawn counterparts. The results show that the products significantly increase the risk of adverse events and serious adverse events. The centrally-acting anti-obesity medicinal products significantly increase the risk of nervous system adverse events – in particular they significantly increase the risk of headache, dizziness and hypo/paraesthesia, and may likely increase the risk of tremors. The centrally-acting anti-

obesity medicinal products significantly increase the risk of psychiatric adverse events – in particular they significantly increase the risk of anxiety and insomnia. The products significantly increase the risk of vascular adverse events, specifically hypertension, and possibly palpitation. The risk of gastrointestinal adverse events is also significantly increased by the centrally-acting products – in particular nausea, vomiting, diarrhoea, constipation and dry mouth.

The evidence from pivotal clinical trials shows that centrally-acting anti-obesity products significantly increase the risk of overall discontinuation because of adverse events. Discontinuations because of nervous system adverse events are significantly increased by the products – in particular the risk of discontinuation because of headache, dizziness and hypo/paraesthesia is significantly increased. The centrally-acting products also significantly increase the risk of discontinuation because of psychiatric adverse events; individual adverse events of anxiety and insomnia showed a trend towards significantly increased risk of discontinuation. The risk of discontinuation because of gastrointestinal adverse events was significantly increased with the centrally-acting products – discontinuation because of nausea or constipation was significantly increased, while discontinuation because of vomiting approached statistical significance ($P = 0.07$). The adverse event and discontinuation rates for presently approved products are comparatively similar to those of their withdrawn counterparts. Discontinuation rates because of withdrawal of consent and loss-to-follow-up was significantly greater with placebo compared with the centrally-acting anti-obesity products.

9.4.2 Overall completeness and applicability of evidence

The results of this review suggest that the centrally-acting anti-obesity products can generate significant reductions in body weight from baseline, but their use is associated with increased risks of harms and medication discontinuation. The applicability of the results is limited by the heterogeneity observed in some of the analyses (because of variation in baseline participants' demographics (including comorbidities), differences in types of lifestyle adjustments, and variation dosages (within pivotal trials of same product) and duration of intervention (both within pivotal trials of same product and across the five products), and an imbalance in sample populations between intervention and placebo groups. Of note, across pivotal trials of the individual products, substantial heterogeneity was also observed for our primary outcomes, and several secondary outcomes. Furthermore, all the included trials were conducted in the USA.

9.4.3 Quality of the evidence

Overall, the quality of the evidence varied from very low to high, and there are inconsistencies in how the frequency of adverse events are reported across journal publications of pivotal trials of the same product, and between journal publications and regulatory documents of products.

The quality of the evidence for the ITT proportion of participants with $\geq 5\%$ weight reduction from baseline was rated low because of moderate risk of bias, substantial heterogeneity, and $RR > 2$ (SoF Table 9.1); in the per-protocol population, the quality of the evidence was rated very low because of moderate risk of bias, substantial heterogeneity, wide confidence interval, and $RR > 2$.

The quality of the evidence for overall adverse events was downgraded to very low because of moderate risk of bias and substantial heterogeneity (SoF Table 9.2). The quality of the evidence for serious adverse events and psychiatric adverse events was downgraded to moderate because of moderate risk of bias (see SoF Table 9.2 for the quality of the evidence for adverse events outcomes and reasons for the ratings).

The quality of the evidence for overall risk of discontinuation was downgraded to low because of moderate risk of bias and moderate heterogeneity (SoF Table 9.3). The quality of the evidence for discontinuation due to nervous system adverse events as well as headache was downgraded to moderate because of moderate risk of bias (see SoF Table 9.3 for the quality of the evidence for discontinuations due to adverse events outcomes and reasons for the ratings).

9.4.4 Agreements and disagreements with other studies or reviews

The findings from this review are largely consistent with several published reviews which reported beneficial effects of centrally-acting anti-obesity products on body weight. In a recent review of currently approved anti-obesity products, the authors reported high attrition rates for the included trials at one year [41]. In a meta-analysis of lorcaserin trials, the authors noted significantly increased risks of headache and dizziness compared with placebo [42]. In a recent systematic review examining the benefits and harms of topiramate for obesity management, the authors cautioned against use of the product because of significantly increased risks of overall adverse and serious adverse events [43]. In systematic reviews including sibutramine and/or rimonobant trials, the authors reported significantly increased risks of psychiatric and nervous system adverse events, and significantly increased risks of discontinuation because of adverse events with the products

[44,45,46]. The results are also consistent with findings from the European Union Eudravigilance adverse event reporting system which showed that cardiac and psychiatric disorders were amongst the most commonly reported serious adverse reactions attributed to anti-obesity medicines [47].

9.4.5 Potential biases in the review process

This is the first systematic review which synthesizes the evidence from pivotal trials of centrally-acting anti-obesity medicinal products. Great effort was made at accurately identifying pivotal clinical trials used as justification for approval of centrally-acting anti-obesity medicinal products. The risk of bias in included trials was independently assessed, the overall quality of included studies was accounted for, and the consistency of reporting of data across various studies was compared. In addition, NNT was computed for several outcomes to enable comparison of benefits and harms. Furthermore, the results of sensitivity and subgroup analyses were largely consistent with our overall analyses.

However, several limitations are recognized. Some trials have reported adverse events data per patient, rather than overall frequency; the extent to which such discrepancy could influence the direction of our study results is difficult to ascertain. The number of pivotal trials per medicinal product (and the number of participants) varied; however, majority have large sample sizes, and these trials were used as basis for granting of marketing authorizations. The pivotal trials were powered to detect efficacy and not harms; therefore the effect sizes for harms observed in our analyses may be underestimates of the true effect. The high discontinuation rates across the trials, coupled with heterogeneity observed in some of the analyses casts doubts on the validity of the effect estimates for some outcomes across products; however, analyses of presently approved *versus* withdrawn products generally showed low heterogeneity. The first reviewer (IJO) could

not gain access to data for some trials included in the review (e.g. trial registry results for the withdrawn products); however, it is unlikely this would have significantly influenced the direction of the overall results. Of note, the first reviewer's (IJO) attempts to obtain additional information from the authors of the trials for one product included in the review was unsuccessful – the corresponding author did not have access to the primary data and referred us to another source, who in turn referred us to a third source, who in turn referred us to the journal publication. Because the first reviewer (IJO) could not access data on MEdDRA reporting of adverse events for two withdrawn products on clinical trials.gov, there was an inability to completely verify the accuracy of the event rates reported in the journal publications.

9.4.6 Implications for research

The results of this review, in conjunction with our previous report on the post-marketing withdrawal of anti-obesity products in Chapter 7 suggest that the rationale for use of monoamine analogues for obesity treatment is questionable. Because obesity and overweight are risk factors for hypertension [48], it is thought that reductions in body weight can improve cardiovascular risk factors [49]. However, the evidence from the meta-analysis does not indicate that centrally-acting anti-obesity medicinal products reduce the risk of hypertension, but may actually increase the risk. Whether the overall weight losses outweigh the risk of harms is uncertain; because this class of products act through similar mechanistic pathways, are approved for same indication, and have similar benefit-harm profile, a model to determine a cut-off point for benefit-harm balance should be developed.

Although the pivotal trials all reported high discontinuation rates, the overall rates were almost always similar between the intervention and placebo groups. The significantly

greater rates of loss-to-follow-up and/or withdrawal of consent in the placebo groups suggest that the centrally-acting products were effective at generating weight losses; however, it is unclear whether there is a differential process for ensuring compliance between groups in the pivotal trials and this arouses suspicion of administrative bias [50]. Some authors have argued for more detailed reporting of loss-to-follow-up in randomised trials, especially where the rates are high [51]. Investigators should also more explicitly describe the interventions used in their trials. For instance, the use of the term “matching placebos” does not necessarily imply that the active and placebo interventions are identical in shape, taste and colour [52]. More detailed reporting of blinding methodology in journal publications of clinical trials has been suggested [53].

9.4.7 Implications for clinical practice

Low quality evidence from pivotal clinical trials indicates that the use of centrally-acting anti-obesity medicinal products can cause significant reductions in body weight. However, their use can also increase the risk of hypertension, and moderate quality of evidence suggests that this class of products likely increase the risk of experiencing serious adverse events. The nervous and psychiatric adverse events associated with the use of these products may result in poor adherence to therapy, and can result in increased healthcare costs [54]. Physicians should be aware that the effect estimates from clinical trials “do not correlate directly with patient responses in real-world clinical practice” [55].

9.4.8 Implications for future drug regulation and policy

As the findings in Section 9.3.5 (and appendix 11) show, rare and very rare adverse events are more likely to be reported in regulatory documents compared with their corresponding journal publications. The implication of this is that journal publications appear to portray

the products as less harmful than they may actually be. Therefore, the reporting of adverse events should be consistent between regulatory documents and journal publications; this is because most clinicians are more likely to access information from journal publications rather than in regulatory documents when considering the use of a medicinal product.

The high discontinuation rates reported in the pivotal trials indicate that there is an increased likelihood for poor adherence with the use of the products [56]; medication nonadherence is a major contributor to avoidable increased healthcare costs and also affects health outcomes [57,58]. The annual cost of such medicines “wastage” is estimated at £300 million (\$380 million) in the UK [59], and between \$2.4 billion and \$5.4 billion in the USA [60]. One study estimates that 14% of such costs are related to medicines discontinuation because of adverse effects [61]. Consequently, future cost-benefit assessment of centrally-acting anti-obesity medications, if any, should include the economic estimates related to medicines nonadherence. In addition, because long-term lifestyle interventions in overweight and obese patient have showed comparable levels of weight loss to those reported in the included pivotal trials [62,63], further research on non-drug methods for weight reduction should be a priority for health organizations, as this may be more cost-saving.

The review results showed that per-protocol adverse event rates were scarcely reported in journal publications, and were not sufficiently documented in regulatory documents; this is of interest because such data were reported for efficacy. In future, when authors report adverse event rates, the rates should also be reported separately for completer population of the study drug. Where the rates are no different from the general sample population, it could be that the product has a more favourable benefit-to-harm balance amongst the

completers while also taking account of any specific baseline demographics; such ancillary data could be reported as an online supplementary file in journal publications.

The high discontinuation rates observed in the trials indicate that the frequency of adverse events is most likely underreported; and it has been shown that lower number of adverse events are reported in published articles when compared to unpublished ones [64].

Therefore, systematic reviews and meta-analysis of this class of products using data from clinical study reports (CSRs) should be conducted to allow for more comprehensive assessments of their benefits and harms [65,66,67]; I have already had positive

correspondence with the EMA for access to CSRs for one such product in this regard.

Public and independently funded trials could also be conducted to mitigate potential biases in the reporting of clinical trial outcomes [68,69].

There should be greater consistency in how trial results are interpreted by drug regulators when new clinical trial results of approved anti-obesity products become available, both in the pre- and post-marketing phases. For instance, the results of a large prematurely terminated non-inferiority trial of N-B (n = 8,910) showed that central nervous system adverse events were significantly greater compared with placebo [70]; the authors concluded that the cardiovascular safety of the product remained uncertain and will require “a new adequately powered outcome trial” – this product is presently available. In contrast to this, sibutramine was withdrawn from the market following the results of a post-marketing Sibutramine Cardiovascular Outcome Trial (SCOUT) of comparative sample size (n = 9,800) [71]; the trial results had shown that the risk of serious cardiovascular events was increased with sibutramine. Both studies involved overweight and obese individuals with CVD risk factors. In addition, there were differences in how the harms

from three of the products included in the review were interpreted by the EMA and FDA (see Box 9.1); this resulted in discrepancies in regulatory decisions regarding marketing approval applications. Such inconsistency in results' interpretation within one regulatory agency, and lack of uniformity in harms assessment across regulatory authorities could be due to corporate bias [72].

The investigators in one included study reported that they received an unrestricted educational grant from the drug manufacturer to conduct their trial [31]; however, only two of the authors in the study reported financial relationships with the sponsor. Similar publications of unrestricted grants to institutions for drug research have begun to appear in the literature [73]. Although conflict of interest does not necessarily imply that trials results are biased, there should be greater transparency in the disclosure of financial interests when reporting trial results. A clearer definition of what constitutes a conflict is also required in cases where drug manufacturers provided funding either directly or indirectly to public or not-for-profit institutions for specific research purposes.

Box 9.1: Differences between EMA and the FDA in harms assessment in pre-marketing studies of centrally-acting anti-obesity medicinal products

Medicinal Product	Grounds for refusing approval (EMA)	Risk interpretation/management (FDA)
Lorcaserin	Potential risk of tumours, particularly with long-term use in rats	Risk demonstrated in rats, but not observed in mice
	Potential risk of psychiatric disorders	Observed in supra-therapeutic doses: dose should not exceed 10mg bid; discontinue if depression or suicidal thoughts develop at therapeutic dose
	Potential risk of valvulopathy	Low-potency 5HT2B agonist: avoid combination with serotonergic and dopaminergic drugs that are potent 5-HT2B receptor agonists
Phentermine-topiramate	Risk of long-term psychiatric effects	Avoid alcohol while on medication; reduce dose or stop medication if symptoms continue
	Risk of cognitive defects	Caution when operating hazardous machinery
	Increased heart rate	Clinical significance unclear: monitor heart rate regularly; reduce dose or discontinue if increased heart rate is sustained
	Known teratogenicity of topiramate	Use restricted: available through a limited program under the REMS; distribution only by certified pharmacies
Medicinal product	Risk interpretation/management (EMA)	Grounds for refusing approval (FDA)
Rimonabant*	Actively monitor for signs and symptoms of psychiatric disorders, especially depression. If depression is diagnosed during therapy, stop treatment immediately; monitor and treat patient appropriately	Increased risk of neuropsychiatric adverse reactions, including suicidality

*Withdrawn in Europe in 2007 – within a year of marketing authorization

Abbreviations: EMA: European Medicines Agency; FDA: US Food and Drugs Administration; 5HT: 5-hydroxytryptamine; REMS: Risk Evaluation and Mitigation Strategies

9.5 CONCLUSIONS

Low quality evidence from pivotal clinical trials suggests that centrally-acting anti-obesity medicinal products significantly generate weight losses from baseline compared with placebo. The risks of headache, dizziness, insomnia, hypo- or paraesthesia, hypertension, nausea, vomiting, diarrhoea and constipation are significantly increased with the use of centrally-acting anti-obesity products. The risks of medication discontinuation because of dizziness, nausea and constipation are significantly increased with the use of centrally-acting anti-obesity products. The benefit and harms of presently approved products are no different from those withdrawn from the market at the time of regulatory approval. The quality of the evidence from pivotal clinical trials is variable, and greater consistency in the

reporting of adverse events across journal publications and regulatory documents should be a priority in drug regulation. More clarity about how discontinuations occur is desirable, and CSRs of pivotal trials should be made accessible. Public and independently funded trials will help improve transparency in reporting of trial results.

9.6 Differences between this systematic review and published protocol

Body weight was reported as a primary outcome. The changes in body weight were reported using dichotomous outcomes instead of continuous outcomes. This allowed direct comparison of efficacy with harms outcomes. Discontinuation due to adverse events was reported as a primary outcome, and overall discontinuations reported as a secondary outcome. The GRADE approach was used to assess the quality of evidence and this included 'Summary of findings' tables. Individual adverse events within the gastrointestinal system sub-category were assessed because they are among the most commonly reported adverse events attributed to anti-obesity medicinal products. These were not pre-specified in the published protocol.

9.7 Chapter Summary

- Centrally-acting anti-obesity medicinal products can generate significant reductions in body weight from baseline
- The use of centrally-acting products is also associated with increased risks of adverse and serious adverse events
- Their use is also significantly associated with increased risk of discontinuation because of adverse events
- The high discontinuation rates because of adverse events suggest that patients are likely to have poor adherence to these products, thereby wasting resources
- The quality of the evidence from pivotal trials used to gain marketing authorizations for the products is generally poor
- The benefits and harms of currently available products are no different from those of the withdrawn ones at the time of regulatory approval
- Drug regulatory authorities have not been consistent in their assessment of the benefits and harms of different centrally-acting anti-obesity products, some having been withdrawn and some still being available

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Chapter 10 Summary and recommendations

10.1 What the results of the DPhil research show

Over the last three years of conducting extensive reviews on post-marketing withdrawal patterns, the research results have shown that the decision-making processes to withdraw approved medicinal products from the market because of adverse reactions (or to approve new ones) arise from a complex interplay of scientific, bureaucratic, and financial considerations.

Improvements in pharmacovigilance since 1950 have resulted in quicker detection of adverse reactions caused by approved medicinal products, but there have been no corresponding improvements in how quickly products are withdrawn from the market following reports of harms. The number of withdrawn products is only a small proportion of the overall number of product approvals, suggesting that there has also been considerable effort by drug regulators to ensure that products with unfavourable benefit-to-harm balances are not granted marketing licences. However, the speed with which adverse reactions are reported following regulatory approval of some products strongly suggests selective reporting of harms in the pre-marketing phase.

Anecdotal reports (Level 4 evidence in the Oxford CEBM system) are the most commonly used method for making withdrawal decisions when medicinal products are suspected of causing harms; however, the frequency of use of such reports has reduced over time. Off-target pharmacological effects caused the adverse reactions that resulted in over 95% of the withdrawals that occurred worldwide; the withdrawals were mostly instigated by the manufacturers. Differences in how drug regulatory authorities interpret the evidence for

harms (e.g. how to assign causality) has led to inconsistencies in the post-marketing withdrawal of products across geographical regions. In some countries, there is little or no information on medicinal products that have been withdrawn from the market because of adverse reactions. Harmful products are more likely to remain on the market for longer (and also less likely to be withdrawn) in Africa where pharmacovigilance is weak (lack of functional spontaneous reporting systems). However, there is a paucity of information on the year medicinal products were introduced in most African countries; consequently, the actual extent to which the delays to withdrawal in Africa compare with other continents following adverse reaction reports is uncertain, and needs to be investigated further.

When medicinal products are suspected of causing drug-attributed deaths, the first reports of deaths are almost always reported in Europe or North America. Products that cause deaths are withdrawn from the market quicker if the interval between the first reported adverse reaction (attributed to the product) and first reported death is shorter. Medicinal products are also withdrawn quicker if they caused deaths at therapeutic doses, compared with deaths caused by misuse (overdose). An overwhelming majority of studies have confirmed the association between withdrawn products and fatalities, indicating that the decisions to withdraw those products were justified – the use of algorithms could have led to faster regulatory action, and reduced the numbers of deaths, because the products would have been withdrawn from the market sooner.

When approved medicinal products are suspected of causing adverse reactions in animals, they are likely to be quickly withdrawn if the adverse reactions were mutagenesis or carcinogenesis. Confirmatory studies in humans are seldom conducted when products have been withdrawn from the market because of adverse reactions in animals: when these have

been conducted, the evidence for harms was not consistent with that observed in animals in 80% of instances. Although there are uncertainties about how to extrapolate the results of harms in animals to humans, evidence from animal studies has not been used to make withdrawal decisions in the past 15 years.

There are inconsistencies in the methods used by drug regulatory authorities to approve new medicines, and the evidence demonstrates that there is currently no standard way of determining the benefit-to-harm balance. Some classes of medicinal products are being developed despite evidence that their benefit-to-harm balance are either unfavourable, or are not more effective than similar classes of products already in the market.

The reporting of harms in journal publications is not consistent with what is observed in regulatory documents – reported adverse events rates are generally fewer in journal publications. Even within the same pivotal clinical trials programme for a product, there is inconsistency in the degree to which harms are reported. When pre-marketing pivotal trials report high discontinuation rates because of adverse events, such statistics are largely not considered in evaluating the economic benefits of such new products. Public and independently funded drug clinical trials are hardly ever conducted.

10.2 Limitations of the research approach

Throughout this thesis there have been a number of limitations that have limited the conclusions of this research. These limitations include: the possibility that some products withdrawn from the market because of adverse reactions were missed; an inability to identify all countries where withdrawn medicinal products were approved (or marketed); low-level evidence used for making withdrawal decisions in majority of instances; and lack

of success in soliciting additional clinical trials data from authors of published journal articles.

10.3 Key Recommendations

The findings throughout this thesis means there are a number of recommendations that apply to regulatory authorities, clinical trialists, clinicians, researchers, policy makers and patients. Many of the recommendations cut across these groups, and have been matched to the corresponding DPhil research results:

Results of DPhil Research	Matched recommendations
1. Lower rates of post-marketing withdrawal in Africa compared with other continents	Pharmacovigilance systems should be strengthened in low-resource settings, and established in countries where they are non-existent; all efforts should be made to ensure that the proposed establishment of the Africa Medicines Agency by the WHO in 2018 materialises
2. Inconsistency in withdrawal patterns across geographical regions	Universally accepted algorithms and/or guidelines for confirming drug-adverse event relationships should be developed; whether it is feasible to tailor the algorithms or guidelines to specific settings requires further research
3. Lack of information on launch dates for medicinal products in different countries	A mechanism or database for tracking the sales of approved medicinal products across all geographical regions should be developed and promoted
4. Negative publication bias by drug manufacturers	More active engagement of health professionals and patients in reporting suspected adverse drug reactions should be encouraged
5. Poor reporting of suspected adverse reactions by clinicians	Credits could be given as a reward to enhance reporting of suspected serious adverse reactions. In the UK, for example, practitioners who promptly report any serious unexpected suspected adverse reactions to the MHRA could receive credits through the Quality Outcomes Framework (QOF) system, although this could lead to over-reporting of suspected adverse drug reactions
6. Use of low-level evidence for making withdrawal decisions	The conduct of rapid/ad-hoc systematic reviews should be a priority when serious adverse reactions are suspected; however, case reports are appropriate for making withdrawal decisions in some instances

7. Failure to use frameworks or algorithms to investigate drug-adverse event relationships	Regulatory authorities should be encouraged to use algorithms to determine regulatory courses of action when serious adverse reactions are suspected; temporary suspensions or restrictions could be considered
8. Inconsistency in withdrawal patterns when there is worldwide withdrawal	There should be greater co-ordination across regulatory authorities when adverse reactions are attributed to medicinal products
9. Possible reporting bias in confirmatory studies investigating drug-adverse event associations	Confirmatory studies in humans should be instigated when medicinal products are suspected of causing serious adverse reactions; this could involve publicly and independently funded entities
10. Delays to withdrawal in cases of drug-attributed deaths	When medicinal products are suspected to have caused deaths, more precautionary criteria may be used in determining their withdrawal from the market; e.g., using 90% confidence intervals instead of 95%
11. Regulatory approval of medicinal products with similar mechanisms of actions	Statistical models for determining regulatory approval cut-offs for medicinal products in the same class, and with comparable benefit-harm profiles should be developed
12. High rates of trial discontinuations because of adverse events	Cost-benefit estimates for new medicinal products should take into account the rates of discontinuation owing to adverse events when computing economic models in situations where the events are high – a cut-off point should be developed and promoted
13. Variations in the frequency of reporting of adverse events	There should be consistency in harms reporting across journal publications and regulatory documents, and within pivotal clinical trials programmes of a new product
14. Low quality evidence in pivotal phase III trials of centrally acting anti-obesity medicinal products	The study designs in pivotal trials should be improved – the quality of the evidence from such trials should be taken into consideration when making approval decisions
15. Differences in harms interpretation between EMA and FDA when clinical trials results are available	The methods used by investigators and regulators to adjudicate and classify harms in pivotal clinical trials of medicinal products should be improved
16. Regulatory decisions being influenced by financial considerations	An independent group of experts should be responsible for determining whether new medicinal products should be approved; individuals with vested interests should be excluded from such panels

10.3 Conclusion

This thesis set out to address the lack of evidence-base in the post marketing withdrawal of medicinal products because of suspected harms. This thesis has closed some of this gap by providing a resource base for medicinal products withdrawn from the market by regulatory authorities because of adverse drug reactions.

10.4 Epilogue

During my DPhil, I received several correspondence emails from individuals within and outside academia, and residing across low- to high-income countries, who were concerned about the flaws in current pharmacovigilance methods. I cannot conclude this thesis without including excerpts of one such email from an international colleague, who has testified to drug regulatory committees as an expert witness:

*“...I would suggest that you look to the underlying cause(s) of this problem some of which reside at...others from the most prominent universities including my own are well paid “researchers” and promoters of these drugs...
... if you look at international marketing and regulation you will find that it is unregulated in Africa, Asian and Latin America but it is run out of the...and other...countries. It is a combination of off label and absent side effects.”*

My future research focus will aim to tackle these challenges.

APPENDICES

Appendix 1: Search strategy* lists of accessed sources used to identify medicinal products withdrawn from the market because of adverse reactions

The United Nations (UN) Consolidated List of Products whose consumption and/or sale have been banned, withdrawn, severely restricted, or not approved by governments: Issue 6 (pgs. 5-197); Issue 8 (pgs. 30-264); Issue 12 (pgs. 31-203); and Issue 14 (pgs. 3-26)

W.H.O. Drug Information: Regulatory Matters Section

2014: Vol. 28, Nos 1-4

2013: Vol. 27, Nos 1-4

2012: Vol. 26, Nos 1-4

2011: Vol. 25, Nos 1-4

2010: Vol. 24, Nos 1-4

2009: Vol. 23, Nos 1-4

2008: Vol. 22, Nos 1-4

2007: Vol. 21, Nos 1-4

2006: Vol. 20, Nos 1-4

2005: Vol. 19, Nos 1-4

2004: Vol. 18, Nos 1-4

2003: Vol. 17, Nos 1-4

2002: Vol. 16, Nos 1-2

2001: Vol. 15, Nos 1-4

2000: Vol. 14, Nos 1-4

1999: Vol. 13, Nos 1-4

1998: Vol. 12, Nos 1-4

1997: Vol. 11, Nos 1-4

1996: Vol. 10, Nos 1-4

1995: Vol. 9, Nos 1-4

1994: Vol. 8, Nos 1-4

1993: Vol. 7, Nos 1-2

1992: Vol. 6, Nos 1-4

1991: Vol. 5, Nos 1-3

1990: Vol. 4, Nos 1-4

1989: Vol. 3, Nos 1-4

1988: Vol. 2, Nos 1-4

1987: Vol. 1, Nos 1-3

W.H.O. Pharmaceuticals Newsletters: Regulatory Matters Section

2014: Newsletter Nos. 1-6

2013: Newsletter Nos. 1-6

2012: Newsletter Nos. 1-6

2011: Newsletter Nos. 1-6

2010: Newsletter Nos. 1-6

2009: Newsletter Nos. 1-5

2008: Newsletter Nos. 1-6

2007: Newsletter Nos. 1-6

2006: Newsletter Nos. 1-6

2005: Newsletter Nos. 1-5

2004: Newsletter Nos. 1-6

2003: Newsletter Nos. 1-5

2002: Newsletter Nos. 1-4

2001: Newsletter Nos. 1-3

2000: Newsletter Nos. 1-4

1999: Newsletter Nos. 1-12

1998: Newsletter Nos. 1-12

1997: Newsletter Nos. 1-12

European Medicines Agency (EMA)

Find Medicine > Human Medicines > “Include: withdrawn post-approval, suspended, refused”

Find Medicine > Human Medicines > Referrals > Browse by topic > Safety issues > “Include: Opinion provided by Committee for Medicinal Products for Human Use, European Commission final decision”

US Food and Drug Administration (FDA)

Home > Safety > Recalls, Market Withdrawals, & Safety Alerts > Archive for Recalls, Market Withdrawals & Safety Alerts

The UK Medicines and Healthcare products Regulatory Agency (MHRA)

Home > Drug safety update > Therapeutic area [select all] > Published after 1950 > “search withdrawn”

Stephens' Detection of New Adverse Drug Reactions, 5th edition, 2004 (pgs. 667-702)

Pharmaceutical Manufacturing Manual, 3rd edition, 2006

The Merck Index, 15th edition, 2013

Meyler's Side Effects of Psychiatric Drugs 1st edition, 2009

Meyler's Side Effects of Cardiovascular Drugs 1st edition, 2009

PubMed/Medline search strategy

“[Drug name]” AND “toxicity”

“[Drug name]” AND “adverse”

“[Drug name]” AND “side effect”

“[Drug name]” AND “poison”

“[Drug name]” AND “fatal*”

“[Drug name]” AND “fatality”

“[Drug name]” AND “death”

“[Drug name]” AND “withdrawal”

“[Drug name]” AND “withdrawn”

“[Drug name]” AND “recall”

“[Drug name]” AND “voluntary recall”

“[Drug name]” AND “banned”

“[Drug name]” AND “prohibited”

“[Drug name]” AND “remov*”

“[Drug name]” AND “discontinued”

“[Drug name]” AND “refus*”

[Sort by level of evidence: meta-analysis/systematic review > observational studies > case series/reports]

Google Scholar search strategy

Find articles with all of the words [drug name] > with the exact phrase [adverse or toxic or side effect or fatal or death or withdrawn or withdrawal or recall or banned or prohibited or discontinued or suspended] > Return articles dated between 1950-2015
[Sort by level of evidence: meta-analysis/systematic review > observational studies > case series/reports]

*Both pharmacological and trade names were used to search sources

List of English Language drug regulatory websites searched for information on medicinal products withdrawn from the market because of adverse drug reactions

1. **Australia:** Therapeutic Goods Administration (TGA): <https://www.tga.gov.au/>
2. **Bahamas:** Bahamas National Drug Agency (BNDA): <http://www.corp.phabahamas.org/hospitals-services/bnda/>
3. **Bhutan:** Drug Regulatory Authority: <http://dra.gov.bt/>
4. **Botswana:** Ministry of Health, Republic of Botswana: <http://www.moh.gov.bw/> (no Medicines Regulatory Authority)
5. **Canada:** Health Canada Drug Product Database (DPD): <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php>
6. **Europe:** European Medicines Agency (EMA): <http://www.ema.europa.eu/ema/>
7. **Gambia:** Medicine Regulatory Authority newly established
8. **Ghana:** Ghana Food and Drugs Authority (FDA): <http://www.fdaghana.gov.gh/>
9. **India:** Central Drugs Standard Control Organization (CDSCO): <http://www.cdsc.nic.in/forms/Default.aspx>
10. **Jamaica:** Ministry of Health, Kingston, Jamaica: <http://moh.gov.jm/?s=drug+regulation>
11. **Kenya:** Pharmacy and Poisons Board, Kenya: <http://pharmacyboardkenya.org/>
12. **Liberia:** Liberian Medicines Health Products Regulatory Authority: https://healthresearchweb.org/en/liberia/research_regulation_4284 (no drug information; email delivery system failed)
13. **Malta:** Malta Medicines Authority: <http://www.medicinesauthority.gov.mt/home?l=1>
14. **Namibia:** Namibia Medicines Regulatory Council: <http://www.nmrc.com.na/>
15. **New Zealand:** New Zealand Medicines and Medical Devices Safety Authority: <http://www.medsafe.govt.nz/index.asp>
16. **Nigeria:** National Agency for Food and Drug Administration and Control (NAFDAC): <http://www.nafdac.gov.ng/>
17. **Pakistan:** Drug Regulatory Authority of Pakistan (DRAP): <http://www.dra.gov.pk/gop/index.php?q=aHR0cDovLzE5Mi4xNjguNzAuMTM2L2RyYXAv>
18. **Philippines:** Food and Drug Administration, Philippines (FDA): <http://www.fda.gov.ph/>

19. **Rwanda:** Ministry of Health, Republic of Botswana: <http://www.moh.gov.rw/index.php?id=2> (no Medicines Regulatory Authority)
20. **Sierra Leone:** Pharmacy Board of Sierra Leone: <http://www.pharmacyboard.gov.sl/>
21. **Singapore:** Health Sciences Authority: <http://www.hsa.gov.sg/content/hsa/en.html>
22. **South Africa:** South Africa Medicines Control Council (MCC): <http://www.mccza.com/>
23. **Sri Lanka:** Cosmetics, Devices and Drug Regulatory Authority: <http://www.cdda.gov.lk/>
24. **Tanzania:** Tanzania Food and Drugs Authority (TFDA): <http://www.tfda.or.tz/>
25. **Thailand:** Food and Drug Administration, Thailand: <http://www.fda.moph.go.th/eng/index.stm>
26. **Trinidad and Tobago:** Ministry of Health, Trinidad and Tobago:
<http://www.health.gov.tt/sitepages/default.aspx?id=93>
27. **Uganda:** National Drug Authority: <http://www.nda.or.ug/>
28. **United Kingdom:** Medicines and Healthcare products Regulatory Agency (MHRA):
<https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency>
29. **USA:** Food and Drug Administration (FDA): <http://www.fda.gov/>
30. **Zambia:** Pharmaceutical Regulatory Authority (PRA): <http://www.zamra.co/>
31. **Zimbabwe:** Medicines Control Authority of Zimbabwe (MCAZ): <http://www.mcaz.co.zw/>

Appendix 2: Search terms specifically used to identify analgesic medicinal products withdrawn from the market because of adverse reactions

European Medicines Agency (EMA)

Find Medicine > Human Medicines > Browse by therapeutic area > Diseases > Symptoms and general pathology > Signs and Symptoms > Pain > “Include: withdrawn post-approval, suspended”

PubMed search strategy

“[Analgesic drug name]” AND “toxicity”
“[Analgesic drug name]” AND “adverse”
“[Analgesic drug name]” AND “side effect”
“[Analgesic drug name]” AND “poison”
“[Analgesic drug name]” AND “fatal*”
“[Analgesic drug name]” AND “fatality”
“[Analgesic drug name]” AND “death”
“[Analgesic drug name]” AND “withdrawal”
“[Analgesic drug name]” AND “withdrawn”
“[Analgesic drug name]” AND “recall”
“[Analgesic drug name]” AND “voluntary recall”
“[Analgesic drug name]” AND “banned”
“[Analgesic drug name]” AND “prohibited”
“[Analgesic drug name]” AND “remov*”
“[Analgesic drug name]” AND “discontinued”
“[Analgesic drug name]” AND “refus*”
[Sort by Publication date]

Google Scholar search strategy

Find articles with all of the words [analgesic drug name] > with the exact phrase [adverse or toxic or side effect or fatal or death or withdrawn or withdrawal or recall or banned or prohibited or discontinued or suspended] > Return articles dated between 1950-2016

*These sources were also used to document data on launch year, year of first adverse reaction report, year of first withdrawal, country or countries of withdrawal, and the mechanism through which the adverse reaction occurred.

Appendix 3: Search terms specifically used to identify anti-obesity medicinal products withdrawn from the market because of adverse reactions

European Medicines Agency (EMA)

Find Medicine > Human Medicines > Browse by therapeutic area > Diseases > Nutritional and Metabolic Diseases > Nutrition Disorders > Overnutrition > Obesity > “Include: withdrawn post-approval, suspended”

United States Food and Drug Administration

Drugs@FDA: FDA Approved Drug Products > Search by Drug Name, Active Ingredient, or Application Number > [Marketing Status] or [Approval Date(s) and History, Letters, Labels, Reviews]

Medline search strategy

“[Anti-obesity drug name]” AND “toxicity”
“[Anti-obesity drug name]” AND “adverse”
“[Anti-obesity drug name]” AND “side effect”
“[Anti-obesity drug name]” AND “poison”
“[Anti-obesity drug name]” AND “fatal*”
“[Anti-obesity drug name]” AND “fatality”
“[Anti-obesity drug name]” AND “death”
“[Anti-obesity drug name]” AND “withdrawal”
“[Anti-obesity drug name]” AND “withdrawn”
“[Anti-obesity drug name]” AND “recall”
“[Anti-obesity drug name]” AND “voluntary recall”
“[Anti-obesity drug name]” AND “banned”
“[Anti-obesity drug name]” AND “prohibited”
“[Anti-obesity drug name]” AND “remov*”
“[Anti-obesity drug name]” AND “discontinued”
“[Anti-obesity drug name]” AND “refus*”
[Sort by Publication date]

Google Scholar search strategy

Find articles with all of the words [anti-obesity drug name] > with the exact phrase [adverse or toxic or side effect or fatal or death or withdrawn or withdrawal or recall or banned or prohibited or discontinued or suspended] > Return articles dated between 1950-2016.

Appendix 4: Profiles of 23 centrally-acting anti-obesity medicinal products withdrawn over the last 50 years because of adverse drug reactions

Amfepramone

- Mechanism of action: serotonin-norepinephrine-dopamine releasing agent
- Introduced as an anti-obesity agent in 1957
- Pickwickian syndrome attributed to its use first reported in 1974 [1]
- Withdrawn in several countries in 1974
- Fatal case of primary pulmonary arterial hypertension attributed to its use reported in the UK in 1995 [2]
- Reintroduced in the UK in 2002 with restrictions

Amfetamine

- Mechanism of action: serotonin-norepinephrine-dopamine releasing agent
- Initially used for narcolepsy
- Observed that patients with narcolepsy lost weight while taking amfetamine
- Approved in 1939 as an obesity treatment when the results of a trial showed that it was effective [3]
- Over dosage with its use as an anorectic first reported in 1957 [4]
- Several studies showed that it had a potential for abuse [5]
- Withdrawn as an anti-obesity agent in 1973
- Still largely consumed illegally as a psychostimulant
- Several cases of deaths from its misuse have been published since its withdrawal [6]

Aminorex

- Mechanism of action: serotonin reuptake inhibitor
- First introduced in 1962
- Became available within three years of introduction as an over-the-counter weight loss pill
- Between 1965 and 1972, there was a large increase in the incidence of primary pulmonary hypertension [7]
- The pulmonary hypertension epidemic ended in 1972 following withdrawal of aminorex from the market

Benfluorex

- Mechanism of action: serotonin reuptake inhibitor
- Approved in 1976 as an add-on treatment in obese patients with diabetes mellitus
- Cases of valvulopathy attributed to its use began to appear from 2003
- Withdrawn in 2009 following an epidemic of valvulopathy attributed to its use

- Several deaths reported
- To date over 3000 hospitalizations and at least 1300 deaths attributed to its use in France alone [8]

Chlorphentermine

- Mechanism of action: serotonin reuptake inhibitor
- Approved for obesity treatment in 1962 based on the results of short-term clinical trials [9,10]
- In 1969, animal studies began to emerge consistently suggesting an association with an increased risk of pulmonary phospholipidosis [11,12]
- Withdrawn in the same year
- No case reports of pulmonary hypertension in humans

Clobenzorex

- Mechanism of action: serotonin-norepinephrine-dopamine releasing agent
- Approved in 1966 as an appetite suppressant
- Cases of drug abuse and psychiatric adverse reactions appeared from 1986 [13]
- Withdrawn from the market in 2000

Cloforex

- Mechanism of action: serotonin reuptake inhibitor
- A prodrug of chlorphentermine (see above)
- Introduced for obesity treatment in 1965
- Cases of suspected pulmonary hypertension attributed to its use reported in Germany
- Animal studies suggested an association with pulmonary vasculopathy [14]
- Withdrawn in 1967

Dexfenfluramine

- Mechanism of action: serotonin reuptake inhibitor
- Approved in 1995 as an anti-obesity agent
- Several cases of cardiovascular adverse reactions reported shortly after [15]
- Withdrawn within two years of approval
- Cases of pulmonary hypertension attributed to its use were reported before regulatory approval [16,17]

Fenbutrazate

- Mechanism of action: norepinephrine-dopamine releasing agent
- Approved for use in obesity in 1957
- Cases of drug abuse reported in France [18]
- First withdrawn in 1969, and then withdrawn in all of Europe in 1995 [19]

Fenfluramine

- Mechanism of action: serotonin reuptake inhibitor
- First approved in 1973
- Reports of pulmonary hypertension first appeared in 1981
- Several other case reports subsequently published
- Epidemiological studies showed an association between fenfluramine and pulmonary hypertension [20]
- Withdrawn worldwide in 1997

Fenproporex

- Mechanism of action: norepinephrine releasing agent
- First approved as an anti-obesity drug in 1966
- Cases of drug abuse attributed to its use first reported in 1997 [21]
- Withdrawn in Europe and Brazil within two years of the initial reports
- A recent systematic review evidence concluded that its abuse potential and amphetamine-like adverse effects remain a cause of concern [22]

Levamisfetamine

- Mechanism of action: serotonin-norepinephrine-dopamine releasing agent
- Introduced in 1944 as an anti-obesity agent
- Within 10 years of approval, cases of psychiatric reactions due to misuse were reported [23]
- Several cases of abuse and dependence (with psychoses) were subsequently reported [24]
- Withdrawn from the market in 1970

Mazindol

- Mechanism of action: norepinephrine-dopamine releasing agent
- Approved as an anti-obesity drug in 1970
- Neurotoxicity due to an interaction with lithium reported in 1980 [25]
- Several cases of testicular pain attributed to its use also reported [26]
- Further cases of psychiatric adverse reactions subsequently published [27]
- Withdrawn from the market in 1987

Meferonex

- Mechanism of action: serotonin-norepinephrine-dopamine releasing agent
- Approved for treatment of obesity in 1966
- Serious neuropsychiatric adverse reactions due to abuse reported in 1995
- Withdrawn in Europe four years later [28]

Metamfetamine

- Mechanism of action: serotonin-norepinephrine-dopamine releasing agent

- First approved for obesity treatment in 1944
- Cases of abuse-related suspected psychiatric adverse reactions first appeared 10 years later [29]
- Several cases of abuse resulting in neurotoxicity or cardiotoxicity subsequently reported
- By 1968 reports of deaths from its use had appeared [30]
- A further case series of harms was reported two years later [31]
- Withdrawn in 1973

Phendimetrazine

- Mechanism of action: Norepinephrine-dopamine releasing agent
- First approved for obesity management in 1961
- Cases of abuse were first reported in 1979 [32]
- Withdrawn in 1982

Phenmetrazine

- Mechanism of action: norepinephrine-dopamine releasing agent
- First approved for management of obesity in 1956
- Cases of drug abuse and addiction appeared within three years of approval [33]
- Withdrawn as an anti-obesity agent in 1982

Phentermine

- Mechanism of action: norepinephrine-dopamine releasing agent
- First approved in 1959
- Several cases of lung phospholipidosis in animals and humans reported thereafter
- Reports of deaths began to appear in 1974 [34]
- Withdrawn from most countries where it was marketed in 1981
- Still available for short-term management of obesity in the USA

Phenylpropanolamine (norpseudoephedrine)

- Mechanism of action: norepinephrine-dopamine releasing agent
- Initially used as a nasal decongestant
- Introduced in 1947 for obesity
- Cases of psychosis attributed to its use began to appear in 1966 [35]
- Cases of intracranial haemorrhage reported in 1985 [36]
- Withdrawn within two years of the reports of haemorrhages

Pipradrol

- Mechanism of action: norepinephrine-dopamine reuptake inhibitor
- Approved as an adjunct to dietary management of obesity in 1953
- Associated with several cases of drug abuse [37]

- Withdrawn as an anti-obesity agent in 1982
- Still available for management of ADHD and narcolepsy

Pyrovalerone

- Mechanism of action: norepinephrine-dopamine releasing agent
- Introduced as a weight loss drug in 1974
- Within a year of introduction, cases of abuse started to appear [38]
- Withdrawn as an anti-obesity 1979 owing to problems associated with abuse and dependence
- A derivative, methylenedioxypyrovalerone (MDPV), is marketed illegally as a designer recreational drug under the name of “Bath Salts” [39]

Rimonabant

- Mechanism of action: cannabis CB₁ receptor antagonist/inverse agonist
- Approved in Europe in 2006 for obesity treatment
- Within 1 year of approval, cases of severe psychiatric adverse reactions were reported [40]
- 5 deaths attributed to its use in the UK
- Withdrawn in 2007

Sibutramine

- Mechanism of action: serotonin-norepinephrine reuptake inhibitor
- Approved in 1997 in the USA and Europe in 2001
- Within a year of its European approval, serious cardiovascular adverse reactions were reported, resulting in temporary withdrawal in Italy [41]
- Several cases of severe cardiovascular adverse reactions, including deaths, subsequently reported [42]
- Withdrawn in Europe and the USA in 2010

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- 26 McEwen J, Meyboom RH. Testicular pain caused by mazindol. *Br Med J (Clin Res Ed)* 1983; 287(6407): 1763-4.
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- 30 Cravey RH, Baselt RC. Methamphetamine poisoning. *J Forensic Sci Soc* 1968; 8(2): 118-20.
- 31 Smith DE, Fischer CM. An analysis of 310 cases of acute high-dose methamphetamine toxicity in Haight-Ashbury. *Clin Toxicol* 1970; 3(1): 117-24.
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- 35 Kane FJ Jr, Green BQ. Psychotic episodes associated with the use of common proprietary decongestants. *Am J Psychiatry* 1966; 123(4): 484-7.
- 36 Kikta DG, Devereaux MW, Chandar K. Intracranial hemorrhages due to phenylpropanolamine. *Stroke* 1985; 16(3): 510-2.
- 37 Goldberg L. Drug abuse in Sweden. *Bull Narcot* 1968; 1: 1-31. <http://www.lycaeum.org/research/researchpdfs/1722.pdf> [Last accessed 20th July, 2016].
- 38 Deniker P, Lôo H, Cuche H, Roux JM. Utilisation abusive par les toxicomanes d'un psycho-stimulant, la pyrovalérone [Abuse of pyrovalerone by drug addicts.] *Ann Med Psychol (Paris)* 1975; 2(4): 745-8.
- 39 Prosser JM, Nelson LS. The toxicology of bath salts: a review of synthetic cathinones. *J Med Toxicol*. 2012; 8(1): 33-42.
- 40 Gadde KM. Effect of rimonabant on weight and cardiometabolic risk factors. *JAMA*. 2006 Aug 9;296(6):649-50; author reply 650-1.
- 41 Anonymous. Italy suspends sibutramine licence. *Pharm J* 2002; 268(7190): 385-391.
- 42 Woollorton E. Obesity drug sibutramine (Meridia): hypertension and cardiac arrhythmias. *CMAJ*. 2002;166(10):1307-8.

Appendix 5: Search strategies used to identify total deaths and confirmatory studies investigating the drug-adverse event association for medicinal products withdrawn because of drug-attributed deaths*

PubMed search strategy

“[Drug name]” AND “toxicity”

“[Drug name]” AND “adverse”

“[Drug name]” AND “side effect”

“[Drug name]” AND “poison”

“[Drug name]” AND “fatal*”

“[Drug name]” AND “fatality”

“[Drug name]” AND “death”

[Sort by Publication date]

[Sort by level of evidence: meta-analysis/systematic review > observational studies > case series/reports]

Google Scholar search strategy

Find articles with all of the words [Drug name] > with the exact phrase [adverse or toxic or side effect or fatal or death] > Return articles dated between 1950-2015

[Sort by level of evidence: meta-analysis/systematic review > observational studies > case series/reports]

W.H.O. Pharmaceuticals Newsletters: Regulatory Matters Section: 1997 – 2016

W.H.O. Drug Information: Regulatory Matters Section: 1997 - 2016

Stephens’ Detection of New Adverse Drug Reactions, 5th edition, 2004 (pgs. 667-702)

*Both pharmacological and trade names were used to search sources

Appendix 6: A proposed strategy for regulatory action when a new serious adverse reaction is suspected: (from Aronson JK, Price D, Ferner RE. A strategy for regulatory action when new adverse effects of a licensed product emerge. Drug Saf. 2009; 32(2): 91-8)*

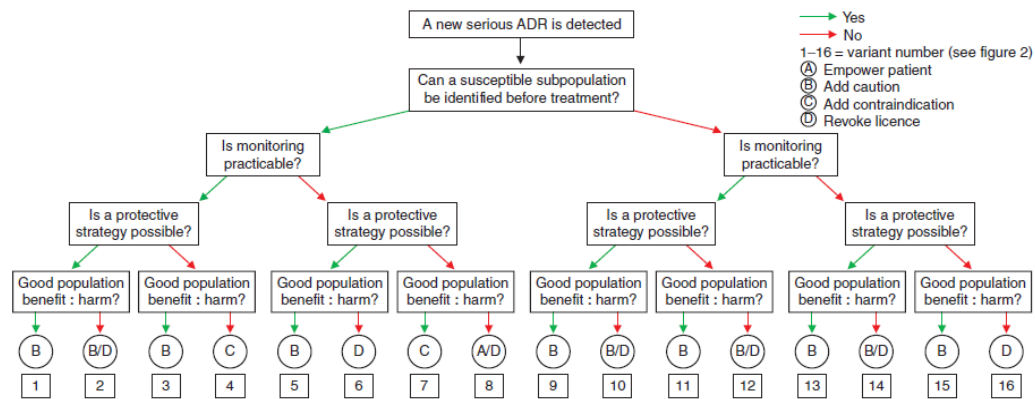


Fig. 1. A regulatory strategy based on individual susceptibility, the distinguishability of a subgroup, the availability of a monitoring strategy, the availability of a protective strategy, and the population benefit-to-harm balance. **ADR** = adverse drug reaction.

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Drug Safety 2009; 32 (2)

*Figure 2 referred to in the schematic diagram has not been included in the appendix file because it describes examples of regulatory actions following new serious adverse reaction reports. Variant 1-16 refers to the final course of regulatory action as shown in the chart.

Appendix 7: Links to regulatory documents used for assessing information on adverse events for pivotal trials of centrally-acting anti-obesity medicinal products

LORCASERIN

European Medicines Agency

Committee for Medicinal Products for Human Use (CHMP). Assessment report: Belviq. International non-proprietary name: Lorcaserin. Procedure No. EMEA/H/C/002597. 17 January 2013 EMA/CHMP/15137/2013 Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Application_withdrawal_assessment_report/human/002597/WC500148196.pdf [Last accessed 15th December, 2016]

U.S. Food and Drug Administration

Lorcaserin Hydrochloride. Briefing Document for FDA Advisory Committee Meeting. 06 April 2012. Available at: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM303200.pdf> [Last accessed 15th December, 2016]

FDA Briefing Document. NDA 22529. Lorcaserin Hydrochloride Tablets, 10 mg Sponsor: Arena Pharmaceuticals Endocrinologic and Metabolic Drugs Advisory Committee Meeting – May 10, 2012. Available at: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM303198.pdf> [Last accessed 15th December, 2016]

NALTREXONE-BUPROPION

European Medicines Agency

Committee for Medicinal Products for Human Use (CHMP). Mysimba (naltrexone/bupropion). Procedure No. EMEA/H/C/003687. Applicant: Orexigen Therapeutics Ireland Limited. Assessment report for an initial marketing authorisation application. 18 December 2014 EMA/805547/2015. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003687/WC500185582.pdf [Last accessed 18th December, 2015]

U.S. Food and Drug Administration

FDA Briefing Document. NDA 200063. Contrave (Naltrexone 4mg, 8mg/Bupropion HCL 90mg extended release tablet). Sponsor: Orexigen Therapeutics Inc. Advisory Committee – December 7, 2010. Available at:

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM235671.pdf> [Last Accessed 18th December, 2016]

PHENTERMINE-TOPIRAMATE

European Medicines Agency

Committee for Medicinal Products for Human Use (CHMP). Assessment report. Qsiva. International non-proprietary name: Phentermine/topiramate. Procedure No.

EMA/H/C/002350/0000. 21 February 2013 EMA/CHMP/108692/2013. Available at:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002350/WC500144300.pdf [Last accessed 20th December, 2016]

U.S. Food and Drug Administration

VI-0521 (QNEXA®) ADVISORY COMMITTEE BRIEFING DOCUMENT NDA 022580 Endocrinologic and Metabolic Drugs Advisory Committee Meeting February 22, 2012. Available at:

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM292317.pdf> [Last accessed 22nd December, 2016]

VI-0521 (QNEXA®) ADVISORY COMMITTEE BRIEFING DOCUMENT NDA 022580 Endocrinologic and Metabolic Drugs Advisory Committee Meeting July 15, 2010. Available at:

<http://www.fda.gov/downloads/advisorycommittees/.../drugs/.../ucm218821.pdf> [Last accessed 22nd December, 2016]

U.S. Food and Drug Administration. Notice: Archived Document. Available at:

<http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm218824.pdf> [Last accessed 22nd December, 2016]

RIMONABANT

U.S. Food and Drug Administration

SR141716 ZIMULTI (rimonabant). NDA 21-888. Briefing Information for FDA Advisory Committee Meeting Department: Regulatory Development 10 May 2007. Available at: <http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4306b1-01-sponsor-backgrounder.pdf> [Last accessed 23rd December, 2016]

FDA Briefing Document NDA 21-888 Zimulti (rimonabant) Tablets, 20 mg Sanofi Aventis Advisory Committee – June 13, 2007. Available at: <http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4306b1-fda-backgrounder.pdf> [Last accessed 23rd December, 2016]

SIBUTRAMINE

U.S. Food and Drug Administration

Center for Drug Evaluation and Research. Application number: 020632. Administrative documents. Part 4. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/97/020632a_administr_thru_corr.pdf [Last accessed 27th December, 2016]

Advisory Committee Briefing Document for Meridia® (sibutramine hydrochloride monohydrate). Endocrinologic and Metabolic Drugs Advisory Committee Meeting on 15 September 2010. Available at: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM225573.pdf> [Last accessed 27th December, 2016]

Center for Drug Evaluation and Research. Approval package for Application number: 020632. Approval date: 11/22/97. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/97/020632a_aplthr_thr_%20mor.pdf [Last accessed 13th December, 2016]

Appendix 8: Identification matching for pivotal clinical trials of centrally acting anti-obesity medicinal products approved for use in Europe and the USA since 1995

Medicinal product	Regulatory ID	Trial ID	PubMed ref. (PMID)	Journal ID
Lorcaserin	BLOOM (APD356-009)	NCT00395135	20647200	Smith 2010
	BLOOM-DM (APD356-010)	NCT00603291	22421927	O'Neil 2012
	BLOSSOM (APD356-010)	NCT00603902	21795446	Fidler 2011
Naltrexone/bupropion	NB-301	NCT00532779	20673995	Greenway 2010
	NB-302	NCT00456521	20559296	Wadden 2011
	NB-303	NCT00567255	23408728	Apovian 2013
	NB-304	NCT00474630	24144653	Hollander 2013
Phentermine/topiramate	OB-301	NCT00563368	24136928	Aronne 2013
	OB-302	NCT00554216	22051941	Allison 2011
	OB-303	NCT00553787	21481449	Gadde 2011
Rimonabant	EFC4735	NCT00029835	16291982	Després 2005
	EFC4733	NCT00386061	15836887	Van Gaal 2005
	EFC4736	NCT00029848	17098084	Scheen 2006
	EFC4743	NCT00029861	16478899	Pi-Sunyer 2009
Sibutramine	BPI 852	None	10102256	Bray 1999
	SB 1047	None	11407998	Smith 2001

Appendix 9: Support for judgements of risk of bias

Allison 2011

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Pseudo-random number generator: not truly random because it is completely determined by a relatively small set of initial values
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias)	Low risk	The study drug and placebo were visually indistinguishable. All study participants, study physicians, site staff, and sponsor representatives involved in the study conduct were blinded to patient assignment until after the trial was complete
Blinding of outcome assessment (detection bias)	Unclear risk	There was an independent, unblinded data and safety monitoring board
Incomplete outcome data (attrition bias)	Low risk	Safety analyses were conducted on all randomized subjects who received 1 dose of study drug; no significant differences in drop-out rates between groups
Selective reporting (reporting bias)	Unclear risk	High drop-out rates; outcomes reported as specified in methods
Other bias	High risk	All study authors had financial ties with sponsor

Apovian 2013

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Interactive voice response system
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Unclear risk	"Matching placebo"
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Unclear risk	the safety population included all randomized participants who took >1 tablet of study drug and had 1 investigator contact/assessment at any time after the start of study treatment
Selective reporting (reporting bias)	Unclear risk	High drop-out rates; outcomes reported as specified in methods
Other bias	High risk	All authors had financial ties with the drug sponsor

Aronne 2013

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias)	Low risk	Study drug capsules were masked to look identical for all drugs and doses. Study subjects, staff, and sponsors were masked to assignment until after the trial was complete.
Blinding of outcome assessment (detection bias)	Unclear risk	Not specified
Incomplete outcome data (attrition bias)	Low risk	Safety analyses were conducted on all randomized subjects who received 1 dose of study drug; no significant differences in drop-out rates between groups
Selective reporting (reporting bias)	Unclear risk	High drop-out rates; outcomes reported as specified in methods
Other bias	High risk	All authors had financial ties with the study sponsor

Bray 1999

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization sequence
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias)	Unclear risk	Not specified
Blinding of outcome assessment (detection bias)	Unclear risk	Not specified
Incomplete outcome data (attrition bias)	Unclear risk	For the analyses of safety information, all observed data were evaluated
Selective reporting (reporting bias)	Unclear risk	High drop-out rates; outcomes reported as specified in methods
Other bias	High risk	Authors had financial ties with the drug sponsor.

Despres 2005

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified

Blinding of participants and personnel (performance bias)	Unclear risk	Not specified
Blinding of outcome assessment (detection bias)	Low risk	Independent, unblinded data safety monitoring board comprising five permanent members. At each meeting of the data safety monitoring board, it was mandatory to have at least three permanent independent members, including a clinician, a safety expert, and a statistician.
Incomplete outcome data (attrition bias)	Low risk	All randomised subjects included in safety analyses. Reasons for drop-outs reported
Selective reporting (reporting bias)	Unclear risk	High drop-out rates; outcomes reported as specified in protocol
Other bias	High risk	All authors had financial ties to the drug sponsor

Fidler 2011

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomization code was generated programmatically by a statistician not directly involved with the study
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias)	Unclear risk	Appearance and packaging of active and placebo products not reported
Blinding of outcome assessment (detection bias)	Unclear risk	The randomization code was not broken until after database lock. Each echocardiogram was independently read in a blinded fashion by two cardiologists with the primary reader for each patient remaining constant. Differences in interpretation were adjudicated by a third cardiologist.
Incomplete outcome data (attrition bias)	Unclear risk	All randomized patients with at least one dose included in safety analysis. Significantly greater withdrawals in the placebo group vs lorcaserin (769/1601 vs 1015/2402; $p = 0.0003$).
Selective reporting (reporting bias)	Unclear risk	High drop-out rates; outcomes reported as specified in methods
Other bias	High risk	5 authors were employees of the sponsor, and 2 authors were advisors to the sponsor

Gadde 2011

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated algorithm that was implemented through an interactive voice response system
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias)	Low risk	Study drugs were administered as capsules that were identical in size and appearance. Investigators, patients, and study sponsors were masked to treatment assignment

Blinding of outcome assessment (detection bias)	Unclear risk	Not specified
Incomplete outcome data (attrition bias)	Unclear risk	All randomized participants who received at least one dose of medication were included in safety analysis; drop-out rates were significantly greater in the placebo group (429/994 vs 514/1493; $p < 0.0001$)
Selective reporting (reporting bias)	Unclear risk	High drop-out rates; outcomes reported as specified in methods
Other bias	High risk	All authors have had financial ties with either the sponsor or other drug companies

Greenway 2010

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised, computer-generated, web-based system
Allocation concealment (selection bias)	Low risk	Participant enrolment and assignment to trial groups was done by an automated system
Blinding of participants and personnel (performance bias)	Low risk	Active drug and placebo tablets were identical in appearance. Study site personnel, participants, and the study team were masked to treatment assignment; blinding was maintained apart from in an emergency
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	All participants who received at least 1 dose of medication included in ITT analysis. No significant differences in drop-out rates between groups
Selective reporting (reporting bias)	Unclear risk	High drop-out rates; outcomes reported as specified in methods
Other bias	High risk	All study authors have, or have had financial ties with the study sponsor

Hollander 2013

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel	Unclear risk	Matching placebo: Not specified whether identical in appearance, shape or taste

(performance bias)		
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	Safety analyses were performed on all randomized participants who took one or more tablets of the study drug and had at least one contact or assessment with the investigative site at any time after beginning the study. No significant difference in drop-out rates between groups
Selective reporting (reporting bias)	Unclear risk	High drop-out rates; outcomes reported as specified in methods
Other bias	High risk	All authors had financial ties with the study sponsor

O'Neil 2012

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias)	Unclear risk	Patients, investigators, and sponsors remained blinded to treatment assignments throughout the trial. Appearance of interventions not specified
Blinding of outcome assessment (detection bias)	Unclear risk	Patients, investigators, and sponsors remained blinded to treatment assignments throughout the trial
Incomplete outcome data (attrition bias)	Low risk	Safety analyses were performed on all randomized participants who took one or more tablets of the study drug
Selective reporting (reporting bias)	Unclear risk	High drop-out rates; outcomes reported as specified in protocol
Other bias	High risk	All authors had affiliation with drug sponsor

Pi-Sunyer 2006

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Pre-defined block randomisation
Blinding of participants and personnel (performance bias)	Unclear risk	Not specified
Blinding of outcome assessment (detection bias)	Unclear risk	Not specified
Incomplete outcome data (attrition bias)	Unclear risk	The 1-year modified intent-to-treat (ITT) population was defined as all randomized patients who received at least 1 dose of the double-

		blind study drug during the first year and had at least 1 postbaseline trial assessment
Selective reporting (reporting bias)	Unclear risk	High drop-out rates; outcomes reported as specified in protocol
Other bias	High risk	Two authors have had financial relationships with sponsor

Scheen 2006

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Interactive voice response system
Allocation concealment (selection bias)	Low risk	Centrally generated block randomisation
Blinding of participants and personnel (performance bias)	Unclear risk	Not specified
Blinding of outcome assessment (detection bias)	Low risk	Safety assessment was done regularly by an independent data safety and monitoring board and included standard adverse event reporting, vital signs, pulse-rate-corrected QT interval, and the Hospital Anxiety and Depression (HAD) scale
Incomplete outcome data (attrition bias)	Unclear risk	modified ITT; reasons for discontinuations reported
Selective reporting (reporting bias)	Unclear risk	High drop-out rates; outcomes reported as specified in protocol
Other bias	High risk	All authors had financial relationships with the sponsor

Smith 2001

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	Prepackaged identical capsules
Blinding of participants and personnel (performance bias)	Unclear risk	Not specified whether appearance
Blinding of outcome assessment (detection bias)	Unclear risk	Not specified
Incomplete outcome data (attrition bias)	Unclear risk	There was incomplete reporting of event rates
Selective reporting (reporting bias)	High risk	Adverse event and serious adverse event rates not reported
Other bias	High risk	COIs not declared. The authors reported the sponsors as the competing interest

Smith 2010

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Interactive Voice Response System
Allocation concealment (selection bias)	Low risk	Interactive Voice Response System
Blinding of participants and personnel (performance bias)	Unclear risk	Colour, taste and appearance of intervention and placebo not specified
Blinding of outcome assessment (detection bias)	Unclear risk	Only echocardiographic assessments were reported as blinded. Randomization code was not broken until after database lock
Incomplete outcome data (attrition bias)	Unclear risk	All randomized participants who received at least 1 medication included in safety analysis. Significantly more participants withdrew from the study in the placebo group vs controls (645/1584 vs 521/1593; $p < 0.05$)
Selective reporting (reporting bias)	Unclear risk	High drop-out rates; outcomes reported as specified in methods
Other bias	High risk	All authors had confidentiality agreements with the sponsor during the planning and conduct of the study. Some authors had affiliation with industry

Van Gaal 2005

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	interactive voice responding system according to the predefined randomisation list
Allocation concealment (selection bias)	Low risk	The randomisation code list, with a block size of five, was generated centrally by the sponsor
Blinding of participants and personnel (performance bias)	Unclear risk	Not specified
Blinding of outcome assessment (detection bias)	Low risk	An independent Data Safety Monitoring Board was in place to ensure the safety of the patients by review and analysis of the unblinded safety data, on a regular basis
Incomplete outcome data (attrition bias)	Low risk	Reasons for attrition reported. All randomised subjects included in ITT analyses
Selective reporting (reporting bias)	Unclear risk	High drop-out rates; outcomes reported as specified in protocol
Other bias	High risk	Authors had financial ties with the sponsor

Wadden 2011

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralized automated voice response system
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	Unclear risk	Not described
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	The safety analysis set includes all randomized subjects who are administered at least one tablet of study treatment and have at least one investigator contact/assessment at any time after the start of study treatment, regardless of whether or not they discontinue the study. No significant difference in drop-out rates between groups
Selective reporting (reporting bias)	Low risk	High drop-out rates; outcomes reported as specified in methods
Other bias	High risk	All academic authors received research grants from Orexigen Therapeutics; and they have had financial ties with the drug sponsor (as employees, or paid consultants, or honoraria for advisory roles)

Appendix 10: Pattern of reporting of adverse events and discontinuation across trials and regulatory documents of centrally-acting anti-obesity medicinal products

Medicinal product	Study ID	Frequency of adverse events (AEs) reported	
		Journal publication	Regulatory documents
Lorcaserin	Fidler 2011	Reported AEs with frequency $\geq 5\%$; reported psychiatric system AEs of interest	Reported AEs with frequency $>1\%$
	O'Neil 2012	Reported AEs with frequency $\geq 5\%$	
	Smith 2010	Reported AEs with frequency $\geq 3\%$; reported serious AEs by system	
Naltrexone-bupropion	Apovian 2013	Reported AEs with frequency $\geq 5\%$; reported psychiatric system AEs with incidence $>1\%$	Reported pooled data for placebo group - AEs with frequency $\geq 1\%$ included
	Greenway 2010	Reported AEs with frequency $\geq 5\%$; reported psychiatric system AEs with incidence $>1\%$	
	Hollander 2013	Reported AEs with frequency $\geq 5\%$	
	Wadden 2011	Reported AEs with frequency $\geq 5\%$	
Phentermine-topiramate	Allison 2011	Reported AEs with frequency $\geq 5\%$	Reported pooled data for placebo group - AEs $\geq 2\%$
	Aronne 2013	Reported AEs with frequency $> 5\%$	
	Gadde 2011	Reported psychiatric and cognitive AEs with frequency $\geq 2\%$, and other adverse events arising at a frequency $\geq 5\%$	
Rimonabant	Després 2005	Reported AEs defined as "treatment-related". AEs included if frequency $\geq 5\%$ of either rimonabant group; serious AEs reported according to system organ class	Reported AEs reported in $\geq 2\%$ in the rimonabant 20-mg group and $\geq 1\%$ over placebo
	Pi-Sunyer 2009	Did not specify frequency. Discontinuations due to AEs reported by system for nervous and psychiatric.	
	Scheen 2006	Reported AEs with an frequency of $\geq 5\%$ in any group; discontinuations due to AEs reported by system for nervous and psychiatric	
	Van Gaal 2005	Reported AEs with frequency of $\geq 5\%$ in any group. Serious AEs and discontinuations due to AEs reported by system	
Sibutramine	Bray 1999	Reported AEs with frequency $\geq 3\%$	Reported AEs and discontinuations due to AEs as pooled data - AEs were reported in $\geq 1\%$; used cardiovascular instead of cardiac and vascular; pooled data includes results of some other smaller placebo-controlled studies. Serious AEs of interest reported.
	Smith 2001	Reported AEs with frequency $> 5\%$	

Appendix 11: Description of reports of deaths in pivotal trials of centrally-acting anti-obesity medicinal products

Lorcaserin trials

Fidler 2011: 1 death in placebo group (RTA).

Naltrexone-bupropion trials

Greenway 2010: 1 death in N-B group (acute MI).

Phentermine-topiramate trials

Gadde 2011: 1 death in placebo group (cardiorespiratory arrest); not reported in journal publication, but reported in FDA regulatory document.

Rimonabant trials

Van Gall 2005: 2 deaths, 1 in each group: Uterine adenocarcinoma (rimonabant 20 mg); haemorrhagic CVA (placebo).

Scheen 2006: 5 deaths, 1 in placebo run-in phase due to cardiac arrest. 4 other deaths were: septic shock (rimonabant 5 mg); passenger in RTA (rimonabant 20 mg); 2 CVD (rimonabant 20 mg).

Pi-Sunyer 2006: Two deaths were reported in the 5-mg rimonabant group: 1 male patient was found dead by gunshot and 1 female patient with a history of long QT syndrome died from cardiac arrest.