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REVIEW ARTICLE

Drug Withdrawal Due to Safety: A Review of the Data Supporting Withdrawal Decision

Nuno Sales Craveiro[1,3*], Bruno Silva Lopes[2], Lara Tomás[3] and Sofia Fraga Almeida[4]

[1]*Faculty of Health Sciences, University of Beira Interior, Viseu, Portugal;* [2]*Tondela-Viseu Hospital Centre, Viseu, Portugal;* [3]*Lusitana Family Health Unit, Viseu, Portugal;* [4]*Alves Martins Family Health Unit, Viseu, Portugal*

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Abstract: ***Introduction*:** Several drugs were withdrawn from the market due to safety.

***Objective*:** The aim of this study was to describe data supporting drug withdrawal from the market due to safety reasons in countries belonging to the World Health Organization.

***Methods*:** We analyzed drugs withdrawn from the market between 1990 and 2010. All medicine agencies of the countries belonging to the Program for International Drug Monitoring of the World Health Organization were contacted. To complete data, Medline, reference books and available drug databases were also searched. Information sources on which authorities based their withdrawal were categorized and the average time between the first date of exposure and withdrawal was calculated and stratified.

***Results*:** A total of 133 drugs that met the inclusion/exclusion criteria were withdrawn from the market due to safety reasons in the period reviewed (1990 - 2010). Hepatotoxicity (n=36, 27.1%), cardiac disorders (n=25, 18.8%), hypersensitivity (n=17, 12.8%) and nephrotoxicity (n=14, 9.8%) were the major reasons responsible for 69.2% of all drugs withdrawn. In most cases, Information Sources for drug withdrawal were spontaneous reports and/or case reports (n=86, 64.7%), followed by clinical trials (n=24, 18.0%). The average time between the introduction of a drug and its withdrawal due to safety reasons was 20.3 years (SD±13.8).

***Conclusion*:** According to available and published evidence, there is no gold standard to identify risks associated with drug exposure. These findings strengthen the role of different information sources within the drug safety review process.

Keywords: Hepatotoxicity, nephrotoxicity, program for international drug monitoring, clinical trials, observational studies, laboratory studies.

1. INTRODUCTION

Several drugs were withdrawn from the market due to safety problems that were not identified during the research and development process [1-4]. Lasser *et al.,* showed that 10.2% of the new molecular entities that were introduced in the United States of America between 1975 and 1999 were recalled or acquired new black box warning due to safety-related issues [3]. Onakpoya *et al.,* refer that the average time until drug withdrawal has shortened over the last years, but the method of withdrawal following a serious Adverse Drug Reaction (ADR), did not improve consistently over the last 60 years [5, 6]. The delay between drug introduction and drug withdrawal due to safety reasons, as well as the methodologies used to identify previously unknown risks are still a major concern and there is no gold standard described in the literature [5, 6]. There are not many studies that review the methods used for identifying safety problems. Arnaiz *et al.* in Spain [2] and Olivier *et al.,* in France [1] showed that 82% and 90% of the safety issues identified in drugs withdrawn from the market, were recognized through case reports of ADR. The aim of this study was to describe data that supports drug withdrawal due to safety reasons from the market in countries belonging to the World Health Organization (WHO) [7].

2. MATERIALS AND METHODS

We analyzed drugs that were withdrawn from the market between 1990 and 2010. All medicine agencies of the countries belonging to the Program for International Drug Monitoring of the WHO were contacted and inquired about drugs withdrawn and their respective safety issues related. Medline and reference books were also searched in order to identify other sources of information about drugs withdrawn [8, 9].

*Address correspondence to this author at the Faculty of Health Sciences, University of Beira Interior, Viseu, Portugal;
Tel: 00351913503080; E-mail: Craveiro.nuno@gmail.com

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Finally, available drug databases were also searched in order to complete data provided by agencies and literature search.

Two authors introduced the data in a standardized extraction table while two other authors verified it independently. Drugs in which it was not possible to identify a reference with a year of first exposure to the population were classified as introduced in 1963. Drugs introduced before 1963, were also classified as introduced in 1963. Definition of drug withdrawal was based on authorization, suspension or revocation due to safety reasons. Abuse, dependence and lack of efficacy were considered as safety issues. Drugs that were withdrawn and later returned to the market were included. Drugs in which the regulatory action focused on pharmaceutical formulations or drugs with more than one active ingredient were excluded.

Information sources on which authorities based their withdrawal were classified as follows: R (spontaneous reports, case reports and case series), CT (clinical trials), C (observational studies), MA (meta-analysis and pooled analysis of clinical trials), EL (laboratory studies), EA (animal studies), RA (review of safety data available), LE (lack of evidence) and N/I (information source not identified).

Finally, the average time between the first date of exposure and the respective drug withdrawal date was calculated. This time analysis was stratified according to the following periods: 1990-2000, 2000-2010 and 1990-2010. A descriptive analysis of the information sources used to identify drug-related problems was also performed.

3. RESULTS

The World Health Organization and 97 out of the 131 full member countries of the PIDM/WHO were contacted. A total of 133 drugs that met the inclusion/exclusion criteria were withdrawn from the market because of safety reasons in WHO programme members during the period in review (1990 - 2010). The data is from 72 countries and 5 continents. Table **1** presents drugs withdrawn worldwide in the period between 1990- 2000 and Table **2** refers to the period of 2000-2010.

Table 1. Drugs Withdrawn because of Safety between 1990 and 2000 [1-38].

Drug Withdraw	Year of First Introduction	Safety Problem	Information Source
Acetylleucine[¥]	<1963	Lack of evidence of efficacy	LE
Acitretin[¥]	1989	Teratogenicity/Myopathy	EL
Alpidem[ǂ,¥]	1991	Hepatotoxicity	R
Amfepramone HCL[ǂ,¥]	1971	Lack of evidence of efficacy, Pulmonary arterial hypertension	R, C
Amineptine[ǂ,¥]	1978	Drug abuse/dependence/hepatotoxicity	-
Amobarbital[ǂ,¥]	<1963	Drug abuse/poisoning	N/I
Aristolochic acid[ǂ,¥]	1964	Nephrotoxicity/carcinogenicity	R
Beclobrate[¥]	1985	Hepatotoxicity	R
Benzarone[ǂ,¥]	1964	Hepatotoxicity	R
Bromfenac[ǂ,¥]	1997	Hepatotoxicity	R
Chlormezanone[ǂ,¥]	<1963	Hypersensitivity	R, C
Chloroform[¥]	<1963	Carcinogenicity	EA
Cinchophen[¥]	<1963	Hepatotoxicity	R
Clobenzorex[¥]	1972	Lack of evidence of efficacy	C
Clometacin[¥]	1971	Hepatotoxicity	R
Codeine[¥]	<1963	Drug abuse/Intentional drug misuse	N/I
Coumarin[¥]	1986	Hepatotoxicity	R
Cyclandelate[¥]	<1963	Lack of evidence of efficacy	LE
Dantron[ǂ,¥]	<1963	Genotoxicity	EA
Dexfenfluramine hydrochloride[ǂ,¥]	1986	Cardiotoxicity, Pulmonary hypertension	R, CT, C
Dilevalol[ǂ,¥]	1989	Hepatotoxicity	R
Dinoprostone[ǂ,¥]	1972	Fetal distress/hypertonia	R

Table 1. Contd…

Drug Withdraw	Year of First Introduction	Safety Problem	Information Source
Droxicam¥	1990	Hepatotoxicity	R
Ebrotidine[ǂ,¥]	1997	Hepatotoxicity	R
Encainide HCL[ǂ,¥]	1986	Cardiotoxicity	CT
Erythrityl tetranitrate[¥]	<1963	Lack of evidence of efficacy	LE
Etretinate[ǂ,¥]	1981	Teratogenicity/Myopathy	R
Fenetylline[¥]	1966	Drug abuse	N/I
Fenfluramine HCL[ǂ,¥]	1972	Cardiotoxicity, Pulmonary hypertension	R, CT
Flosequinan[ǂ,¥]	1992	Increased mortality, Cardiotoxicity	CT
Flunitrazepam[ǂ,¥]	1974	Drug abuse	R
Furazolidone[ǂ,¥]	<1963	Carcinogenicity	CT, C
Germander[ǂ,¥]	1989	Hepatotoxicity	R
Glafenine[¥]	1965	Anaphylactic reaction/Hepatotoxicity/nephrotoxicity	R
Glycerol, iodinated[ǂ]	<1963	Carcinogenicity	EA
Ketorolac[ǂ,¥]	1989	Nephrotoxicity	R
Loperamide	1975	Paralytic ileus	R
L-Tryptophan[ǂ,¥]	<1963	Eosinophilia-myalgia syndrome	R
Medifoxamine[ǂ,¥]	1983	Hepatotoxicity	R
Mesna[¥]	1984	Hypersensitivity	R
Methapyrilene[¥]	<1963	Carcinogenicity	EA
Methylrosanilinium Chloride[¥]	<1963	Hypersensitivity, Carcinogenicity	R, EA
Mibefradil[ǂ,¥]	1997	Drug interactions	R
Minaprine[ǂ]	1979	Drug abuse, psychiatric disorder	R
Moxisylyte[ǂ,¥]	<1963	Hepatotoxicity	C
Naftidrofuryl[ǂ,¥]	1974	Cardiotoxicity, neurotoxicity, nephrotoxicity hepatotoxicity	R
Nandrolone[ǂ,¥]	<1963	Lack of evidence of efficacy	RA
Nebacumab[ǂ,¥]	1991	Mortality Increased	CT
Noscapine[ǂ,¥]	<1963	Genotoxicity	EL
Orgotein[ǂ,¥]	1968	Anaphylactic reaction	R
Oxeladin[ǂ,¥]	1970	Carcinogenicity	N/I
Oxyphenbutazone[¥]	<1963	Bone marrow disorder	R
Phenobarbital[ǂ,¥]	<1963	Hypersensitivity	R
Phenolphthalein[ǂ,¥]	<1963	Carcinogenicity	EA
Phentermine[ǂ,¥]	<1963	Lack of evidence of efficacy	RA
Piperazine[ǂ,¥]	<1963	Hypersensitivity/Nephrotoxicity	R
Pirprofen[ǂ,¥]	1982	Hepatotoxicity, Dysmenorrhea	R
Progabide[¥]	1965	Hepatotoxicity	R
Proxibarbal[ǂ,¥]	1965	Thrombocytopenia	R

Table 1. Contd…

Drug Withdraw	Year of First Introduction	Safety Problem	Information Source
Quinacrine[¥]	<1963	Carcinogenicity, Ectopic pregnancies	CT
Remoxipride[ǂ,¥]	1991	Aplastic anemia	R
Secobarbital[ǂ,¥]	<1963	Drug abuse/poisoning	N/I
Sertindole[¥]	1996	Cardiotoxicity	R
Sulfacarbamide[¥]	<1963	Hypersensitivity, nephrotoxicity, blood disorders	RA
Sulfadicramide[¥]	<1963	Hypersensitivity, nephrotoxicity, blood disorders	RA
Sulfadimidine[¥]	<1963	Hypersensitivity, nephrotoxicity, blood disorders	RA
Sulfaguanidine[¥]	<1963	Hypersensitivity, nephrotoxicity, blood disorders	RA
Sulfamerazine[¥]	<1963	Hypersensitivity, nephrotoxicity, blood disorders	RA
Sulfanilamide[¥]	<1963	Hypersensitivity, nephrotoxicity, blood disorders	RA
Sulfisomidine[¥]	<1963	Hypersensitivity, nephrotoxicity, blood disorders	RA
Temafloxacin[ǂ,¥]	1991	Hepatotoxicity/Nephrotoxicity/Anaphylactic reaction/Hemolytic Anemia	R
Temazepam¥	1969	Drug abuse/poisoning	N/I
Terconazole[ǂ,¥]	1980	Influenza like illness	R
Terfenadine[ǂ,¥]	1985	Cardiotoxicity	R
Terodiline[ǂ,¥]	1965	Cardiotoxicity	R
Tienilic acid/Ticrynafen[¥]	1976	Hepatotoxicity	R
Tilbroquinol[ǂ,¥]	1969	Hepatotoxicity, Lack of efficacy	R, CT
Tolcapone[ǂ,¥]	1998	Hepatotoxicity	R
Tolrestat[ǂ,¥]	1988	Hepatotoxicity	R
Triazolam[ǂ,¥]	1977	Psychiatric disorders	R
Troglitazone[ǂ,¥]	1997	Hepatotoxicity	R
Trovafloxacin[ǂ,¥]	1998	Hepatotoxicity	R
Zipeprol[ǂ,¥]	1973	Neurotoxicity, Drug abuse, Dependence	R

ǂ - Information identified through Medline search; ¥ - Information provided by national authorities/Who;C - observational studies; CT - clinical trials; EA - animal studies; EL - laboratory studies; MA - meta-analysis and pooled analysis of clinical trials; LE – Lack of evidence; N/I - information source not identified; R - spontaneous reports, case reports and case series; RA - review of safety data available.

Table 2. Drugs Withdrawn because of Safety between 2000 and 2010 [1-38].

Drug Withdraw	Year of First Introduction	Safety Problem	Information Source
Alosetron[ǂ,¥]	2000	Severe constipation	R
Amphetamine[¥]	<1963	Sudden death	R
Aprotinin[¥]	<1963	Increased mortality	CT
Astemizole[ǂ,¥]	1983	Cardiotoxicity	R, C, EA
Benfluorex[¥]	1976	cardiotoxicity	R, CT
Benzbromarone[¥]	1976	Hepatotoxicity	R
Bicalutamide[¥]	1995	Prostate cancer	CT
Bufexamac[¥]	1974	Hypersensitivity	R, C

Table 2. Contd…

Drug Withdraw	Year of First Introduction	Safety Problem	Information Source
Camelia sinensis[¥]	1999	Hepatotoxicity	R
Celecoxib[¥]	1998	Cardiovascular disorder	CT
Cerivastatin[‡,¥]	1997	Rhabdomyolysis	R
Cisapride[‡,¥]	1988	Cardiotoxicity	R
Clobutinol[‡]	<1963	Cardiotoxicity	R
Dextropropoxyphene[¥]	<1963	Cardiotoxicity, poisoning	R
Droperidol[‡,¥]	<1963	Cardiotoxicity	R
Efalizumab[¥]	2003	Progressive multifocal leukoencephalopathy	R
Ephedra[‡,¥]	<1963	Cardiovascular disorder	R
Gemtuzumab ozogamicin[¥]	2000	Vascular disorders	CT
Grepafloxacin HCL[‡,¥]	1997	Cardiotoxicity	R, CT
Kava Kava[‡]	<1963	Hepatotoxicity	R
Levacetylmethadol[‡,¥]	1993	Cardiotoxicity	R
Levamisole[‡,¥]	1990	Encephalitis/Mortality	R
Lindane[‡,¥]	<1963	Neurotoxicity, Hepatotoxicity, Nephrotoxicity, Carcinogenicity	R, EA
Lumiracoxib[¥]	2003	Hepatotoxicity	R
Metamizole sodium[¥]	<1963	Agranulocytosis	R
Miglustat[¥]	2002	Cognitive disorder	CT
Natalizumab[¥]	2004	Progressive multifocal leukoencephalopathy	CT
Nefazodone[‡,¥]	1994	Hepatotoxicity	R
Nevirapine[¥]	1996	Hepatotoxicity	R
Nimesulide[‡,¥]	1985	Hepatotoxicity	R
Nitrofural[¥]	<1963	Mutagenic Effect/Carcinogenicity	EL
Orciprenaline[‡,¥]	1972	Cardiotoxicity	CT
Orphenadrine[‡,¥]	<1963	Poisoning and toxicity	R
Pemoline[‡,¥]	1972	Hepatotoxicity	R
Pergolide[¥]	1988	Cardiac valve disease	C
Phenylbutazone[¥]	<1963	Agranulocytosis/Aplastic anaemia	R
Phenylpropanolamine[‡,¥]	<1963	Haemorrhagic stroke	R, C
Rapacuronium[‡]	1999	Bronchospasm	R
Rimonabant[¥]	2006	Psychiatric disorder	CT
Rofecoxib[¥]	1999	Cardiovascular disorder	CT
Rosiglitazone[¥]	1999	Cardiotoxicity	MA
Sibutramine[‡,¥]	1997	Cardiovascular disorder	R, CT
Sitaxentan[¥]	2006	Hepatotoxicity	R
Strychnine[‡,¥]	<1963	Convulsions	R, EA
Technetium (99mTc) fanolesomab[¥]	2004	Cardiopulmonary arrest/Life-threatening reaction	R

Table 2. Contd…

Drug Withdraw	Year of First Introduction	Safety Problem	Information Source
Tegaserod[¥]	2002	Cardiovascular disorder	MA
Thioridazine[ǂ,¥]	<1963	Cardiovascular disorder	RA
Valdecoxib[¥]	2001	Hypersensitivity	R
Veralipride[¥]	1979	Psychiatric disorders	R
Ximelagatran/megalatran[¥]	2004	Hepatotoxicity	CT

ǂ - Information identified through Medline search; ¥ - Information provided by national authorities/Who; C - observational studies; CT - clinical trials; EA - animal studies; LE – Lack of evidence; EL - laboratory studies; MA - meta-analysis and pooled analysis of clinical trials; N/I - information source not identified; R - spontaneous reports, case reports and case series; RA - review of safety data available.

Table **3** presents the top 10 reasons why the drugs were withdrawn. The major reasons were hepatotoxicity (n=36, 27.1%), cardiac disorders (n=25, 18.8%), hypersensitivity (n=17, 12.8%) and nephrotoxicity (n=14, 9.8%), accounting for 69.2% of all drugs withdrawn.

Table 3. Top 10 safety problems identified in drugs withdrawn between 1990 and 2010.

Safety Problem	n	%
Hepatotoxicity	36	27.1%
Cardiac disorders	25	18.8%
Hypersensitivity	17	12.8%
Nephrotoxicity	14	10.5%
Blood disorders	13	9.8%
Carcinogenicity	11	8.3%
Nephrotoxicity	9	6.8%
Drug abuse	9	6.8%
Lack of evidence of efficacy	7	5.3%
Vascular disorders	6	4.5%

Information Sources in which the authorities and/or Market Authorization Holders relied on, in order to remove the drugs from the market, are presented in Table **4**. Most cases (n=86, 64.7%) were identified by spontaneous reports and/or case reports. In twenty-four drugs (18.0%) the safety information was identified through clinical trials. In twenty-two out of those twenty-four drugs, the analysis of individual clinical trials was enough, however, in two of them, a pooled analysis of several clinical trials (n = 1; 0.75%) or meta-analysis (n = 1; 075%) was required in order to identify the safety problem. Observational studies were the source of information for 10 (7.5%) regulatory actions, as well as reviews of safety data (n = 10; 7.5%). Animal studies were the source of information for 9 regulatory actions (6.8%) and laboratory studies to 3 (2.3%) regulatory actions.

In addition, Table **4** also features the average time between the drug market introduction and its subsequent withdrawal for each different information source. According to this study, meta-analysis, pooled analysis of clinical trials or analysis of individual clinical trials showed an average time of 8.0 years (SD ± 3.0), individual clinical trials analysis showed an average time of 14.3 years (SD ± 14 .0), spontaneous reporting and/or case reports displayed an average time of 18.7 years (SD ± 13.7), laboratory studies presented an average time of 24.3 years (SD ± 16.9), observational studies showed an average time of 27.3 years (SD ± 8.1), animal studies presented an average time of 31.8 years (SD ± 6.2) and review of safety data available showed an average time of 32.1 years (SD ± 4.3).

Among the sample of countries studied, the average time between the introduction of a drug and its subsequent withdrawal due to safety reasons was 20.3 years (SD ± 13.8). The drug with the least time interval between its introduction and withdrawal was alosetron (0 years). Although this drug was later reintroduced in the market (2002) with restrictions. The drug with the longest time interval on the market until its withdrawal was propoxyphene (53 years), introduced in the USA before 1963 (1957) and withdrawn in 2010 due to cardiac problems (ADR identified by spontaneous reports and reports of cases and later confirmed by a clinical trial phase IV).

Table **5** provides the average time between the introduction of a drug and its market withdrawal in different continents. The American continent showed the shortest average time with 17.5 years (SD ± 14.6), followed by Australia with 19.6 years (SD ± 15.2), Europe with 19.7 years (SD ± 13.3), Asia with 22.7 years (SD ± 14.0) and finally Africa with 23.0 years (SD ± 11.5). The American and the European continents showed an average time before withdrawal higher in the period 2000-2010 when compared to the period from 1990-2000. On the other hand, the African and Asian continents managed to reduce the average time prior to withdrawal in the last decade.

3.1. Strengths and Limitations

The main limitation of this work was the lack of response from some drug regulatory agencies. However, the methodology used in this paper was designed to have multiple sources for the same information. African countries are among the least responsive, but an important part of them had no drug regulatory agency as of 2009 [39]. This lack of response was addressed with information found in the literature or with the information provided by the World Health Organization. We may also not have identified all medicines withdrawn from the market for safety reasons due to publication bias. Once again, this limitation has been addressed by the various sources of information aimed at reducing the number of withdrawn drugs not identified by our methodology.

Table 4. Sources of information on which the authorities and/or Markets Authorization Holders relied to remove the drugs from the market.

Source of Information	ΔT (years ±SD)	n (%)
Meta-analysis and pooled analysis of clinical trials	8.0 ± 3.0	2 (1.5%)
Clinical trials	14.3 ± 14.0	22 (16.5%)
Spontaneous reports, case reports and case series	18.7 ± 13.7	86 (64.7%)
Laboratory studies	24.3 ± 16.9	3 (2.3%)
Observational studies	27.3 ± 8.1	10 (7.5%)
Animal studies	31.8 ± 6.2	9 (6.8%)
Review of safety data available	32.1 ± 4.3	10 (7.5%)

Table 5. Average time between the first introduction of a drug and its withdrawal because of safety issues in different continents.

Location	Average Time (SD), Min – Max (years)
Worldwide, withdrawal period:	-
1990 to 2010, n=133	20.3 (±13.8), 0 – 47
1990 to 2000, n=83	20.5 (±12.1), 0 – 44
2000 to 2010, N=50	20.0 (±16.2), 0 – 47
Africa, withdrawal period:	-
1990 to 2010, n=15	3.3 (±2.8), 0 - 10,0
1990 to 2000, n=9	23.0 (±11.5), 1 – 39
2000 to 2010, n=6	22.8 (±10.8), 12 – 39
America, withdrawal period:	-
1990 to 2010, n=59	17.5 (±14.6), 0 – 47
1990 to 2000, n=26	16.8 (±13.0), 1 – 44
2000 to 2010, n=33	18.1 (±15.7), 0 – 47
Asia, withdrawal period:	-
1990 to 2010, n=53	22.7 (±14.0), 1 – 47
1990 to 2000, n=31	23.4 (±11.9), 0 – 39
2000 to 2010, n=22	21.8 (±16.5), 0 – 46
Australia, withdrawal period:	-
1990 to 2010, n=17	19.6 (±15.1), 1 – 46
1990 to 2000, n=6	19.7 (±10.4), 1 – 28
2000 to 2010, n=11	19.6 (±17.2), 4 – 46
Europe, withdrawal period:	-
1990 to 2010, n=104	19.7 (±13.3), 0 – 46
1990 to 2000, n=69	19.0 (±11.8), 0 – 37
2000 to 2010, n=35	21.2 (±15.8), 2 – 46

4. DISCUSSION

Many adverse drug reactions are known only after the drug enters the market. The greater the number of individuals exposed to a particular drug and the longer the time on the market, the greater the safety information of that drug. The results obtained, in addition to providing a comprehensive list of medicines withdrawn from the market for safety reasons, allow us to draw 4 important conclusions. The first regarding average time until withdrawal, is that the average time until withdrawal varied from country to country and from region to region. The average time until withdrawal that we found globally was 20.3 years for all drugs withdrawn from the market due to safety reasons. Considering drugs introduced from 1990 to 2000 and from 2000 to 2010 (n = 40, table 5), the withdrawal average time was much lower (4.6 + (- 3.6) and 3.3 + (- 2.8), respectively). Different drug policies may have different results in access to medicines. This article also shows that even in the most developed countries, namely those in Europe and the United States of America, there is some variation in decisions about keeping or withdrawing a drug from the market for safety reasons. Nevertheless, these data have as bias the short time to document infrequent and important side effects, and the market time is a cumulative risk for market withdrawal. The average time until withdrawal was also smaller in the 2000-2010 decade when compared with the 1990-2000 decade, results that are consistent with findings from Onakpoya *et al*. [5, 6]. This average time is different from previous findings from Fung *et al*. and Lasser *et al*. but these differences are mainly methodological [3, 4]. The second important finding is related to average time until withdrawal considering the information source. Clinical trials were the information source with the shortest average time until drug withdrawal (14 years compared with 19 years for spontaneous reports or clinical reports; this was true for 16% of drugs withdrawn). The third finding refers to the type of ADR. The 3 main ADR that led to drug withdrawal from the market were hepatotoxicity (in the first place), followed by cardiovascular disorders and hypersensitivity disorders. These results are consistent with previous findings found in literature. Finally, a fourth important conclusion is related to the information source in which withdrawal is supported. The main source of information that leads to market drug withdrawal is still spontaneous reports or clinical reports (individual or in series).

CONCLUSION

According to available and published evidence, there is no gold standard to identify risks associated with drug exposure [40, 41]. These findings strengthen the role of spontaneous reports as a source of information that can support drug withdrawal. Safety drug agencies should pay more attention to stimulate these. More research is needed in order to reduce time until withdrawal, so fewer patients are exposed to the potential harm of drugs with unfavourable benefit-risk ratio.

RECOMMENDATIONS

- There should be an effort to improve the drug evaluation and re-evaluation process, especially in low-income countries.
- More investment is required for drug safety monitoring processes, especially in low-income countries.
- Standardized guidelines for withdrawing drugs from the market due to safety reasons should be promoted.
- Activities that promote increased spontaneous reporting and awareness among health professionals about the need to report serious adverse drug reactions should be encouraged.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Olivier P, Montastruc JL. The nature of the scientific evidence leading to drug withdrawals for pharmacovigilance reasons in France. Pharmacoepidemiol Drug Saf 2006; 15(11): 808-12. [http://dx.doi.org/10.1002/pds.1248] [PMID: 16700082]

[2] Arnaiz JA, Carné X, Riba N, Codina C, Ribas J, Trilla A. The use of evidence in pharmacovigilance. Case reports as the reference source for drug withdrawals. Eur J Clin Pharmacol 2001; 57(1): 89-91. [http://dx.doi.org/10.1007/s002280100265] [PMID: 11372600]

[3] Lasser KE, Allen PD, Woolhandler SJ, Himmelstein DU, Wolfe SM, Bor DH. Timing of new black box warnings and withdrawals for prescription medications. JAMA 2002; 287: 2215-20. [http://dx.doi.org/10.1001/jama.287.17.2215]

[4] Fung M, Thornton A, Mybeck, K, Hsiao-hui J, Hornbuckle K, Muniz E. Evaluation of the characteristics of safety withdrawal of prescription drugs from worldwide pharmaceutical markets – 1960 to 1999. Drug Inf J 2001; 35: 293-317. [http://dx.doi.org/10.1177/009286150103500134]

[5] 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; 14: 10. [http://dx.doi.org/10.1186/s12916-016-0553-2] [PMID: 26843061]

[6] 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; 13: 26. [http://dx.doi.org/10.1186/s12916-014-0262-7] [PMID: 25651859]

[7] WHO. Pharmaceuticals: Restrictions in use and availability (update of the Eighth Issue) Update of the. 8th ed. Geneva: World Health Organization 2005.

[8] WHO. Pharmaceuticals: Restrictions in use and availability (Update of the Fourteenth Issue). Geneva: World Health Organization 2010.

[9] WHO. Pharmaceuticals: Restrictions in use and availability (Update of the Twelfh Issue). Geneva: World Health Organization 2008.

[10] Arlt VM, Stiborova M, Schmeiser HH. Aristolochic acid as a probable human cancer hazard in herbal remedies: A review. Mutagenesis 2002; 17(4): 265-77. [http://dx.doi.org/10.1093/mutage/17.4.265] [PMID: 12110620]

[11] UN. Consolidated list of products whose consumption and/or sale have been banned, withdrawn, severely restricted or not approved br governments. 12th ed. New York: United Nations 2005.

[12] UN. Consolidated list of products whose consumption and/or sale have been banned, withdrawn, severely restricted. New York: United Nations 2009.

[13] UN. Consolidated list of products whose consumption and/or sale have been banned, withdrawn, severely restricted or not approved br governments. New York: United Nations 2009.

[14] Bunniran S, McCaffrey DJ III, Bentley JP, Bouldin AS. Pharmaceutical product withdrawal: Attributions of blame and its impact on trust. Res Social Adm Pharm 2009; 5(3): 262-73. [http://dx.doi.org/10.1016/j.sapharm.2008.10.002] [PMID: 19733827]

[15] Sittig M. Pharmaceutical manufacturing encyclopedia. 3rd ed. Norwich, New York, U.S.A.: William Andrew Publishing 2007.

[16] Lee MH, Graham GG, Williams KM, Day RO. A benefit-risk assessment of benzbromarone in the treatment of gout. Was its withdrawal from the market in the best interest of patients? Drug Saf 2008; 31(8): 643-65. [http://dx.doi.org/10.2165/00002018-200831080-00002] [PMID: 18636784]

[17] Administration FD. List of drug products that have been withdrawn or removed from the market for reasons of safety or effectiveness--FDA. Proposed rule. Fed Regist 1998; 63(195): 54082-9. [PMID: 10185826]

[18] Ibáñez L, Ballarín E, Pérez E, Vidal X, Capellà D, Laporte JR. Agranulocytosis induced by pyrithyldione, a sedative hypnotic drug. Eur J Clin Pharmacol 2001; 27: 305-13.

[19] Attia SM. Deleterious effects of reactive metabolites. Oxid Med Cell Longev 2010; 3(4): 238-53. [http://dx.doi.org/10.4161/oxim.3.4.13246] [PMID: 20972370]

[20] Sander M1, Spies CD, Martiny V, Rosenthal C, Wernecke KD, von Heymann C. Mortality associated with administration of highdose tranexamic acid and aprotinin in primary open-heart procedures: A retrospective analysis. Crit Care 2010; 14: R148. [http://dx.doi.org/10.1186/cc9216] [PMID: 20682059]

[21] Liu HH. Safety profile of the fluoroquinolones: Focus on levofloxacin. Drug Saf 2010; 33(5): 353-69. [http://dx.doi.org/10.2165/11536360-000000000-00000] [PMID: 20397737]

[22] Goldkind L, Laine L. A systematic review of NSAIDs withdrawn from the market due to hepatotoxicity: Lessons learned from the bromfenac experience. Pharmacoepidemiol Drug Saf 2006; 15(4): 213-20. [http://dx.doi.org/10.1002/pds.1207] [PMID: 16456879]

[23] Ibáñez L, Ballarín E, Pérez E, Vidal X, Capellà D, Laporte JR. Agranulocytosis induced by pyrithyldione, a sedative hypnotic drug. Eur J Clin Pharmacol 2000; 55(10): 761-4. [http://dx.doi.org/10.1007/s002280050011] [PMID: 10663456]

[24] Kasper D, Fauci A, Longo D, Hauser S, Jameson JL, Loscalzo J. Toxic and drug-induced hepatitis. Harrison's Principles of Internal Medicine. USA: McGraw-Hill 2011.

[25] Ross JS, Madigan D, Hill KP, Egilman DS, Wang Y, Krumholz HM. Pooled analysis of rofecoxib placebo-controlled clinical trial data: Lessons for post-market pharmaceutical safety surveillance. Arch Intern Med 2009; 169(21): 1976-85. [http://dx.doi.org/10.1001/archinternmed.2009.394] [PMID: 19933959]

[26] Abraham J, Davis C. A comparative analysis of drug safety withdrawals in the UK and the US (1971-1992): Implications for current regulatory thinking and policy. Soc Sci Med 2005; 61(5): 881-92. [http://dx.doi.org/10.1016/j.socscimed.2005.01.004] [PMID: 15955393]

[27] Krayenbühl JC, Vozeh S, Kondo-Oestreicher M, Dayer P. Drug-drug interactions of new active substances: Mibefradil example. Eur J Clin Pharmacol 1999; 55(8): 559-65. [http://dx.doi.org/10.1007/s002280050673] [PMID: 10541773]

[28] Brunton LL, Hilal-Dandan R, Knollmann BC. The pharmacological bases of Goodman and Gilman Therapeutics. 13th Ed. Rio de Janeiro: McGraw-Hill 2018.

[29] Agnelli G, Eriksson BI, Cohen AT, *et al.* Safety assessment of new antithrombotic agents: Lessons from the EXTEND study on ximelagatran. Thromb Res 2009; 123(3): 488-97. [http://dx.doi.org/10.1016/j.thromres.2008.02.017] [PMID: 18485453]

[30] Diane K. Wysowski, L.S., Adverse drug event surveillance and drug withdrawals in the United States, 1969-2002. Arch Intern Med 2005; 165: 1363-9. [http://dx.doi.org/10.1001/archinte.165.12.1363]

[31] Fau D, Lekehal M, Farrell G, *et al*. Diterpenoids from germander, an herbal medicine, induce apoptosis in isolated rat hepatocytes. Gastroenterology 1997; 113: 1334-46. [http://dx.doi.org/10.1053/gast.1997.v113.pm9322529]

[32] CDER. Report to the Nation: Improving public health through human drugs. Rockville, Maryland: U.S. Food and Drug Administration 2005.

[33] CDER. Report to the Nation: Improving public health through human drugs. Rockville, Maryland: U.S. Food and Drug Administration 2004.

[34] CDER. Report to the Nation: Improving public health through human drugs. Rockville, Maryland: U.S. Food and Drug Administration 2003.

[35] CDER. Report to the Nation: Improving public health through human drugs. Rockville, Maryland: U.S. Food and Drug Administration 2001.

[36] CDER. Report to the Nation: Improving public health through human drugs. Rockville, Maryland: U.S. Food and Drug Administration 2002.

[37] CDER. Report to the Nation: Improving public health through human drugs. Rockville, Maryland: U.S. Food and Drug Administration 2000.

[38] CDER. Report to the Nation: Improving public health through human drugs. Rockville, Maryland: U.S. Food and Drug Administration 2007.

[39] List of Globally identified Websites of Medicines Regulatory Authorities. Available from: http://www.who.int/medicines/areas/quality_safety/regulation_legislation/ListMRAWebsites.pdf2019.

[40] Hauben M, Bate A. Decision support methods for the detection of adverse events in post-marketing data. Drug Discov Today 2009; 14(7-8): 343-57. [http://dx.doi.org/10.1016/j.drudis.2008.12.012] [PMID: 19187799]

[41] Chan KA, Hauben M. Signal detection in pharmacovigilance: Empirical evaluation of data mining tools. Pharmacoepidemiol Drug Saf 2005; 14(9): 597-9. [http://dx.doi.org/10.1002/pds.1128] [PMID: 16134080]