# Post-marketing withdrawal of analgesic medications because of adverse drug reactions: a systematic review

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**ABSTRACT**

**Introduction:** Many analgesics have been withdrawn from the market because of adverse drug reactions. Controversy still surrounds the use of some approved analgesics for pain management. However, the trends and reasons for withdrawal of analgesics when harms are attributed to their use have not been systematically assessed.

**Areas covered:** We conducted searches in PubMed; Embase; Google Scholar; clinicaltrials.gov; WHO databases of withdrawn products; websites of the European Medicines Agency, the US Food and Drug Administration, the UK Medicines and Healthcare products Regulatory Agency; Meyler's *Side Effects of Drugs*; *Stephens' Detection of New Adverse Drug Reactions*; the *Pharmaceutical Manufacturing Encyclopedia*; and the *Merck Index*. We included licensed analgesics that were withdrawn after marketing because of adverse reactions between 1950 and March 2017. We excluded herbal products, non-human medicines, and non-prescription medicines. We used the Oxford Centre for Evidence Based Medicine criteria to document the levels of evidence, and chi-squared tests to compare withdrawal patterns across geographical regions.

**Expert opinion:** Pharmacovigilance systems in low-resource settings should be strengthened. Greater co-ordination across regulatory authorities in assessing and interpreting the benefit-harm balance of new analgesics should be encouraged. Future reporting of harms in clinical trials of analgesics should follow standardized guidelines.

**Keywords:** adverse reactions; analgesics; drug withdrawal; systematic review

## 1. INTRODUCTION

New medicines are approved when they demonstrate a favourable benefit-to-harm balance, but the harm profile of the medicine may change after regulatory approval, when more people are exposed to it. In some cases, data on harms may be serious enough to warrant market withdrawal of a product [1,2]. The evidence used for making such withdrawals can be based on anecdotal reports, observational studies, clinical trials, or systematic reviews. Withdrawals of products can be controversial, especially when the drug-adverse event relationship has not been clearly demonstrated, and can result in loss of effective compounds, loss of confidence in pharmaceutical products, and loss of revenue for drug manufacturers [3].

Analgesic and anti-inflammatory products (hereafter referred to as analgesics) have been used for the management of various pain conditions for thousands of years [4]. Analgesics are the most common over the counter products [5] and are most commonly used in palliative care [6]. This high frequency of use has led some authors to advocate continuous education of clinicians on appropriate prescribing, to ensure rational use [7,8].

Many analgesic medications have been withdrawn over the past few decades because of concerns about harms, and they have been the most common class of medicines withdrawn worldwide because of adverse reactions [9]. However, controversy still surrounds the use of some analgesics for management of pain [4,10] and there has been no systematic examination of the patterns and reasons for withdrawal. We therefore identified analgesic medications that have been withdrawn because of adverse drug reactions, documented the reasons for withdrawal, ascertained the levels of evidence used for making the withdrawal decisions, determined the mechanisms by which the adverse reactions occurred, and explored the trends in withdrawals over time.

## 2. METHODS

### 2.1 Search strategy

We searched for analgesic products that were withdrawn from the market because of adverse drug reactions between 1950 and March 2017, using the following sources:

- PubMed
- Embase
- Google Scholar
- 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 1–31);
- the WHO's Pharmaceuticals Newsletter (1997– No. 1, 2017);
- *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 [11];
- *the Pharmaceutical Manufacturing Encyclopedia,* 3rd edition [12];
- *The Merck Index,* 15th Edition [13];
- the website of the UK Medicines and Healthcare products Regulatory Agency (MHRA);
- the database of withdrawn drugs of the European Medicines Agency (EMA);
- the website of the US Food and Drug Administration (FDA);
- clinicaltrials.gov.

For each product identified, we searched the following databases for the first reported adverse drug reaction: PubMed, Medline, Embase, and 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).

The full search strategy is included as a web appendix 1. If we could not find information for an analgesic using its chemical name, we used the trade name or code name of the product for electronic searches. We 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, we used the first published dates of any such reactions.

**2.2 Inclusion/exclusion criteria**

To be included in the review, a product must have been withdrawn from the market because of reports of suspected adverse reactions, or problems related to hazards or harms. We included products that had previously been withdrawn because of adverse reactions or other problems related to harms, but had been re-marketed or re-introduced in other formulations. We excluded herbal products, non-human medicines, non-prescription medicines, and products for which there was documented regulatory evidence that they had been voluntarily withdrawn by marketing authorization holders (MAHs) solely for commercial reasons.

**2.3 Assessing the types of evidence**

We documented the highest level of available evidence before the year of first withdrawal, using the Oxford Centre for Evidence Based Medicine (OCEBM) criteria for harms [14], as follows: Level 5: mechanism-based reasoning (lowest); Level 4: case-series or case-control studies; Level 3: non-randomized, cohort or follow-up studies; Level 2: randomized clinical trials; and Level 1: systematic reviews (highest). One reviewer (IJO) documented the levels of evidence, which were independently verified by a second reviewer (JKA). Discrepancies were resolved through discussion.

### 2.4 Data extraction

We extracted data based on the strategy used in our previous publications [3,9]. For each withdrawn product, we extracted data on: the date of first marketing authorization or launch date; the drug class and therapeutic indication [15]; 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. One reviewer (IJO) extracted the data and a second reviewer (JKA) verified them independently. When there were discrepancies in the attributed dates, both reviewers re-checked the dates together and arrived at a consensus by discussion.

### 2.5 Statistical analyses

We used summary tables 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 dispersion. We used scatter plots to explore the relationships between launch dates and times to first reports of adverse drug reactions and

withdrawals. We used the chi-square statistic to compare withdrawal patterns across different geographical regions and different mechanisms of action; a P value of <0.05 was considered statistically significant.

## 3. RESULTS

We identified 101 withdrawn products (Figure 1). We excluded 52 because they were withdrawn from the market before regulatory approval and two because they were marketed as herbal or over-the-counter preparations. We therefore included 47 products in the review. The withdrawals occurred between 1965 and 2011. The key characteristics of the withdrawn products, including the reasons for withdrawal, are shown in Table 1.

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; 10 were withdrawn worldwide (21%), and 19 (40%) were withdrawn in only one country: Europe 13, North America 3, Asia 2, and Africa 1. Of the analgesics that were identified as having been withdrawn anywhere, significantly more were withdrawn in Europe than in any of the other five continents: $P < 0.001$ for each comparison except for Asia ($P = 0.005$) (Table 2). For 16 products that were marketed in both Europe and the USA but withdrawn in at least one of them (web Appendix Table 1), there was a higher rate of withdrawal in Europe than in the USA: relative risk (RR) 1.5, 95% CI 1.0 to 2.1, $P = 0.08$.

In 42 instances (89%), case reports (Level 4) were used as evidence for withdrawals (Table 1). A systematic review (Level 1) was used as evidence for withdrawal in only one case (2.1%), the results of randomized trials (Level 2) in three cases (6.4%), and an observational study (Level 3) in one case (2.1%). 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 analgesics (68%) were inhibitors of cyclo-oxygenase types 1 and 2 (COX-1 and COX-2) and seven (15%) were predominantly COX-2 inhibitors; six analgesics (13%) acted via opioid receptors and the mechanism for one, bucetin, was unknown.

Hepatotoxicity was reported as the primary reason for withdrawal in 14 cases (30%), immunological adverse reactions in 12 (26%), cardiovascular reactions in five (11%), and carcinogenicity in five (11%) (Table 1). Renal toxicity (n = 4), drug abuse (n = 4), gastrointestinal haemorrhage (n = 3), haematological 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 than the non-selective COX-inhibitors (P = 0.0004). Drug abuse was the commonest reason for withdrawal of analgesics with actions at opioid receptors (67%).

The interval between launch and the first reports of adverse reactions ranged from 0 to 29 years (Table 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 report of an adverse reaction was 3 years (IQR = 6 to 8 years). There was a trend towards quicker reporting of adverse reactions with more recently launched drugs (Figure 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 = 1.5 to 15 years).

The median interval between launch and first withdrawal was 7 years (IQR = 3 to 17 years). In seven instances (15%), the withdrawals occurred within two years of the initial launch. The intervals to first withdrawals shortened with more recent launch dates (web-Appendix Figure 1).

The intervals between the first reports of adverse drug reactions and the first withdrawals ranged from 0 to 47 years (Table 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. The median interval between the first reports of adverse reactions and the first withdrawals was 3 years (IQR = 1 to 8 years). Figure 3 shows an inconsistent shortening in the time to withdrawals following reports of adverse reactions with more recently launched drugs. The speed with which analgesics were withdrawn from the market shortened until the mid-1980s; although the intervals to withdrawals after this period have not been consistent, the median interval to withdrawal has shortened compared with pre-1980: 1.5 years (IQR = 0 to 3 years) versus 4 years (IQR =1 to 11 years). The median interval to withdrawal was shorter for analgesics withdrawn worldwide, 1.5 years (IQR = 0 to 5.5 years). 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 years) versus 4 years (IQR = 1 to 9.5 years). The median interval to the first withdrawal of opioid receptor agonists was 3 years (IQR = 1 to 12 years).

## 4. DISCUSSION

### 4.1 Main findings

We have identified 47 analgesic products that were withdrawn from the market between 1965 and 2011. Anecdotal reports 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 cyclo-oxygenase inhibitors, selective or non-selective. Hepatotoxicity and/or immunological reactions accounted for over half of the withdrawal decisions, and in 11 instances deaths were reported as the reason. The delays between the appearance of reports of adverse reactions after product launch and subsequent withdrawal of the products have shortened over time.

The use of case reports in almost all instances as evidence on which withdrawal decisions were based supports our previous findings that formal confirmatory studies are seldom conducted when adverse reactions are attributed to medicinal products [16,17]. However, for three of the five analgesics introduced since 2000, higher levels of evidence were cited as reasons for withdrawal, suggesting improved pharmacovigilance.

The shortened interval to the first reports of adverse reactions with more recently launched analgesics suggests 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 reporting of harms 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 analgesic, pifoxime, was withdrawn in 1976, within three months of regulatory approval in France, following reports of serious neuropsychiatric adverse reactions [18].

Only six products were launched between 1950 and 1965, during which time there were no withdrawals. That no new withdrawals have occurred over the past five years may be the result of more rigorous assessment of trials results in the pre-marketing phases; however, it may also be due to selective reporting of harms in the post-marketing phase. There may yet be time for withdrawals to occur if rare but serious reactions emerge. It should also be noted that because clinical trials are usually not adequately powered to detect adverse events [19], potentially serious adverse reactions to analgesics may have been missed during product development and testing.

The shortened median interval to withdrawal following reports of adverse reactions until the mid-1980s suggests improved pharmacovigilance over the last few decades, and is consistent with our previous findings, that most withdrawals occurred within 5 years of the reports [16] However, the delay to withdrawals has not been consistent since then (Figure 3); this suggests that there are still challenges in assigning 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 reports of adverse reactions available to regulators that could result in withdrawal decisions, or a combination of the two. For example, bufexamac was withdrawn in Europe in 2010 because of severe allergic reactions attributed to its use [20]; however, it remained available in Taiwan, where have been no reports of severe adverse

reactions [21]. Transdermal fentanyl was withdrawn in Europe in 2009 because of the risk of drug abuse [22]; however, it remained available in the USA, because the adverse reactions were attributed to either inappropriate prescribing or incorrect use by patients [23]; the formulation was subsequently changed from a "gel pouch and membrane" to a "drug in adhesive matrix" design to prevent inappropriate use [24].

The reason for the greater number of withdrawals in Europe (83% of all withdrawn products) compared with other continents (26–45%) is unknown; but there is the possibility 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 web Appendix Table 2). However, the greater rate of withdrawals in Europe than in the USA might also suggest that European regulators have a lower threshold for withdrawing a drug when adverse events are reported after marketing—of 26 branded analgesics approved by the EMA between 1998 and 2016, 7 (27%) were withdrawn; of 17 products approved by the FDA between 1996 and 2015, only 1 (6%) was withdrawn; indeed, the EMA has been accused of being excessively risk averse [25], withdrawing products from the market that could have afforded more benefits than harms. The difference between the agencies is highlighted, for example, by the withdrawal of celecoxib in Europe [26,27] but its continued availability in the USA with "black box" warnings [28], the difference being partly explained by how the agencies interpreted the available evidence (see Box 1). That there were more withdrawals of analgesics in Europe compared with the USA could also be partly because the FDA had a more rigorous approval process than the EMA – this may explain why some analgesic medicinal products approved in Europe were never marketed in the USA.

### 4.2 Comparison with the existing literature

Our results corroborate the reports of others who have analysed trends in the regulatory approval of analgesics. In an analysis of 59 products approved by the FDA for use as analgesics, Kissin concluded that there have been no significant breakthroughs in the development of new analgesic drugs over the last 50 years [29]. In a systematic review of NSAIDs that were withdrawn from the market because of hepatotoxicity, Goldkind and Laine concluded that limited data on harms from clinical trials may have contributed to a failure to detect the risks from exposure to analgesics in the pre-approval phases [30]. 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.

### 4.3 Strengths and weaknesses

We used different methods to search extensively for analgesics that have been withdrawn after regulatory approval. We also extensively cross-checked dates to ensure accuracy of the data for initial launch dates, first reports of adverse reactions, and first withdrawals. Furthermore, we accounted for the levels of evidence used in making withdrawal decisions for first withdrawals. However, we recognize some limitations. We may not have identified all countries in which some analgesics were withdrawn; this is especially true for low-resource settings, where pharmacovigilance is either weak or non-existent. We do not have information on the interval between the actual occurrence of adverse reactions and their first appearance in the published literature. In addition, we do not have data on 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 it had actually been marketed in only 80 countries [31].

### 4.4 Implications for policy

Regulatory authorities could, in conjunction with drug manufacturers, develop a database to 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, and also help increase the number of reporting sources available to pharmacovigilance databases. This would be especially important in developing countries, most of which lack adequate regulatory capacity. It would also encourage uniformity in decision-making about withdrawal of products from the market and expedite withdrawals, 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 an increased risk of cancers is a commendable example. Regulatory authorities could delay the granting of marketing licences of new products until the drug sponsors demonstrated convincing evidence that the product had a favourable benefit-to-harm profile. In addition, rapid evidence synthesis of harms associated with newly approved products 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 analgesics has been proposed [32].

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 speedily applied [33]. 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 [34]. It took another five years before celecoxib was withdrawn from the market after initial reports of serious cardiovascular adverse reactions. Earlier suspension would have protected the public from unnecessary exposure to the harms associated with it.

### 4.5 Implications for future drug development

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 [35,36]; 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 [35,36,37]. 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 [38]. 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 [29]. Furthermore, modified formulations of currently available compounds have been successfully used to improve pain control [39,40,41].

## 5. CONCLUSION

The interval to 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, and formal confirmatory studies are seldom conducted to explore analgesics-adverse event relationships. Few mechanisms have been targeted for the development of new analgesics over the last six decades. Future development should include targeting other mechanistic pathways.

## 6. Expert Opinion

The discovery of analgesics has been one of the great advances in medicine over the last 150 years [42]. However, post-marketing withdrawal of some analgesics because of adverse reactions suggests that we have not markedly improved the way in which we assess harms before marketing licences are granted by drug regulators.

Although we identified 47 analgesics that have been withdrawn over the past 50 years or so, we may have missed some analgesic medicinal products withdrawn in some countries because of lack of adequate information. This is because of weak pharmacovigilance systems in some regions, especially in low resource settings, e.g. Africa [43]. Consequently, inhabitants in those areas remain exposed to potentially harmful analgesics that have been withdrawn from the market in developed regions. Until drug monitoring systems in such settings are strengthened, we will keep missing out on potentially useful information that could help inform decision making processes about benefit-harm profiles. We therefore advocate the development of a database to track the marketing of newly marketed products across geographical regions once they have been approved by regulatory agencies.

When there is uncertainty about the association between an analgesic and a specific adverse event, rapid systematic reviews could be instigated; a collaborative approach could even be used to reduce potential biases. However, this does not imply that case reports are unimportant in trying to establish drug-event associations when cases of suspected adverse reactions emerge; indeed when combined with other strategies (e.g. DoTS [44]), spontaneous reporting could result in faster regulatory actions when adverse reactions are attributed to analgesics.

Although it appears that the COX-2 selective inhibitors are more likely to be withdrawn because of cardiovascular adverse reactions compared with non-selective COX inhibitors, the extent to which the COX-2 selective inhibitors increase the risk of cardiovascular events is uncertain. The evidence from several published reviews assessing the cardiovascular risk of COX-2 inhibitors is also not consistent [45]. Therefore, future research assessing the effects of this class of products, using evidence from clinical study reports and individual patient data, may be beneficial. Reporting of harms in future clinical trials of analgesics should also follow standardized guidelines like those proposed by Smith et al [32].

The discrepancies in withdrawal (and approval) decisions between the EMA and the FDA are sometimes difficult to understand– one would have expected greater uniformity in regulatory actions and decisions between the two bodies. It has been reported that besides the scientific evidence, there may be interplay of legislative and economic interests that determine regulatory courses of action when harms are attributed to medicinal products [46].

The emergence of accelerated approval of analgesics by regulatory authorities can cause important adverse events to be missed by trial investigators in the pre-marketing phases, especially as clinical trials are not usually powered to detect harms. Accelerated initial suspension of such analgesics should therefore be considered when suspected serious adverse reactions are attributed to their use in the post-marketing phase.

The prospect of developing new analgesics is very challenging, and there have been few breakthroughs over the past 50 years [42]. The few recorded successes with modified formulations of already available compounds suggest that fewer resources have been spent in looking for novel molecules.

**Highlights**

- 47 analgesic medicinal products have been withdrawn from the market because of adverse reactions
- Case reports are most commonly cited as evidence for making the withdrawal decisions
- The pattern of post-marketing withdrawal of analgesics suggests inadequate assessment of harms in pre-marketing phases
- COX-2 selective inhibitors are more likely to be withdrawn because of cardiovascular adverse reactions compared with the non-selective COX-inhibitors
- Analgesic products are more likely to be withdrawn in Europe than the USA when serious adverse reactions are attributed to their use

**Funding sources:** IJO receives scholarship funding from the Clarendon Fund for the DPhil programme in Primary Health Care at the University of Oxford. CJH is supported by the National Institute for Health Research School for Primary Care Research.

**Authors' contributions:** IJO was involved in devising the review method, conducting electronic and non-electronic searches, data extraction, data analysis and interpretation, and co-drafting of the manuscript. CJH was involved in devising the review method, data interpretation, and co-drafting of the manuscript. JKA was involved in devising the review method, conducting electronic and non-electronic searches, data extraction, data analysis and interpretation, and co-drafting of the manuscript.

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