Detection of Adverse Drug Reactions in Hospitals

Methodological Issues and Application in Ophthalmology

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PROGRAMA DE DOUTORAMENTO EM

INVESTIGAÇÃO CLÍNICA E EM SERVIÇOS DE SAÚDE - PDICSS

3º CICLO DE ESTUDOS

ORIENTADOR: Prof. Doutor Altamiro Manuel Rodrigues Costa Pereira

Porto, Julho de 2013

3º CICLO DE ESTUDOS (DOUTORAMENTO) em INVESTIGAÇÃO CLÍNICA e em SERVIÇOS DE SAÚDE

U.PORTO

FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

CIDES Ciências da Informação e da Decisão em Saúde
Faculdade de Medicina | Universidade do Porto

Dissertação de candidatura ao grau de Doutor apresentada à Faculdade de Medicina da Universidade do Porto, no âmbito do Programa Doutoral em Investigação Clínica e em Serviços de Saúde.

This PhD thesis is submitted in fulfilment of the requirements for the PhD degree in Clinical and Health Services Research at the Faculty of Medicine – University of Porto, as part of the PhD Program in Clinical and Health Services Research.

Título (Title):

Detecção de Reacções Adversas Medicamentosas em Ambiente Hospitalar - Desenvolvimento de Metodologias e Aplicação em Oftalmologia

Detection of Adverse Drug Reactions in Hospitals - Methodological Issues and Application in Ophthalmology

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Data da prova de admissão ao grau de doutor (Final PhD evaluation date):

7 Janeiro 2014 7th January 2014

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Mário José Cerqueira Gomes Braga

Serafim Correia Pinto Guimarães

Valdemar Miguel Botelho Dos Santos Cardoso

Walter Friedrich Alfred Osswald

Dissertação De Candidatura Ao Grau De

Doutor Apresentada À Faculdade De Medicina

Da Universidade Do Porto

Artigo 48º, & 3º: A Faculdade não responde

pelas doutrinas expendidas na dissertação.

(Regulamento da Faculdade de Medicina

do Porto. Lei nº 19337, de 29 de Janeiro de 1931)

To my husband, Bruno

For unconditional love and

For unconditional support

To my parents,

For believing in me

Thank you!

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ACKNOWLEDGEMENTS

To professor **Altamiro Costa-Pereira**, my supervisor, MD, PhD, Director of *Centre for Research in Health Technologies and Information (CINTESIS),* I would like to express my deepest appreciation for his dedication in helping me, and for his enthusiasm, from when it was a shared dream until the birth of a thesis. Thank you for giving me such wise advices and for allowing rich conversations about everything, from scientific projects to Science and Life itself.

To professor **Luís Azevedo**, MD, PhD, for the patience and support in every methodological aspect of this thesis and several other works. Thank you for your honest advices, your help in overcoming so many obstacles, and above all thank you for all your interest. Thank you for being one of the most altruist scientists I'll ever know. Thank you for being such a great teacher during PDICSS, and for your patience. Thank you the extraordinary guidance during all of my PhD project and even in some articles in Ophthalmology.

To Dr. **Manuela Araújo**, MD, one of my colleagues and co-authors, for all her support and friendship.

To professor **Alberto Freitas**, MD, PhD, for his support and useful material, suggestions and projects.

To Dr. **Fernando Lopes**, MD, for his support, his knowledge and his admirable kindness.

To Dr. **Bernardo Gomes**, MD, for his sharing of thoughts and projects. For all of his collaboration.

To *INFARMED*, Portuguese Authority of Pharmacy and Medicine, that also regulates Pharmacovigilance in Portugal, for kindly sharing data about spontaneous reporting in Portugal.

To everyone in the department of *CINTESIS* (Centre for Research in Health Technologies and Information), for being so kind and helpful at all times.

To all the *teachers of PDICSS*, from whom I learnt so much and who gave me tools (not just methodological, but also general scientific tools) that I will hopefully use for life.

To all in the *Ophthalmology Service in CHUC*, for making me feel I was home.

To all my *friends*, for every relaxing pause from work.

To my *family*, for understanding the sacrifices it takes to fulfill a dream.

To my *husband*, for his loving care and support in every possible way.

LIST OF ABBREVIATIONS

ADE - Adverse drug event

ADR - Adverse drug reaction

ADRs - Adverse drug reactions

ADR_{In} - Adverse drug reaction that occurs during hospitalization, after admission

ADR_{Ad} - Adverse drug reaction that is associated with hospital admission

CI 95% - Confidence interval of 95%

EMEA - European Agency for Evaluation of Medicinal Products

FDA - United States Food and Drug Authority

HSJ - Hospital São João (University Hospital in Oporto, Portugal)

HUCC/CHUC - Central University Hospital of Coimbra (in Coimbra, Portugal)

INFARMED - National Institute of Pharmacy and Medicine (Portuguese National Drug Regulatory System).

PH - number of person-hours (spent in the application of a Pharmacovigilance methodology)

WHO - World Health Organization

OUTLINE OF THE THESIS

This thesis is organized in eight chapters, that intend to guide the reader from **Introduction**, were the Background and *Rationale* are described, to **Aims and Research Questions**, to each of the **Methodologies** that were developed and explored. The application in **Ophthalmology** and the specificities of ophthalmic adverse drug reactions are described in another chapter. Finally, the **Discussion** is presented, with the main findings, limitations and conclusions. Respective **References** are presented. In the **Appendices** chapter, the scientific articles that were built as a result of this work and that were published in peer-reviewed journals are available for consultation.

I. Introduction

In the first chapter, the importance of adverse drug reactions (ADRs) is described, as is the need for the development of new methodologies for ADRs detection. General concepts and definitions of drug-related problems are presented. Adverse drug reactions are approached according to WHO's definition of ADR: “any noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy”. General methodologies of Pharmacovigilance are described, as well as their methodological issues.

II. Aims and research questions

In the second chapter, the aims and the respective research questions are stated, namely regarding the frequency of adverse drug reactions (ADRs), the application of a database methodology for detection of ADRs, and the application of these and other adapted methodologies for the detection of ophthalmic ADRs. The work performed to answer the research questions is described in the following chapters.

III. Frequency of adverse drug reactions in hospitalized patients

In the third chapter, the methodologies and results of one of our systematic reviews are presented, as well as its main conclusions, leading to the characterization and estimate of frequency of ADRs that occur in hospitalized patients. This original research led to publication of a scientific paper, available in appendix 1.

IV. Development of new methodologies for the detection of adverse drug reactions

In the fourth chapter, the methodologies that were approached in this thesis are described. The pilot studies, validation studies, development of new methodologies and respective results for ADR detection are presented, either for the utilization of administrative databases in the detection of ADRs, and for computer-assisted chart review for the detection of ADRs. The methodological issues and study limitations are explored for each of these methodologies. From the study of these methodologies, three scientific papers arose, available for consultation in appendices 2-4.

V. Application in Ophthalmology

In the fifth chapter, the main general ophthalmic adverse drug reactions are characterized and assessed through a general systematic review. A specific systematic review is also presented about ophthalmic adverse drug reactions caused by statins. An original study was additionally performed with the adaptation of the database methodology to the detection of ophthalmic ADRs. The corresponding articles are available in appendices 5-9.

VI. Discussion

In the sixth chapter, the main findings and the answers to the research questions are discussed, as the strengths and limitations of our work. Conclusions and recommendations are then described.

VII. References

The seventh chapter contains the references that were consulted in this thesis.

VIII. Appendices

This chapter includes 10 appendices regarding 8 scientific articles and 2 chapter books; all of them resulted from the original work developed during this thesis.

Appendix 1 is a systematic review about ADRs, published in Pharmacoepidemiology and Drug Safety Journal (PDS). Appendices 2 and 3 are scientific articles published in PDS regarding a methodology using hospital databases to detect ADRs, appendix 4 is a published paper regarding a computerized methodology to detect ADRs. Appendices 5, 6 and 8 are articles about ocular ADRs provoked by systemic drugs and appendix 7 is an article in which a nation-wide estimate of ocular ADRs in Portugal was performed. Appendix 9 is a chapter about ocular ADRs, written for a portuguese Ophthalmology book for residents (which is currently in construction). Appendix 10 is a chapter about ADRs, written after invitation for an international publication about Biotechnology and its recent developments.

LIST OF PUBLICATIONS

The full list of publications is hereby presented (the number in this text corresponds to the appendix number where it can be read, in the end of this thesis):

1. Miguel A, Azevedo L, Araújo M, Costa-Pereira A. Frequency of adverse drug reactions in hospitalized patients: a systematic review and meta-analysis. Pharmacoepidemiol Drug Saf. 2012 Nov; 21(11):1139-54. doi: 10.1002/pds.3309. Epub 2012 Jul 4. *Impact factor of 2.9.*

Article independently selected for commentary and publication in DARE (Database of Abstracts of Reviews of Effects), at http://www.crd.york.ac.uk/CRDWeb/

2. Miguel A, Azevedo L, Lopes F, Freitas A, Costa-Pereira A. Adverse drug reaction detection through administrative databases: evaluation of a methodology. Pharmacoepidemiol Drug Saf. 2013 Jan; 22(1):98-102. doi: 10.1002/pds.3348. Epub 2012 Oct 1. *Impact factor of 2.9.*

3. Miguel A, Marques B, Lopes F, Azevedo L, Costa-Pereira A. Detection of adverse drug reactions through administrative databases - a nationwide study. Pharmacoepidemiol Drug Saf. 2013 Jun 13. doi: 10.1002/pds.3468.

Article independently selected for commentary and publication in MDLinx, at http://www.mdlinx.com/pharmacy/news-article.cfm/4678224.

4. Miguel A, Azevedo L, Silva B, Costa-Pereira A. Resource-Sparing Computerized Tool For Detection Of Adverse Drug Reactions. International Journal of Pharmacy and Technology 2013 Apr; 5(1):5106-5128.

5. Miguel A, Henriques F, Azevedo L, Loureiro A, Costa-Pereira A. Ophthalmic adverse drug reactions to systemic drugs - a systematic review *(Accepted for publication in Pharmacoepidemiology and Drug Safety).*

6. Miguel A, Henriques F, Azevedo L, Loureiro A, Costa-Pereira A. Systematic review of ocular adverse drug reactions caused by statins *(Pilot study performed and protocol finished; with Title Registration by Cochrane Collaboration - Eye).*

7. Miguel A, Henriques F, Marques B, Marques J, Freitas A, Lopes F, Azevedo L, Pereira A. Detection of ophthalmic adverse drug reactions using a database methodology. World J Meta-Anal 2013 August 26; 1(2): 1-5.

8. Miguel A. Adverse Drug Reactions in Ophthalmology - are they a myth? *Invited editorial.* Journal of Ocular Diseases and Therapeutics, 2013; 1: 36-40.

9. Miguel A, Henriques F, Azevedo L, Loureiro A, Costa-Pereira. Adverse drug reactions in Ophthalmology. Chapter of: Pocket Guide of Ophthalmology for Residents (book currently in construction*, publication will be performed by an Ophthalmology pharmaceutical company).*

10. Miguel A, Azevedo L, Costa-Pereira A. Adverse drug reactions. Chapter of: Recent Developments In Biotechnology - In 12 Vols. *Invited chapter. Published by Studium Press LLC.*

RESEARCH PROJECTS

During the period of elaboration of this thesis, I actively participated in a project that was submitted to *Fundação para a Ciência e Tecnologia (FCT)* as a research project and approved for financial support: "Research project HR-QoD - Quality of data (outliers, inconsistencies and errors) in hospital inpatient databases: methods and implications for data modeling, cleansing and analysis (project PTDC/SAU-ESA/75660/2006)."

SUMMARY

Adverse drug reactions (ADRs) are important, costly and fatal events in any healthcare system. However, there are many methodological problems associated with its detection, which hinders the prevention and early treatment of ADRs. This thesis intends to contribute to the improvement of the current methodologies of detection of ADRs and its application in Ophthalmology.

According to the World Health Organization (WHO), an ADR is "any noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy". The prevention through the knowledge gathered by the identification and detection of ADRs represent one of the ways in which it is possible to increase the quality of healthcare while decreasing its related costs.

Several methodologies can be used for ADR detection, namely:

- *Spontaneous reporting* is the main methodology used by WHO's International Drug Monitoring Program and the only one used regularly in the majority of countries. Although it is usually considered one of the cheapest ways to detect ADR, it has also one of the smallest detection rate among all available methods, mainly because of underreporting.
- *Analysis of health databases* (for example, hospital episodes statistics and large insurance claims data) is not commonly used but it might represent a relevant source of ADRs since these datasets contain large amounts of patient clinical data.
- *Computerized systems* is a potentially useful method but attention is needed to build rules and algorithms with high specificity, otherwise it will be too resource consuming. Another problem is its high dependency of structured data i.e. the difficulty with using data from patient narrative notes.
- *Chart review* is also useful for ADR detection but it requires a lot of skilled human resources.
- *Prospective and intensive monitoring* of patients are too costly methods (intensive monitoring has the largest detection rate, being considered by most as the *gold standard*) to allow for their regular use in pharmacovigilance and they are mostly used in short and/or specific drug studies.
- *Postmarketing trials* are seldom used and each of them is also too specific for being developed as a common pharmacovigilance methodology.

In Portugal as in many other countries, there are still many limitations in the current spontaneous reporting system and there are no real and complete data about ADRs that occur during hospitalization (ADR_{In}). In addition, there are too high costs involved in implementing an intensive monitoring programme or in implementing a good computerized system. My main motivation to start this thesis was therefore to try to contribute to overcome some of these issues.

Ophthalmology represents a particular challenge in pharmacovigilance. Many ocular ADRs are detected solely after spontaneous reporting, often lacking causality assessments to determine the probability of an ADR alert being a true ADR, and lacking systematic reviews about ocular ADRs caused by a specific drug. Furthermore, the actual frequency of ophthalmic ADRs remains mostly unknown. Consequently, ophthalmic ADRs are a heterogeneous group of ADRs that still lack systematization and assessment.

Purposes of this thesis

We had several purposes: (a) to identify the frequency of ADRs that occur during hospitalization; (b) to explore methodological issues of several different Pharmacovigilance methods; and (c) to explore,

characterize and validate new methodological Pharmacovigilance approaches. Additionally, with these validated methodological approaches, we intended (d) to contribute to the improvement of the Portuguese pharmacovigilance system namely by building a nation-wide estimate of ADRs. We also aimed (e) to detect and characterize ophthalmic ADRs. Additionally, we intended (f) to build a general systematic review of ophthalmic ADRs and then (g) to perform specific systematic reviews of ophthalmic ADRs to systemic drugs that needed further assessment.

Adverse drug reactions in hospitalized patients

We performed a systematic review to estimate the frequency of ADRs in hospitalized patients. Our meta-analysis indicated that ADRs may occur in 17% (CI95%: 14, 20%) of patients during hospitalization; however, there was significant heterogeneity (I^2 = 99%). The most significant moderators of heterogeneity were: risk of bias, population, ward, and methodology for ADR identification. Low risk of bias studies adjusted for population (pediatric versus adult) had I^2 = 0%.

Development of new methodologies for the detection of ADRs

We developed new methodologies for ADR detection using hospital databases and using a computerized approach. In this thesis we explored spontaneous reporting, administrative databases, chart review and computerized systems that assisted chart review.

Spontaneous reporting is the most commonly used method for Pharmacovigilance due to its reduced costs but has several limitations: underreporting, heterogeneous report quality and risk of bias.

Regarding the database methodology (a methodology developed to allow the detection of ADRs through hospital administrative databases), we performed first a validation study and then a nation-wide study. The validation study was performed in a university hospital of Coimbra: a retrospective analysis was conducted to identify ADRs using 114 diagnostic codes from administrative databases, later validated by chart review. An independent chart review was performed for comparison, as well as assessment of spontaneous reports. 325 ADRs were identified (prevalence of 2.4%, positive predictive value of 88%). Independent chart review identified 9% of ADRs at a cost of 35 person-hours (PH), versus 2 PH in the database methodology. There were 7 spontaneous reports in this period in the same population.

From the application of the database methodology to nation-wide data, we were able to detect 116720 hospital ADRs of 9271122 hospitalizations (prevalence of 1.3%; 97% of the ADRs were ADR_{In}), in public hospitals from Portugal from 2000 to the first semester of 2009.

Two chart reviews were performed in this thesis: the first was performed for comparison with database methodology in simple detection of ADRs (detecting a prevalence of 9% of ADRs with the cost of 35PH), and the second chart review, more detailed (prevalence of 10.2% and cost of 69 PH), was performed for comparison with a computerized methodology and for deep characterization of ADRs.

Finally, a computerized-assisted chart review was developed and validated, with a high detection rate (prevalence of ADRs identified of 25%) with moderate resources needed (29 PH), much lower than manual chart review. This program also provides a list of ADR for each drug, as a memory support tool for inexperienced reviewers. It integrates validation and causality assessment during each assessment. The following table resumes the comparison on several methodologies.

Methodology	Number of ADRs / number of patients exposed	Prevalence (%) of ADRs detected	Resources spent (PH: person-hours)	Adjusted resources (PH per 100 ADRs detected)
Database analysis	325 / 13,471	2.4%	2 PH (per 325 ADRs)	0.6
Spontaneous reporting	7/13,471	0.05%	1 PH (7 ADR reports)	14
Computerized	65 / 117	25%	29.5 PH (65 ADRs)	45
Succint chart review	9/100	9%	35 PH (9 ADRs)	389
Comprehensive chart review	12/117	10%	69 PH (12 ADRs)	575

Application in Ophthalmology

First, we performed a general systematic overview of ophthalmic ADRs to add systematization and to identify specific ADRs lacking assessment. From 562 studies, we included 32 studies that summarized the most known systemic drugs causing ADRs and identified areas lacking specific systematic reviews. Second, we performed specific systematic reviews to drugs in those areas (namely ophthalmic ADRs caused by statins). Third, we utilized that knowledge in the adaptation of our database methodology to the specificities of Ophthalmology to detect ophthalmic ADRs. From all public hospitals in Portugal from 2000 to 2009, 1524 specific probable ocular ADRs were detected through the search of codes that could represent particular ocular ADRs.

Discussion

From the comparison of all methodologies, we can conclude that the methodologies developed in this thesis (database methodology and computerized chart review) are promising and might be integrated as effective and even low resource Pharmacovigilance methodologies. The database methodology validated by us, is resource-sparing for continuous application but with a detection rate higher than spontaneous reporting. Computerized chart review might be an useful Pharmacovigilance methodology, since it may allow regular surveillance with a higher ADR detection with half the resources needed by manual chart review.

Different methods tend to identify different ADRs, therefore, multiple methods for ADR detection should be used complementarily for patient safety enhancement. We suggest that the database methodology is utilized as a screening method for detecting ADRs, and computerized chart review is utilized at high-risk populations.

As for application in Ophthalmology, we conclude that our adapted methodologies were successful in detecting either general and specific ophthalmic ADRs. Ophthalmologists' knowledge about ophthalmic ADRs is essential for its detection and should be stimulated.

RESUMO

As reacções adversas medicamentosas (RAM) são frequentes, caras e podem ser fatais. Todavia, há inúmeros problemas metodológicos associados com a sua detecção, o que reduz a prevenção e o tratamento de RAM. Esta tese pretende dar um contributo na exploração e validação de metodologias para a detecção de RAMs e para a sua aplicação na Oftalmologia.

De acordo com a Organização Mundial de Saúde (OMS), uma reacção adversa medicamentosa (RAM) é: "qualquer efeito nocivo, não programado ou indesejado de um medicamento, que ocorra em doses utilizadas nos humanos para profilaxia, diagnóstico ou terapêutica. A detecção de RAMs representa uma das formas de simultaneamente aumentar a qualidade e reduzir os custos nos Serviços de Saúde.

Várias metodologias podem ser utilizadas para a detecção de RAMs, nomeadamente:

- *Notificação espontânea,* a metodologia mais barata e a única continuamente utilizada em vários países como a base do Programa Internacional de Monitorização de Medicamentos. Contudo, tem a menor taxa de detecção de RAMs de todas as metodologias (devido à subnotificação).
- *Bases de dados* (administrativas, ou bases de dados de seguros, ou bases de dados hospitalares com informação clínica) não são habitualmente utilizadas, mas podem representar uma oportunidade considerando que contêm vasta informação clínica que pode ser utilizada na detecção de RAMs.
- Os *Sistemas computorizados/informáticos* podem representar uma metodologia interessante, mas é necessário construir regras e algoritmos de alta especificidade, caso contrário tornam-se caros. Outros problemas dos sistemas computorizados incluem a necessidade de dados clínicos previamente estruturados e a dificuldade de aproveitar a informação de processos clínicos.
- *A revisão de processos clínicos* é útil para a detecção de RAMs, mas é cara e dependente de peritos.
- As *monitorizações prospectivas e intensivas* (feita por peritos que avaliam regularmente doentes durante o internamento para identificar RAMs) apresentam as taxas de detecção mais altas, mas os custos são tão altos que impossibilitam a sua utilização contínua na farmacovigilância.
- Os *ensaios clínicos randomizados* são habitualmente demasiado restritos a um medicamento ou patologia para serem implementados como método de farmacovigilância geral.

As motivações da presente tese incluem as limitações das notificações espontâneas, o elevado custo da monitorização intensiva e a dificuldade de construir um sistema computorizado nacional para detecção de RAMs, assim como a motivação de complementar o sistema de farmacovigilância português com outras metodologias para além das notificações espontâneas, e a necessidade de estimar a frequência das RAMs que ocorrem em doentes durante o internamento.

A Oftalmologia apresenta um desafio e simultaneamente uma oportunidade na farmacovigilância. Várias RAMs oculares são detectadas apenas por notificação espontânea, frequentemente sem avaliação da causalidade de RAM (cujo objetivo é determinar qual a probabilidade de uma suspeita de RAM corresponder a uma RAM verdadeira). Adicionalmente, há várias revisões narrativas sobre RAMs oculares mas faltam revisões sistemáticas de RAMs oculares provocadas por medicação sistémica com meta-análise e faltam estimativas de frequência de RAMs oculares específicas. Consequentemente, as RAMs oculares integram um grupo de RAMs heterogéneo que necessita de avaliação e sistematização.

Objectivos da tese

Esta tese teve vários objectivos: (a) estimar a frequência de RAMs que ocorrem em doentes durante o internamento, (b) explorar as questões metodológicas de várias metodologias para a detecção de RAMs, e validar novas abordagens para aumentar a detecção de RAMs. Adicionalmente, pretendeu-se (c) realizar uma estimativa das RAMs que ocorreram em Portugal na última década, (d) assim como das RAMs oculares, auxiliando assim a farmacovigilância portuguesa. Pretendeu-se também (e) adaptar as metodologias de detecção de RAMs gerais para a aplicação na detecção de RAMs oculares. Finalmente, pretendeu-se (f) construir uma revisão sistemática geral para clarificação das RAMs oculares a medicação sistémica, e uma (g) revisão sistemática de RAMs oculares provocadas por estatinas.

RAMs em doentes internados

Realizámos uma revisão sistemática para estimar a frequência de RAMs em doentes internados. A meta-análise indicou que as RAMs ocorreram em média em 17% dos doentes (IC95% 13 - 20%); todavia, houve heterogeneidade (I^2 = 99%). Os moderadores de heterogeneidade foram: risco de viés, população, serviço e metodologia usada para identificação da RAM. Os estudos sobre RAMs com baixo risco de viés ajustados para população (pediátrica *versus* adulta) não apresentaram heterogeneidade estatística: I^2 = 0%.

Desenvolvimento de novas metodologias para a detecção de RAMs

Na presente dissertação foram exploradas as seguintes metodologias de detecção de RAMs: notificação espontânea, bases de dados hospitalares, sistemas computorizados e revisão de processos clínicos. Validámos duas metodologias de detecção de RAMs: uma metodologia que utilizou bases de dados hospitalares e outra que utilizou uma abordagem computorizada.

A notificação espontânea tem custos reduzidos, todavia tem limitações como a subnotificação, a qualidade de notificação heterogénea e o risco de viés.

Relativamente à metodologia de bases de dados (metodologia essa em que se utilizou a informação clínica codificada para detectar RAMs), realizámos primeiro um estudo de validação e depois um estudo de prevalência nacional. O estudo de validação foi realizado no Centro Hospitalar e Universitário de Coimbra com exploração retrospectiva de 114 códigos de diagnóstico (procurando identificar os códigos que detectariam maior número de alertas de RAM) e revisão de processos clínicos para validação das suspeitas de RAM (avaliando primeiramente o valor preditivo positivo, VPP, de cada código e seleccionando depois os códigos com maior VPP global). Realizou-se também uma revisão de processos clínicos independente e obtenção do número de notificações espontâneas para a mesma população e período de tempo.

Identificaram-se 325 RAMs através das bases de dados (prevalência de 2%, valor preditivo positivo de 88%). A revisão de processos clínicos independente detectou 9% de RAMs com um custo de 35 pessoas-horas (PH), por oposição a 2 PH na metodologia de bases de dados. Na mesma população e período, obtiveram-se 7 notificações espontâneas.

Aplicou-se a metodologia das bases de dados (com os códigos previamente seleccionados de maior VPP) a bases de dados dos hospitais públicos portugueses de 2000 ao 1º semestre de 2009 e

detectaram-se 116720 RAMs de entre 9271122 hospitalizações (prevalência de 1.3%; 97% das RAMs ocorreram durante o internamento).

Realizaram-se duas revisões de processos nesta tese: uma revisão de processos sumária para comparação com a metodologia de bases de dados (permitiu detectar uma prevalência de 9% de RAMs com um custo de 35 PH); e outra revisão de processos detalhada, para caracterização das RAMs e para comparação com a metodologia computorizada (detectou 10% de RAMs com um custo de 69 PH).

Adicionalmente, desenvolveu-se e validou-se uma metodologia computorizada para auxílio da revisão de processos clínicos, com uma alta taxa de detecção (prevalência de RAMs de 25%) e custo moderado (29 PH), muito menor do que a revisão manual de processos clínicos. Esta metodologia incluiu a construção de um programa (ChartHelper) que mostra uma lista de RAMs possíveis para cada medicamento, funcionando como auxiliar de memória em utilizadores inexperientes; e obriga o utilizador a realizar a avaliação da causalidade da OMS para cada suspeita de RAMs. A tabela seguinte resume a comparação das diferentes metodologias para detecção de RAMs exploradas nesta tese.

Metodologia	Número de RAMs / nº de doentes com medicação	Prevalência(%) de RAMs detectadas	Recursos dispendidos (PH: pessoas-horas)	Recursos ajustados (PH por 100 RAMs detectadas)
Bases de dados	325 / 13471	2.41%	2 PH (por 325 RAMs)	0.6
Notificação espontânea	7/13471	0.05%	1 PH (por 7 notificações)	14
Computorizada	65 / 117	25%	29.5 PH (65 RAMs)	45
Revisão de processos sumária	9/100	9%	35 PH (9 RAMs)	389
Revisão de processos expandida	12/117	10%	69 PH (12 RAMs)	575

Aplicação na Oftalmologia

Primeiro, realizámos uma revisão sistemática geral de RAMs oculares para sistematização e para identificação de RAMs oculares específicas (a medicação sistémica específica com estudos originais mas sem meta-análise), para identificar RAMs oculares que necessitassem ou beneficiassem de avaliação posterior. De 562 estudos, incluímos 32 e sumariámos as RAMs oculares mais frequentes e a respectiva medicação, caracterizando-as. Depois, realizámos revisões sistemáticas de RAMs oculares a medicação sistémica específica (nomeadamente RAMs oculares provocadas por estatinas). Em terceiro lugar, utilizámos o conhecimento obtido para adaptação da metodologia das bases de dados para detecção de RAMs especificamente oculares. De todos os hospitais públicos portugueses de 2000 a 2009, detectaram-se 1524 RAMs oculares prováveis (através da pesquisa de códigos de diagnóstico específicos que pudessem representar RAMs oculares).

Discussão

A partir da comparação de todas as metodologias, podemos concluir que as metodologias exploradas e validadas nesta dissertação (bases de dados e computorizada), são promissoras e poderão ser integradas como efectivas e baratas na farmacovigilância portuguesa.

A metodologia das bases de dados utiliza poucos recursos, permitindo aplicação contínua e com maior detecção da prevalência de RAMs do que a notificação espontânea.

Também a metodologia computorizada (de auxílio à revisão de processos clínicos) pode ser útil na farmacogivilância, uma vez que poderá permitir vigilância e detecção regular de RAMs gastando uma fracção dos recursos que seriam necessários para uma revisão manual de processos.

Tem sido sugerido que diferentes métodos tendem a identificar diferentes RAMs, consequentemente, vários métodos deverão ser utilizados complementarmente para aumentar a segurança do doente. Por exemplo, sugerimos que a metodologia de bases de dados seja utilizada como rastreio para detectar RAMs, e a metodologia computorizada seja utilizada em populações de alto risco.

Quanto à aplicação na Oftalmologia, concluímos que a adaptação de metodologias pode ter sucesso na identificação de RAMs oculares a medicação sistémica. Apesar destas RAMs oculares não serem frequentes relativamente às RAM gerais, os oftalmologistas devem saber reconhecê-las para melhor as poderem tratar. Protocolos de colaboração entre diferentes especialidades é recomendado (para permitir a vigilância por oftalmologistas sempre que há prescrição de drogas de alto risco).

I. INTRODUCTION

"Primum non nocere"

"First, do not harm"

Hippocrates

BACKGROUND: ADVERSE DRUG REACTIONS AND PHARMACOVIGILANCE

History of adverse drug reactions

Adverse drug reactions (ADRs) are frequent, important, expensive and can be fatal (Davies *et al*, 2007).

Since the "disaster of Thalidomide" in 1960's (D'Arcy and Griffin, 1994), public and scientific attention has been drawn to the problem of ADR detection, changing the way drugs are developed, tested and regulated in the World. Physicians first prescribed thalidomide in the late 1950s to treat anxiety, insomnia and, in pregnant women, morning sickness. It was marketed in Europe as well as in Japan, Australia and Canada. It was withdrawn from the market in the early 1960s when scientific community noticed that it caused phocomelia in children exposed to thalidomide during gestation. Besides of the phocomelia (a severe shortening of the limbs), thalidomide also causes malformations in the eyes, ears, gastrointestinal tract, kidneys and genitals (Martínez-Frías, 2012). 40% of the fetuses exposed to thalidomide die before or soon after delivery (Franks *et al*, 2004). Despite this strong teratogenic effect, since there was no ADR monitoring system it took several years, from 1957 to 1961 (Routledge, 1998) to attribute phocomelia to the use of thalidomide during pregnancy, when about 10000 children around the world were already born with major malformations (Franks *et al*, 2004).

Afterwards, in 1963 the World Health Organization (WHO) reunited in Geneva and decided to build an *International Drug Monitoring Program* (WHO, 2005). Also, in the United States the Food and Drug Administration (FDA) reinforced the security monitoring of drugs.

Therefore, an active interest in drug safety and monitoring began worldwide.

Several concepts of drug-related problems arose; to clarify this issue, we present some definitions.

Definitions of drug-related problems and ADRs

An *adverse event* is: "an injury related to medical management, in contrast to complications of disease" (WHO, 2005). Medical management includes all aspects of care, including diagnosis and treatment, failure to diagnose or treat, and the systems and equipment used to deliver care (WHO, 2005).

Drug-related problems are a heterogeneous group that includes ADRs. They are: "a circumstance that involves a patient's drug treatment that actually, or potentially, interferes with the achievement of an optimal outcome (Johnson and Bootman, 1995).

Adverse drug event (ADE): "An injury related to the use of a drug, although the causality of this relationship may not be proven" (Nebeker *et al*, 2004). These events include medication errors (namely the prescription of a wrong dose) and adverse drug reactions.

Medication error: "Any error in the process of prescribing, dispensing or administering a drug, whether there are adverse consequences or not" (Leape *et al*, 1995).

An *adverse drug reaction (ADR)* is: "any noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy", according to WHO's definition of 1972 (WHO, 1972). This definition is the most widely used, but there are others, like Karch and Lasagna's (1975) (whose definition is similar to this but excludes therapeutic failures). The definition of Edwards and Aronson (2000) is conceptually different (it excludes minor ADRs): "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". Some ADRs may be the result of errors, such as the prescription of a drug in the correct dose as recommended in textbooks, but without adjustment in a patient with renal failure.

This thesis follows WHO's definition of ADR.

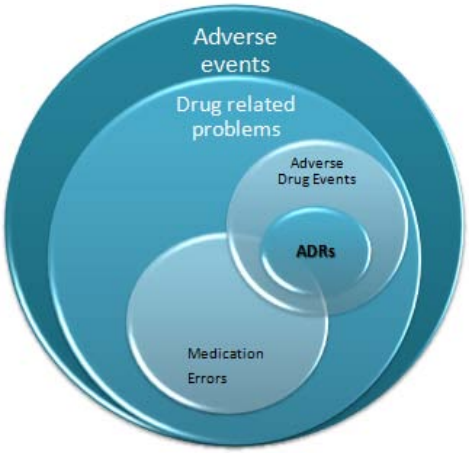


Figure I1. Schematic conceptualization of adverse events. Adverse events are injuries related to medical care. Drug related problems are caused by drugs and include medication errors, adverse drug events (ADE) and adverse drug reactions (ADR). Adapted from WHO, 2005.

Importance of ADRs

ADRs are a major Public Health problem. In a study performed in the United States (US) it was estimated that more than 100000 people die every year as a consequence of fatal ADRs, placing fatal ADRs between the fourth and sixth leading causes of death in the US (Lazarou *et al*, 1998). More recent estimates report that ADRs are the cause of 5.3% hospital admissions (Kongkaew *et al*, 2008), but there are different estimates of the frequency of ADRs (see chapter below). They may lead to US$1.56 billion in direct hospital costs per year in the USA (Classen *et al,* 1997) and drug related morbidity may lead to US$136.8 billion in indirect costs (Johnson and Bootman, 1995). Each ADR may represent a cost of US$2500 per patient (Bates *et al*, 1995).

Therefore, the detection and prevention of ADRs through Pharmacovigilance represent one of the few ways in which it is possible to increase Healthcare quality while decreasing related costs (Stefanovic *et al*, 2011).

Pharmacovigilance

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse drug reactions and of any other drug-related problem (WHO, 2002).

At the time a drug is licensed, information about its ADRs is limited (Lasser *et al*, 2002). Some ADRs are difficult to detect during the clinical research phases prior to commercialization, namely ADRs of low incidence or ADRs that occur several years after administration. This may also be due to the fact that pre-marketing trials are often underpowered, have limited follow-up or that drug information sent from companies to health authorities might sometimes be incomplete (Psaty *et al*, 2004; Ioannidis and Lau, 2001; Ahmed, 2003).

In figure I2 we depict the four stages of clinical trials, in which ADRs of a drug can be detected, before and after a drug commercialization. In Phase 1 trials, researchers test an experimental drug or treatment in a small group of volunteers (20-80) for the first time, to evaluate its general safety. In Phase 2 trials, the experimental study drug is administered to a larger group of people (100-300) to see if it is effective and to further evaluate its safety. In Phase 3 trials, the experimental study drug is administered to large groups of people (1000-3000) under strict inclusion criteria to confirm its effectiveness, to identify further ADRs, to compare it to commonly used treatments and to collect information that will allow the experimental drug or treatment to be used safely. In Phase 4 trials, postmarketing trials identify additional information such as rare or late-effect ADRs. The pyramid (figure I2) represents the increasing number of patients throughout the different trial phases.

After the drug approval, not only postmarketing trials but also postmarketing observational studies can be performed to identify ADRs.

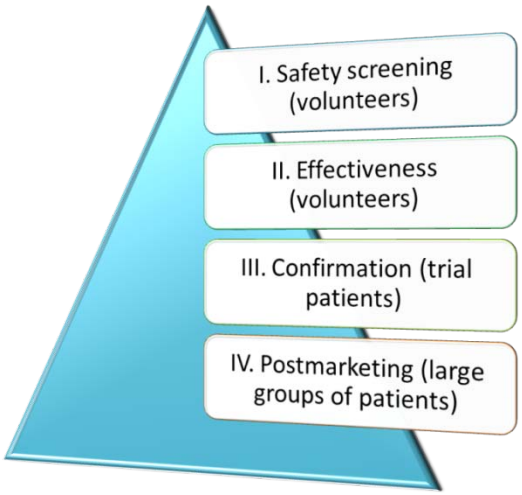


Figure I2. Trial phases and possibilities for ADR detection.

Several drugs have been withdrawn from the market in the last decade after being approved by competent health authorities, such as rofecoxib, that has caused 100000 cardiovascular events in the US before the market withdrawal (Gudbjornsson 2010), among other examples (Graham *et al*, 2010; Giles *et al*, 2004) that we depict in Table I1. These examples demonstrate the importance of postmarketing surveillance.

Drug	Year	Reason
Rosiglitazone (antidiabetic)	2010	Withdrawn in Europe because of increased risk of heart attacks and death. Utilized in the US with some restrictions (Graham *et al*, 2010)
Gemtuzumab ozogamicin	2010	This monoclonal antibody was used to treat acute myelogenous leukemia from 2000-2010. It was withdrawn from market in June 2010, years after a clinical trial showed the drug increased patient death and added no benefit over conventional cancer therapies (Giles *et al*, 2004).
Sibutramine	2010	This weight-loss drug was withdrawn in the US because of an increase of cardiovascular events. It has not been withdrawn in all countries, but a recent systematic review has shown increase in cardiovascular risk (Zhou *et al*, 2012)
Rofecoxib	2004	Risk of increased cardiovascular events such as myocardial infarction (Gudbjornsson 2010)
Co-proxamol	2004	This analgesic was removed due to risk of death in overdoses (Hawton *et al,* 2009)

Table I1. Drugs recently withdrawn from the market. This table mentions some examples of drugs recently withdrawn from the market after previous approval by competent authorities. Adapted from: http://en.wikipedia.org/wiki/List_of_withdrawn_drugs (Accessed December 2013).

Pharmacovigilance - state of the art

The World Health Organization (WHO) has built an International Drug Monitoring Program, that incorporated adverse events' information derived from State Members later in 1971. The number of State Members continuously continues to rise, as shown in figure I3.

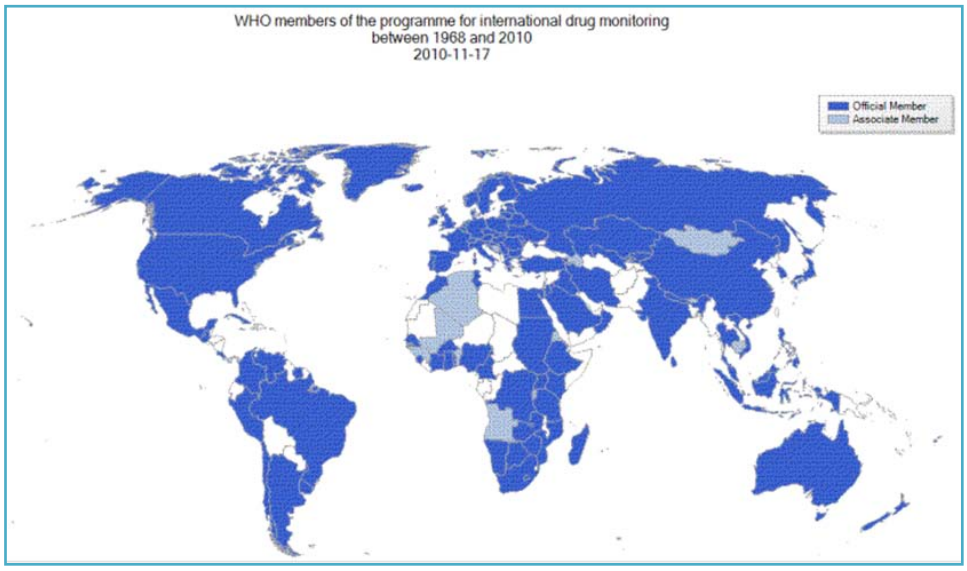


Figure I3. State members involved in the International Drug Monitoring by WHO in 2010.

http://www.who.int/medicines/areas/quality_safety/safety_efficacy/en/index.html.

(used with written permission from WHO)

The Program for International Drug Monitoring relies on spontaneous reports from more than 100 countries including Portugal, and builds a global database to identify possible relationships between the use of a drug and adverse effects and ADRs. Whenever a report of a suspect ADR arises, its data is shared through every State Member. Also, the majority of countries have a *National Health Drug Regulatory Agency*. Portuguese Drug Regulatory Authority is INFARMED (INFARMED, 2012). However, these agencies rely mainly on spontaneous reporting (WHO, 2005; INFARMED, 2012), largely underestimating the real number of ADRs (as will be described below). In summary, National and International Drug Regulatory Agencies currently use spontaneous reporting as a continuous Pharmacovigilance method.

Adverse drug reactions in Ophthalmology

Ophthalmology is perhaps one of the medical specialties in which there are the fewest assessed ADRs, representing a particular challenge in Pharmacovigilance (Fraunfelder 2007).

The eye is a complex organ in which minimal impairment can produce a substantial functional effect (American Academy of Ophthalmology, 2012). Ophthalmic ADRs are usually not continuously detected, although they might be either frequent or specific of a drug or drug group, such as acute angle-closure glaucoma and myopic shift caused by topiramate (Luykx *et al*, 2009), cataracts caused by corticosteroids (Fel *et al*, 2012), floppy iris syndrome caused by tamsulosine (Abdel-Aziz and Mamalis, 2009) and uveitis caused by rifabutin (Cano-Parra and Díaz-Llopis, 2005). Some ADRs are rare but can cause irreversible blindness, such as in optic atrophy caused by ethambutol (Carelli *et al*, 2002), while others are extremely frequent but usually harmful, namely *cornea verticillata* caused by amiodarone (Hollander *et al*, 2004).

There are reports that suggest specific ophthalmic ADRs caused by a systemic drug, but unsupported because no systematic review has been performed. Also, the frequency of ophthalmic ADRs is not known.

In conclusion, ophthalmic ADRs are a heterogeneous group of ADRs that lack assessment and systematization.

RATIONALE: METHODOLOGICAL ISSUES IN THE DETECTION OF ADRS

General methodological issues in the detection of ADRs

The methodologies of ADR detection and monitoring vary widely and are one of the heterogeneity sources found in systematic reviews about ADRs.

The main methods include (Davies *et al*, 2007):

1. *Spontaneous reporting* (in which a health team member reports a presumable ADR) is the main Pharmacovigilance method used in Europe, since it is cheap; however underreporting (Figueiras *et al,* 2006; Herdeiro *et al,* 2008) is a problem.
2. *Administrative databases*. Recurring to national databases is not a widely used method for ADR detection, but it may have some advantages, like low cost and the possibility of a national perspective (Salmerón-García *et al*, 2010).
3. *Chart review* (prospective or retrospective) is a reasonable methodology for ADR (Mullins e*t al*, 2011), however it is also resource and time consuming (Thomas and Brennan, 2000).
4. *Computerized systems* include all methods in which a computerized hospital system generates ADR alerts in several groups of patients, later validated by an expert team (Tinoco *et al,* 2011; Kane-Gill *et al*, 2011). This is an evolving and interesting method of Pharmacovigilance, but attention is needed to build rules and algorithms with high specificity (too many ADR alerts with little specificity consume time in ADR validation and make it unpractical).
5. *Intensive monitoring* is the gold standard, in which an expert team prospectively examines a cohort of patients (recurring to chart review, patient examination and medical team interview) and applies strict criteria to identify and classify ADRs. However, this method is extremely resource and time consuming (Pourseyed *et al,* 2009), making it unpractical to perform regularly.
6. *Prospective monitoring* is a monitoring similar to intensive monitoring but less rigorously (Fattinger *et al*, 2000).

7. *Trials* are usually used for the identification of ADRs caused by a particular drug. Trials are increasingly being used for assessing ADRs as an essential component of a drug evaluation (de Vries and van Roon, 2010).

These methodologies are different although not necessarily mutually exclusive (for example, intensive monitoring can and should include chart review and prospective monitoring), and each of which presents its own advantages and disadvantages.

In this thesis, we have explored 4 methodologies for ADR detection: spontaneous reporting, administrative databases, manual chart review and computer-assisted chart review. However, since the original work of new methodologies' development was performed solely regarding administrative databases and computerized systems, we will assess in the Introduction both the spontaneous reporting and the manual chart review.

1. Spontaneous reporting

In Portugal, the National System of Pharmacovigilance was created in 1992 after the adhesion of Portugal to the European Union. This system has a network of connections and functions, as illustrated in figure I4.

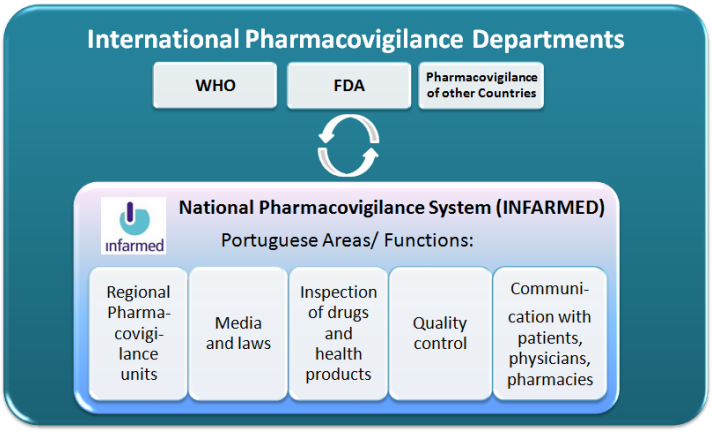


Figure I4. Portuguese National System of Pharmacovigilance and respective connections with International Pharmacovigilance Systems. Adapted with permission from: http://www.infarmed.pt/portal/page/portal/SOBRE_O_INFARMED/ESTRUTURA_E_ORGANIZACAO.

The Portuguese National System of Pharmacovigilance is articulated with the European System of Pharmacovigilance, which includes: the Committee for Proprietary Medicinal Products (CPMP) of European Agency for Evaluation of Medicinal Products (EMEA) and the respective Pharmacovigilance group (Pharmacovigilance working party - PhVWP). INFARMED is also articulated with the WHO International Drug Monitoring, as it is one of its state members who share ADR information, relying particularly in the utilization of spontaneous reports.

The Portuguese National System of Pharmacovigilance relies mainly on spontaneous reports of ADRs, by health professionals. The "Yellow Card", a spontaneous reporting form used in England was adapted to the Portuguese National Pharmacovigilance System in 1992 for reporting of ADRs, as shown in figure I5.

Figure I5. Portuguese Report Forms for Notifying a possible ADR. The Yellow Form is destined to physicians, the purple form to pharmacists and the white form to nurses. (Adapted from: http://www.infarmed.pt/portal/page/portal/INFARMED/PUBLICACOES/TEMATICOS/SAIBA_MAIS_SOBRE/SAIBA_MAIS_ARQUIVO/Farmacovigil%E2ncia.pdf, in INFARMED's site, reproduced with permission).

Spontaneous reporting in Portugal

We have searched through the trends in spontaneous reporting in Portugal in the last years: from 1992, we can identify an increase in the number of reports, with 2696 reports in Portugal in 2011 (figure I6). In figure I7, those reports are classified according to origin (there is a trend of increase in the number of reports performed by

Pharmaceutical Industries). However, the spontaneous reporting rate could still be markedly improved.

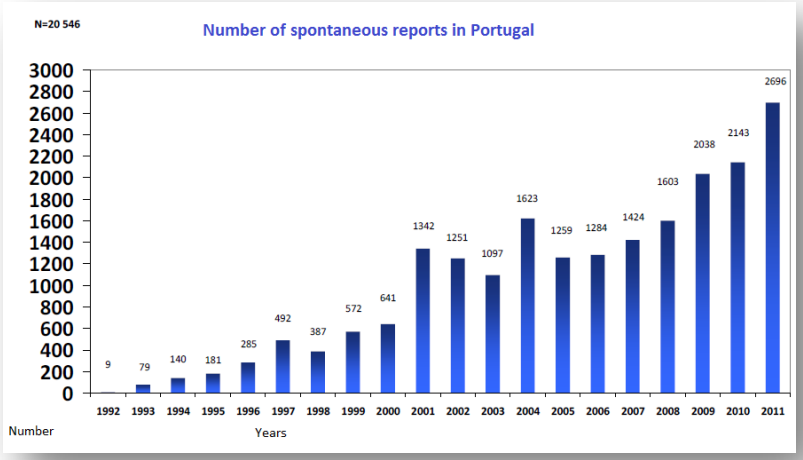


Figure I6. Number of spontaneous reports received by the Portuguese Pharmacovigilance System. Data kindly provided by INFARMED.

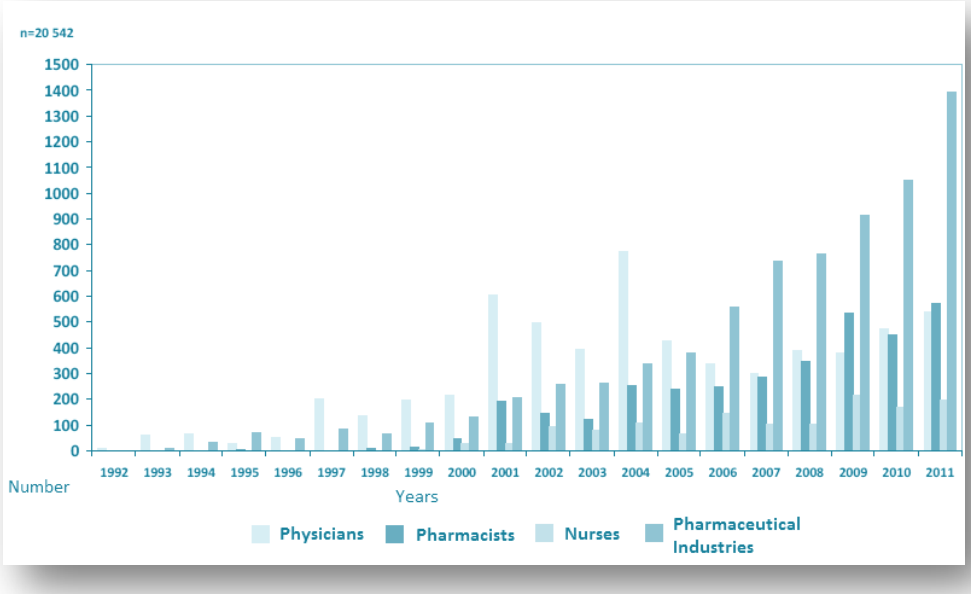


Figure I7. Number of spontaneous reports according to origin. Data kindly provided by INFARMED.

Methodological issues of spontaneous reporting

In spite of being the most commonly used method for Pharmacovigilance due to its reduced costs, there are several limitations to spontaneous reporting: underreporting, heterogeneous report quality and risk of bias.

Underreporting is the main limitation: several studies have estimated that spontaneous reporting only detects 5-10% of ADRs (McGettigan *et al*, 1997; Smith *et al*, 1996). Some studies assessed factors associated with underreporting (Herdeiro *et al,* 2004): intrinsic (knowledge, attitudes) and extrinsic (relationship between health professionals and their patients, the national health system and pharmaceutical companies). An European Survey (Belton, 1997) also identified factors for underreporting, such as lack of availability of report forms, lack of information on how to report, and not having enough time to report.

Some studies have demonstrated that spontaneous reporting rate can be increased (Biagi *et al,* 2012; Figueiras *et al*, 2006), however this effect was temporary. Therefore, health professionals that can report ADRs should be subject to continuous education on Pharmacovigilance, to maintain an acceptable reporting rate, which has costs.

Other limitation is the *report quality*. Since detailed information is required to justify the report of a possible ADR, different quality in reporting will result as different skilled health professionals assess and write that information. Also, in different countries there are different forms, which might result in discrepancy in data captured and inappropriate causality assessment (Bandekar *et al*, 2010).

The third limitation is *methodological bias*. This occurs because a simple report may have uncontrolled information, which in comparison with namely a trial, is more prone to suffer from bias, as suggested by some authors (Pariente *et al,* 2007).

2. Manual chart review

Manual chart review for ADR detection consists of retrospectively or prospectively reviewing patient charts to identify ADRs, generally performed by one or two experts in ADRs, that latter assess concordance for verification of ADRs (Mullins *et al,* 2011; Thomas and Brennan, 2000; Tinoco *et al,* 2011). Specific, strict and objective guidelines are recommended for this assessment (Loke *et al*, 2007; Cornelius *et al,* 2009; McIntosh *et al,* 2004), namely the use of a definition of ADR (usually WHO definition) and causality assessment of ADRs. Causality assessment criteria are objective criteria used to determine the probability that a possible ADR might correspond to a real ADR. The most used causality criteria for an ADR are from Naranjo *et al* (1981) and WHO (2005).

Two chart reviews were performed in this thesis: the first chart review was performed for comparison with database methodology in simple detection of ADRs, and the second chart review was performed for comparison with a computerized methodology and for deep characterization of ADRs. Respective methodologies and results will be discussed with detail in chapter IV and in appendices 2 and 4.

Methodological issues of chart review

Manual chart review has good detection rates and is considered by some (Tinoco *et al,* 2011) as the "gold standard" to identify adverse drug reactions in healthcare organizations (although many other authors consider that the "gold standard" for ADR detection is intensive monitoring (Forster *et al*, 2012)), but it is time and personnel costly: some studies estimated a cost of 55 person-hours per week (Jha *et al*, 1998). For example, our first general chart review detected a prevalence of 9% ADRs with a cost of 35 person-hours (Miguel *et al,* 2013a; appendix 2). Our second chart review, more detailed to further characterize ADRs, unfortunately obtained a similar prevalence of ADRs, 10.2%, at a much higher cost: 69 person-hours (Miguel *et al,* 2013c; appendix 4).

Other limitations of chart review include the methodological heterogeneity between the different studies (Davies *et al*, 2007), namely because of the use of different definitions of ADR, the use of different causality assessment for ADRs, prospective or

retrospective design of study (and different time of data collection), and the use of different number of sources for detection of ADRs: some just search through patient charts (Bates *et al,* 1993), while others also interview health team whenever doubts arise (Somers *et al*, 2003).

Additionally, the quality of records in different hospitals can vary, generating differences in the detection of ADRs through chart review (Davies *et al,* 2007; Cassidy *et al,* 2002; Localio and Landis, 1995), further adding heterogeneity.

Consequently, there is a need to develop a methodology to reduce the costs of chart review. A computerized approach with high level of automation and integration is not yet possible to develop in Portugal, considering that in several portuguese hospitals the patient data is not entirely computerized. Therefore, the development of a computerized-assisted chart review methodology can be an interesting alternative for the detection of ADRs.

Aim

Due to the limitations of spontaneous reporting, the high cost of intensive monitoring, the fact that in Portugal there are no real, complete and continuous data about ADRs that occur during hospitalization, and the particular scientific challenges of ophthalmic ADRs were the motivations of this thesis. This general scope can be described in the research questions, in the next chapter.

II. AIMS AND RESEARCH QUESTIONS

1.

What is known about the frequency of ADRs in hospitalized patients?

2.

What methodologies can be explored for the detection of ADRs besides spontaneous reporting?

2.1 Can a methodology based on hospital databases be developed, validated for detection of ADRs and explored regarding methodological issues?

2.2 Can the database methodology be used to obtain a nation-wide estimate of ADRs in Portugal?

2.3 Can a computerized methodology be developed for ADR detection with low resources and with a good detection rate?

3.

How can ocular ADRs be systematized and characterized?

3.1 What is known about ocular ADRs that occur after systemic medication?

3.2 Can a nation-wide estimate of the frequency of ocular ADRs be built?

3.3 Can specific ocular ADRs be characterized?

III. FREQUENCY OF ADR IN HOSPITALIZED PATIENTS

Many different measures of health and disease are used to describe the health of populations. In order to characterize ADRs as a Public Health Problem, one must assess their frequency. Fundamental measures of disease frequency include prevalence and incidence. For the estimate of ADRs in hospitalized patients (ADR_{In}), we preferred the period prevalence or the cumulative incidence (in incidence rate one would need to know length of stay for each patient, which is rarely possible to assess). This work led to a published article, that is available for further detail in appendix 1.

Frequency of ADRs - aspects to clarify

Types of ADRs according to setting

ADRs can occur in each and every patient that is taking a drug; therefore, they can occur in different clinical scenarios (as illustrated in figure III1):

• ***ADRs that occur in the ambulatory setting*** - a person that takes a drug (either usual medication or medication prescribed because of an acute pathology) may have an ADR (WHO's definition of ADR assumes that the drug is correctly prescribed and administered). At this time, the patient might:

◦ Do nothing, if the ADR is minor and unrecognized (these ADRs are undetected*)*

◦ Go to the emergency department because of the ADR, consequently being treated for the ADR but without the need of being hospitalized (ADRs that are studied in emergency departments)

◦ Be hospitalized due to the ADR (*ADRs that cause hospital admission - ADR_{Ad})*

• ***ADRs that occur during hospitalization* (*ADR_{In}*)** - these ADRs generally occur to medication administered to a hospitalized patient, in spite of the increased clinical surveillance. Hospitalized patients might be at an increased risk of experiencing an ADR, because they have significant comorbidities and are exposed to a higher number of drugs, among other factors (discussed below).

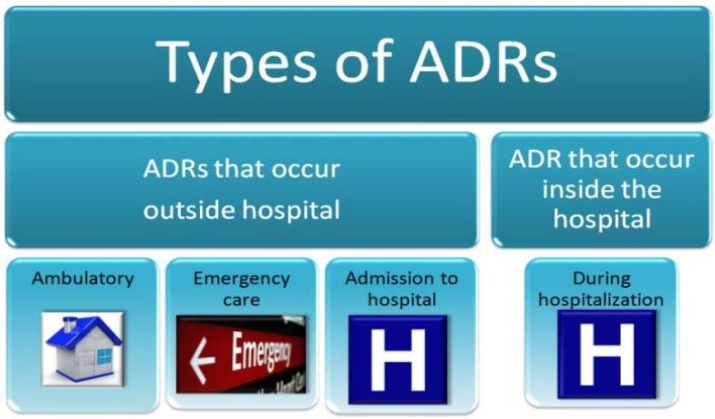


Figure III1. Types of ADRs according to occurrence pattern. ADRs can occur in the ambulatory setting or in the hospital. There are two types of hospital ADRs: ADRs that led to admission (but that occurred in the ambulatory -ADR_{Ad}) and ADRs that occurred during hospitalization (ADR_{In}). The last group (ADR_{In}) is the one that we aim to study in this chapter.

Lazarou (1998) estimated that serious ADRs that occurred in the hospital setting (both ADR_{In} and ADR_{Ad}) had an overall incidence of 6.7% (with a 95% confidence interval of 5.2%-8.2%), placing fatal ADRs between the fourth and the sixth leading causes of death in the US. However, these estimates were criticized because there was heterogeneity (Kvasz *et al*, 2000). There is almost always heterogeneity in systematic reviews of studies about ADRs for several reasons, namely different definition of ADR in different studies, different settings and different methodologies applied for the detection of ADRs. Nevertheless, it is important to try to identify the frequency of ADRs and to try to surpass heterogeneity.

There are several estimates of the frequency of ADR_{Ad}, namely the systematic review performed by Kongkaew *et al* (2008): median incidence of 5.3% (interquartile range 2.7-9.0%), and the prospective study of Pirmohamed *et al* (2004), that analyzed over 18000 patients and estimated a mean prevalence of ADR_{Ad} of 6.5%.

Estimates of ambulatory ADRs are scarce. There are, however, some estimates on adverse drug events that occur in the ambulatory setting: a recent systematic review has estimated that the mean prevalence of ambulatory ADEs in retrospective studies was 3.3% (interquartile range 2.3-7.1%) *versus* 9.6% (interquartile range 3.3-17.3%) in prospective studies (Taché *et al*, 2011). However, ADRs offer some methodological

difficulties such as assessing all over-the-counter drugs, estimating the number of patients that were administered a drug, and particularly estimating the number of patients that were correctly prescribed and administered a drug (such as the definition of ADR implies).

Although there are several studies of ADRs that occur during hospitalization (ADR_{In}), no recent and strict systematic review has been performed, therefore there is a need of a recent global estimate on the number of ADR_{In}.

Difficulties in building a systematic review about ADR_{In}

There are several difficulties in building a good systematic review about ADRs and adverse drug events, such as appointed by many authors (Palaian *et al*, 2006; Lee and Thomas, 2002; Cuervo and Clarke, 2003). Some studies have established useful recommendations specific for ADRs (Loke *et al*, 2007; Cornelius *et al,* 2009; McIntosh *et al,* 2004). There are interesting systematic reviews about ADRs that cause hospital admission (ADR_{Ad}) (Kongkaew *et* al, 2008; Howard *et al*, 2006), however it is still lacking in the literature a current and adequately performed systematic review regarding the frequency of ADRs occurring during hospitalization (ADR_{In}). Moreover, in systematic reviews of general ADRs there is the need for more complete, thorough and meticulous systematic literature search; using a single and standardized definition of ADR; and a more thorough and appropriate heterogeneity analysis.

Objectives of the systematic review

Our primary purpose was to systematically review the literature regarding the frequency of ADR_{In} according to the definition of WHO. Secondary objectives were the characterization of ADRs and their identification by each pharmacovigilance method. We also aimed to undertake a thorough analysis of the methodological quality of the included studies and the evaluation of factors associated with heterogeneity.

Methods

We performed a systematic review of studies that assessed ADR frequency among hospitalized patients after admission, searching through several databases and using strict inclusion criteria (Miguel *et al,* 2012, appendix 1).

Studies were included if they followed all *inclusion criteria* listed below:

1. Prospective studies, that followed hospitalized patients from admission to discharge, assessing in all patients the existence of ADRs prior to discharge, and in which investigators were able to interview physicians, patients or nurses at least once per week. Studies assessing ADRs only at hospital entry or in emergency wards were not included.

2. Studies that previously planned and described a consistent and reproducible methodology for ADR detection, later applied to all patients in a standardized manner. These methodologies included:

2.1. Intensive monitoring applied to all patients. To reduce the high methodological variability of studies that claim to perform intensive monitoring, we created strict criteria for considering a methodology as intensive monitoring:

- Monitoring was performed by specialized team member(s) with experience in ADR identification.
- Monitoring included a daily review of the chart, daily visit of the ward and daily interview of the patient. If necessary, the patient was examined.
- Monitoring included an interview of the health care team at least once a week.
- A daily chart review without patient interview nor examination was not considered intensive monitoring (it was considered chart review).

2.2. Prospective monitoring applied to all patients. This would include studies in which monitoring of patients was performed with assessment of ADRs before discharge, with patient interview or examination or health team interview at least weekly, but without fulfilling all the criteria above for intensive monitoring (even if the authors called it intensive monitoring).

2.3 Prospective chart review applied to all patients, with patient interview or examination or health team interview.

2.4 Computerized monitoring if another methodology (chart review, prospective or intensive monitoring) was also applied to all patients. Computerized monitoring in which only computer alerts were validated were excluded, because it was not a methodology equally applied to all patients.

2.5 Database search if another methodology (chart review, prospective or intensive monitoring) was equally applied to all patients.

2.6 Spontaneous or solicited reporting if another methodology (chart review, prospective or intensive monitoring) was applied to all patients.

3. Studies with sufficient data about frequency of ADRs (if a study focused on ADE, it needed to have separate data on frequency of ADRs)

4. Studies of ADRs that occurred during hospitalization (ADR_{In}). We were not interested on ADRs as a cause of hospital admissions (ADR_{Ad}).

5. Studies that used WHO's definition of ADR (1972). Studies with other similar definitions (like Karch and Lasagna, 1975) were included but analyzed separately (in order to identify if this added heterogeneity). When studies provided their own definition described in detail, we sought inconsistencies with WHO's definition (if inconsistent, they were excluded). When no definition or an imprecise definition was reported, we emailed authors. Studies that claimed to assess frequency of ADEs but provided WHO's definition and criteria of ADRs were included (they studied ADRs although they inappropriately called them ADEs). Studies with Edwards and Aronson's (2000) ADR definition were not included because although it is a good definition, it is rather different from WHO's definition.

We also included studies with different languages (English, Portuguese, Spanish, French, German- we hired a translator), any country, any ward (we included pediatric wards for a comprehensive view), experimental studies (if any) and year of study (although we only included studies after WHO's definition of 1972). We did so to have a more thorough and complete literature search, and to have the opportunity to analyze them as subgroups and identify sources of heterogeneity.

Exclusion criteria were:

1. Studies including only patients with particular pathologies (we did not exclude studies that systematically identified ADRs in particular wards; although we planned

to analyze them separately). 2. Studies for specific drug exposures (specific ADRs such as bleeding were not excluded *per se*). 3. Studies in which the primary objective was not ADR identification (like trials of drug effectiveness), in order to warrant a methodology systematically applied to assess ADRs frequency.

Data collection and analysis

Two independent reviewers, AM and MA, first examined each title and abstract to exclude obviously irrelevant reports, and then independently examined each full text report, to determine eligibility according to inclusion criteria.

We performed a pilot test to evaluate the selection procedure and criteria on a sample of reports, as recommended by the Cochrane approach (Cochrane, 2008). We then performed another pilot test with 100 random studies. We used those tests to refine criteria and train reviewers. Disagreements were solved by consensus, recorded and analyzed using kappa statistics.

Risk of bias assessment

We also performed 2 pilot studies using a standardized form to evaluate the methodological quality of included studies. We did not use scales (discouraged by the Cochrane approach) but criteria from Cochrane (2008), STROBE (Vandenbroucke *et al*, 2007), QUOROM (Moher *et al*, 1999) and PRISMA (Moher *et al,* 2009) adapted to the scope of ADRs frequency evaluation, which included:

- complete description of study design
- verification if all parts of study were prospective
- number of hospitals in which study occurred
- adequate selection criteria
- definition of ADR
- rationale for study size
- causality assessment of ADR
- avoidability assessment of ADR

- description of all statistical methods
- characterization of study participants and of number of participants at each stage
- description of methods to prevent information and selection bias
- intensive monitoring
- description of methods to avoid other bias
- presentation of complete summary measures

The two reviewers independently assessed study quality and risk of bias; disagreements were solved by consensus. Studies were divided in low risk of bias (5 or less parameters with medium, unclear or high risk of bias), medium risk (6 to 9) and high risk (10 or more parameters evaluated as medium, unclear or high risk of bias).

Subgroup analyses

High heterogeneity was expected according to previous studies. Our purpose was to identify heterogeneity sources, therefore, several subgroup analyses were planned:

Study location - subgroups based on continent or country

Methodology for ADR detection - *Intensive monitoring; Prospective monitoring; Chart review*; *Computerized monitoring* that generated ADR alerts - included only if alerts were validated by team and if other methodology was also applied to all patients, such as chart review or prospective or intensive monitoring; *Database monitoring* -included only if other concurrent methodology applied to all patients; Spontaneous or solicited *reporting* - included only if other methodology was concurrently used in all patients.

If several methodologies were concurrently applied in a study, we planned to compare them (only if the population was strictly the same).

Ward type - Internal Medicine, General Surgery, Intensive care unit, Pediatric, Geriatric, Obstetric, or other as reported by authors. We registered if the study was performed on several wards without specifying number of patients for each, and also if ward was not reported.

Hospital type - teaching/university *versus* non teaching hospital - as reported by authors (if conflicting or unreported, we searched the internet).

Risk of bias

Population - adult Vs pediatric (<18 years) Vs geriatric (>64years) population.

ADR definition - WHO's strict definition *versus* Karch and Lasagna's or WHO's definition with slight imprecisions in application.

Study duration (short follow-up studies<3 months, medium 4 to 11 months, long ≥12months).

Results

I. Literature search and selection process

From 4139 studies initially found (corresponding to 2853 distinct studies), 230 were selected to obtain full-text and then 22 studies were included (Figure III2 represents the flowchart of the literature search).

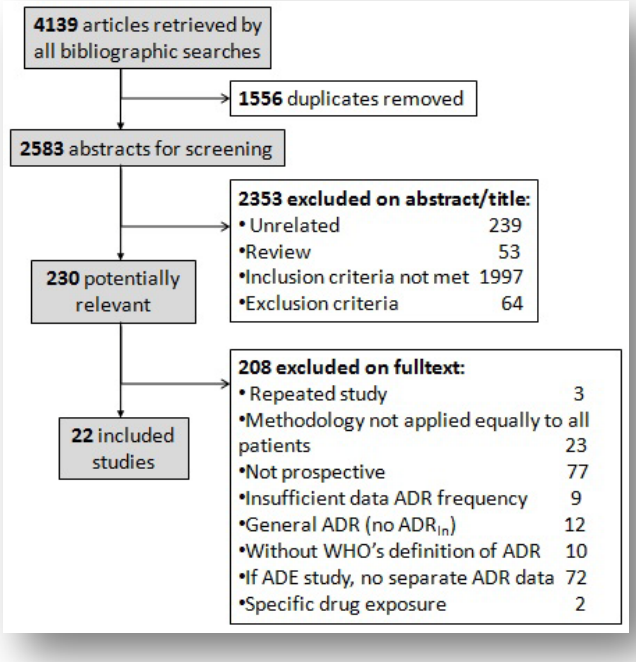


Figure III2. Flowchart of the search strategy.

From the 4139 studies found: Pubmed search yielded 1124 results; EMBASE yielded 653 results; CINAHL 173; Cochrane 7; ISI Conference Proceedings 95; ISI Web of Knowledge 573; International Pharmaceutical Abstracts 887; Google Scholar 60; Scirus 61; NHS economic evaluations database 14; others yielded 492.

During the first phase, Kappa agreement for study inclusion was 0.77; during the full text review, was 0.89 (good agreement).

Characteristics of included studies

From the 22 included studies, there were 18818 hospitalized patients exposed to drugs; 2458 of them suffered an ADR while hospitalized; 3553 ADR_{In} were identified.

In table I2, we present the summary characteristics of included studies.

Study	*Country Hospital Ward*[A]	*Sample*[B] *Dura-tion*	*Method*[C] *for ADR detection*	*ADR incidence* [D]	*Summary of study*	*Remarks* [E]
1993 Bates	United States.1G 7 wards: 2Med,2S, 2Ob,1ICU	420 p 1.2m	P, R, Sl	15 ADR in *15* p I=0.0357 E=0.00901	Prospective cohort in 7 wards of a tertiary hospital, with daily chart review by a nurse and solicited reporting, to evaluate incidence and preventability of ADEs	*ADE study with separate data of frequency of ADRs * Doesn't explicitly report ADR_{In} but "ADR during hospitalization" *2967 patient-days (number of patients with ADR was not explicitly stated but possible to calculate)
1998 Moore	France 1G 1Med	329 p 6 m	Sl, I	21 ADR in 21 p (31ADR_T) I=0.0638 E=0.01345	Prospective cohort with intensive surveillance (daily monitoring) of all patients consecutively admitted to a ward to identify "serious ADRs" (it didn't identify all ADRs)	* Although they present a definition similar to WHO's definition of ADR, there were imprecisions, like: "involuntary over or underdosing were included [as ADR]..." *ADR incidence was calculated (modified data for further precision)
1999 Gholami	Iran 1T 2 Med	370p 10m	S, I	95ADR in 29p (102ADR_T) I=0.0784 E=0.0140	Prospective study, randomized sample, with spontaneous reporting and intensive monitoring (in which a pharmacist daily reviewed patient charts, laboratory data and interviewed patient)	* Randomized sample * "ADRs increased an average length of stay in 29.9% of patients" * "ADRs were more predictable if the reaction was hematologic"
1999 Martíne z-Mir	Spain 1 T 2 Ped	409p 6.7m	I, S, Sl, C, Co, R	56 ADR in *56*p (112ADR_T) I=0.137 E=0.0170	Prospective study to assess the extent, pattern and profile risk for ADRs in hospitalized patients aged 1-24 months. Records were screened daily and there was parent interview and daily visit wards.	*Authors specify number of patients exposed to drugs: 409 * "Consistent relation between nr drugs and cumulative incidence of ADR" * Children with ADR had longer hospital stay; female had more risk of having ADR * We excluded 1unlikely ADR reported by authors: modified data
2000 Bemt	Nether-lands 2 G 2 Med	538p 2m	S, Sl, I	248 ADR in149p I=0.280 E=0.0193	Prospective cohort study in a medical ward in two hospitals, to identify ADR and its risk factors, by several methods: spontaneous reporting, solicited reporting and intensive monitoring by a pharmacist, daily	*Authors say "adverse drug event" but use WHO's definition of ADR *They present adjusted Odds Ratio(OR) to: age, sex, nº drugs and time of stay *Authors propose intensive monitoring if ≥7 drug/ patient *Modified data
2000 Fattinge r	Switzer-land 2 T 2 Med	3624p 36 m	P, R, Co, C	317 ADR in *317p* (461 ADR_T) I=0.0875 E=0.00469	Prospective cohort of two teaching hospitals in which all consecutive patients were admitted and data recorded (like symptoms, laboratorial data, ICD10 codes) to a computerized system generating alerts of ADRs, confirmed by a physician. Chart review was performed in all patients; intensive monitoring only of ADR alerts.	*From several data: possibly drug related events, drug related disease, unrelated and ***clinically relevant ADRs***, we chose the last. We calculated ADR_{In} from table 2 (text and table had some inconsistencies): 461 ADR_T - 144 ADR_{Ad}= 317 ADR_{In} (modified data) * ADR's definition of Karch and Lasagna; they didn't exclude all cases of involuntary overdosing (and don't report its number) * "Clinically relevant ADRs": not all ADRs were identified.
2002 Buajord et	Norway 1T 1 Ped	579 p 5m	S, Sl, R	407ADR in 161p I=0.278 E=0.0186	Prospective pediatric ADE study (with daily chart review) that includes frequency of ADRs	*Authors specify that all participants are taking drugs *Study about ADE that has separate ADR data (however, does not specify if they are only referring to ADR_{In}) *Authors call it "intensive" but doesn't match our criteria
2002 Weiss	Germany 1G 1Ped	214p 8m	Sl, R, C	64 ADR in 46p [68ADR_T] I=0.215 E=0.0281	An 8-month prospective study in a 10-bed pediatric ward using computerized system, chart review weekly and solicited reporting to identify ADRs	*Intensive monitoring was only applied to ADR suspects * Modified data to include only ADR_{In}
2003 Egger	Germany 1G 1 Ger	163 p 4m	R, C, P	153 ADR in 99p (Computer identified 64 ADRs) I=0.607 E=0.0383	Prospective monitoring of all patients admitted to a geriatric ward to compare the ADR rate predicted by a computerized pharmaceutical database to that determined by direct observation	*They didn't explicitly exclude ADR_{Ad}, but studied "ADRs during hospitalization" * "Computerized drug databases are a useful tool for detecting and avoiding ADRs." * Authors report intensive monitoring but it doesn't fulfill our criteria of intensive
2003 Ramesh	India 1T	3717 p 7m	S, Sl, R, P	244 ADR in *138 p* (270 ADR_T)	Spontaneous and solicited notification and chart review of all patients from one hospital. Intensive monitoring was	*Authors say that they used WHO's causality criteria but don't report respective results

	R			I=0.0371 E=0.00310	performed in patients *suspects* of having an ADR.	*Authors don't explicitly state ADR_{In}, but possible to calculate ("3.7%"): modified data *Ward type not reported
2003 Somers	Belgium 1T 1Ger	56 p *(see remarks)* 8m	P, Sl	21 ADR in *12*p I=0.214 E=0.0548	Pilot study of all patients admitted to a geriatric ward, comparing two methods of ADR identification: prospective monitoring (with patient interview at admission by pharmacist with standardized forms, and chart review 3times/week, and discussion with medical team weekly) Vs solicited reporting.	* The authors call it spontaneous reporting but describe solicited reporting * "No formal causality assessment was made..." *12 notifications of 168 patients; 32 ADR in 22 patients of 56 interviewed. We only considered the 56 patients eligible for prospective assessment and interview. *WHO's definition of ADR was used but :"this does not exclude that some events are categorized as not related to the treatment after causality assessment"
2003 Vargas	Spain 1G 1ICU	401 p 20m	Sl, I, R	39 ADR in37p I=0.0922 E=0.0145	Patients from a surgical ICU were prospectively followed to identify ADR and evaluate their effect on length of stay, daily. Authors don't report it but describe intensive monitoring.	*ADR's definition of Karch& Lasagna (which excludes lack of efficacy, unlike WHO's)
2005 Fattahi	Iran 1T 1 Ped	380p 5m	S, Sl, I, R	82 ADR in 40p (94 ADR_T) I=0,105 E=0,0157	Prospective study in children < 14 years to identify ADR as a cause of admission and ADR that occurred during hospitalization (separate data). Intensive monitoring was performed with daily evaluation.	* The incidence calculated by the authors includes nr of participants (404) but only 380 patients were exposed to drugs (we used the number 380: modified data) * "Consistent relationship between number of drugs and number of ADR"
2005 Haffner	Germany 1T 3 Ped	703p 3m	C, I	124 ADR in 99p (101ADR_T) I=0.141 E=0.0131	Prospective study to identify ADR in which 2 methods were compared: intensive monitoring(101ADR_T) Vs automated search (45 ADR_T). Children were assessed daily(except weekends), there were parent and medical team interviews.	*703 participants for intensive monitoring but only 636 for computerized analysis; slightly different follow-up time (45 ADR identified by PC): modified data *Responded to email with useful data *"ADRs occur as frequently in pediatric as in adult patients."
2006 Camarg o	Brazil 1T 5 Med	333p 9m	P, R	119 ADR in 86p I=0.258 E=0.0239	Prospective study (until discharge) with previously trained researchers that performed chart review before patient discharge (however, patient interview is not reported).	*333 participants, but only "268 were followed until discharge"(losses to follow-up) *ADR results in table don't match with text; we used data from table 1 *One of the few studies with a randomized sample and the only included study that previously calculated sample size (data collection interrupted after an interim analysis) *Although authors refer intensive monitoring, it doesn't match our criteria
2006 Santos	Brazil 1G 1Ped	265p 5m	I, R	47 ADR in 33p I=0.124 E=0.0203	Prospective study with intensive daily monitoring of a pediatric ward (children from 0 to 16 years) with 36 beds to identify ADEs.	*Studies ADEs but has separate data for ADRs *ADRs were more frequent with more drugs (p<0,081), longer hospital stay (p<0,008) and younger age (p<0,020) *"265 patients exposed to drugs from 273 participants"
2006 Tribiño	Colombia 1G 1Med	836p 5m	S, SI, P, R	268 ADR in 208p I=0.249 E=0.0150	Prospective monitoring study over 5 month in a medical ward to identify ADRs and calculate its costs.	*Doubtful ADRs were excluded *"Solicited reporting, chart review, and patient exam and interview when necessary". However, doesn't specify daily patient evaluation *Direct costs were calculated from the perspective of the payer; calculated range of costs from ADR: USD$ 35011.92 to 45011.94
2007 Arulman i	India 1G 3 wards: 1med, 1 S,1ICU	1682 p 9m	P, Sl, R	63 ADR in *63p* (121ADR_T) I=0.0375 E=0.00463	Prospective cohort study of patients admitted to 3 wards, using solicited reporting and monitoring to ascertain ADR frequency, severity and costs.	* The authors say spontaneous reporting but describe solicited, e.g.: "during the ward rounds, these pharmacists encouraged the doctors to report suspected ADR" *Some sums of results don't match with the text (e.g. table 1: ADR_{In}: 23 male & 43 female; total 6**4** ADR_{In}; in text: "6**3** ADR_{In}"); we used data from the text. *"Pharmacists attended ward rounds and [...] encouraged doctors to

						report [...], several forms were designed..."
2008 Zopf	Germany 2 T 2 Med	907 p 6m	I, R	566 ADR in 319p I=0.352 E=0.0158	Cohort of all patients admitted to 2 medical wards in 2 university hospitals, with intensive monitoring (daily, by a trained team of 3 physicians, 1 pharmacologist and 2 pharmacists) to characterize risk factors associated with ADRs after admission	*Included 26 intoxications diagnosis, which we excluded: modified data *Slight problems with table sums: "90**7** patients, from which 480 men and 42**3** women" *Doesn't explicitly exclude ADR_{Ad}, although mentions "ADRs *following* admission". *"The predictability of ADR depends on: raised temperature, low erythrocytes, low thrombocytes, high number of drugs and female sex"
2009 Joshua	India 1T 1ICU	728p 12m	P, C	239 ADR in 188p (294 ADR_T) I=0.258 E=0.0162	Prospective study of 12 months to identify ADRs in an intensive care unit, by a team that accompanied clinicians 6 days in a week, viewed patients records. They mention intensive monitoring but no patient interview nor examination is reported.	*Nr of comorbidities was higher in patients with ADR: 5,7±1,7 versus 4,6±1,6(p<0,0001) *Authors mention 902 participants but don't justify why only "included 728" *Authors wrote "of the 222 patients with ADRs, 188 developed ADRs (n=239) during hospital stay"; but in the table:"2**94** ADRs"; we considered the text: modified data
2009 Poursey ed	Iran 1T 1Med	400 p 3.75m	I, R	63 ADR in 40p (47ADR_T) I=0.100 E=0.0150	Prospective cohort with intensive monitoring (by a pharmacist and a pharmacologist) with two questionnaires to characterize ADRs and "all patients [...]were followed daily until discharge".	*Authors exclude: hospital stay <1 day, administrative errors and non compliance *3276 patient-days were studied *Explicitly mention: "patients who did not consume any drugs were omitted"
2009 Santos	Brazil 1T 1Ped	1764 p 24m	R, S	302 ADR in *302p* I=0.0081 E=0,0045	Chart review of all patients (children < 16 years) were performed 3 times a week.	*"Pharmacy interns were trained to detect and report suspected ADRs, under the supervision of pharmacists"

Table III1. General characteristics on included studies of ADR_{In}.

[A] **Second column: Hospital type**: Defines number of hospitals and hospital type: ***T***: teaching or university hospital; ***G:*** *non teaching hospital (for example, "2T" means 2 teaching hospitals).* **Wards:** Number and type of wards in which study occurred. The following abbreviations were used for ***type of ward***: Med: Internal Medicine, S: surgery, ICU: intensive care unit, Ped: pediatric ward, Ger: geriatric ward/unit, Ob: Gynecology/Obstetrics, **R**: not reported (for example, "1Ped" means the study was performed in 1 pediatric ward.

[B] **Third column. Sample size:** number of patients exposed to drugs (**p:** patients). **Duration** of study (**m:** months).

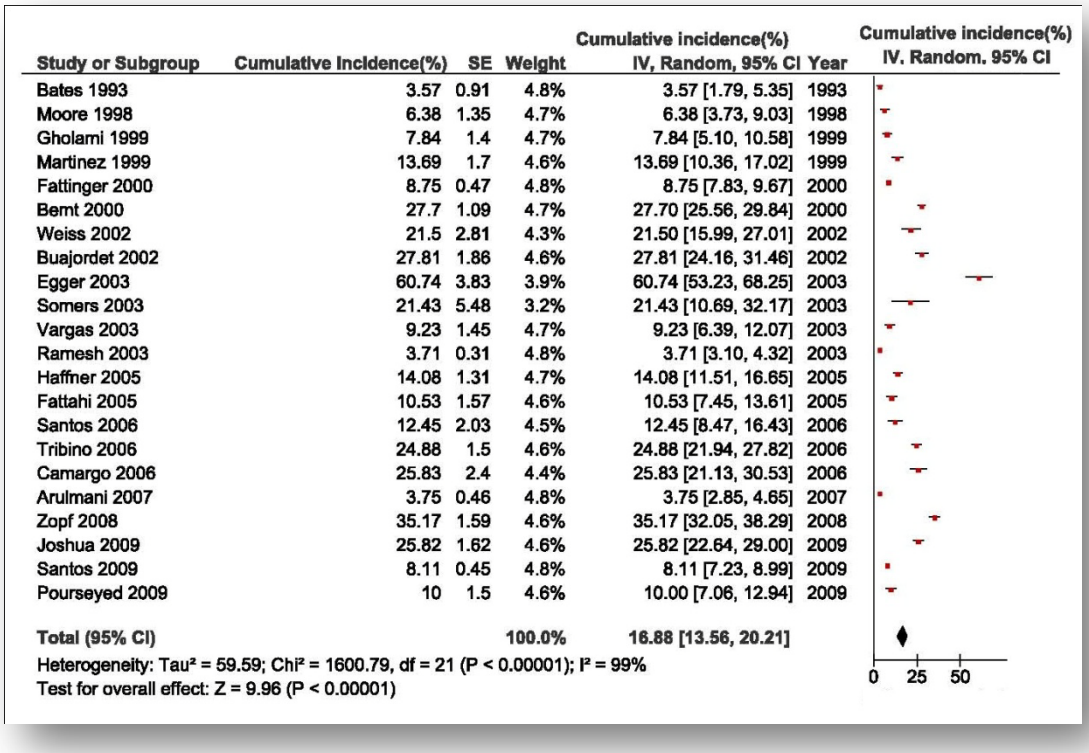
[C] **Fourth column**. **Method for ADR identification**: Every method that authors used for ADR identification is reported, according to our criteria (see text). Abbreviations used: ***S***: spontaneous reporting, ***Sl***: Solicited reporting, ***I:*** Intensive monitoring, ***P:*** prospective monitoring, ***C***: computerized system with investigation of every alert to validate ADR; ***Co:*** Codification/codes; ***R***: chart review.

[D] **Fifth column**: **ADR incidence*: Number of ADRs, patients with ADRs, cumulative incidence of ADR*** and ***Standard Error*** are represented. For example: "21 **ADR** in 21 **p** (31**ADR_T**). **I**=0.0639 ; **E**=0.0135" means that: 21 ADR_{In} (**ADR**) were identified in 21 patients(**p**), the number of total ADR (**ADR_T**, which includes ADR_{In} and ADR_{Ad}) was 31, the calculated cumulative incidence of ADRIn(**I**) was 0.0639 and its Standard Error (**E**) was 0.0135. Note: when the number of patients is *italic underlined*, it means that we had to assume number of ADR was equal to number of patients that suffered an ADR, because number of patients with ADR_{In} was not supplied (just number of ADR_{In} was reported).

[E] **Remarks**: some authors' remarks for each study are presented. "Modified data" refers to studies in which we didn't use raw data in order to correct inconsistencies or to exclude ADR_{Ad}.

ADR incidence

The pooled ADR cumulative incidence estimated in the meta-analysis was 16.88% (CI95% 13.56,20.21%), however there was heterogeneity: I^2=99% (as shown in figure III3).



Study or Subgroup	Cumulative Incidence(%)	SE	Weight	Cumulative incidence(%) IV, Random, 95% CI	Year
Bates 1993	3.57	0.91	4.8%	3.57 [1.79, 5.35]	1993
Moore 1998	6.38	1.35	4.7%	6.38 [3.73, 9.03]	1998
Gholami 1999	7.84	1.4	4.7%	7.84 [5.10, 10.58]	1999
Martinez 1999	13.69	1.7	4.6%	13.69 [10.36, 17.02]	1999
Fattinger 2000	8.75	0.47	4.8%	8.75 [7.83, 9.67]	2000
Bemt 2000	27.7	1.09	4.7%	27.70 [25.56, 29.84]	2000
Weiss 2002	21.5	2.81	4.3%	21.50 [15.99, 27.01]	2002
Buajordet 2002	27.81	1.86	4.6%	27.81 [24.16, 31.46]	2002
Egger 2003	60.74	3.83	3.9%	60.74 [53.23, 68.25]	2003
Somers 2003	21.43	5.48	3.2%	21.43 [10.69, 32.17]	2003
Vargas 2003	9.23	1.45	4.7%	9.23 [6.39, 12.07]	2003
Ramesh 2003	3.71	0.31	4.8%	3.71 [3.10, 4.32]	2003
Haffner 2005	14.08	1.31	4.7%	14.08 [11.51, 16.65]	2005
Fattahi 2005	10.53	1.57	4.6%	10.53 [7.45, 13.61]	2005
Santos 2006	12.45	2.03	4.5%	12.45 [8.47, 16.43]	2006
Tribino 2006	24.88	1.5	4.6%	24.88 [21.94, 27.82]	2006
Camargo 2006	25.83	2.4	4.4%	25.83 [21.13, 30.53]	2006
Arulmani 2007	3.75	0.46	4.8%	3.75 [2.85, 4.65]	2007
Zopf 2008	35.17	1.59	4.6%	35.17 [32.05, 38.29]	2008
Joshua 2009	25.82	1.62	4.6%	25.82 [22.64, 29.00]	2009
Santos 2009	8.11	0.45	4.8%	8.11 [7.23, 8.99]	2009
Pourseyed 2009	10	1.5	4.6%	10.00 [7.06, 12.94]	2009
Total (95% CI)			**100.0%**	**16.88 [13.56, 20.21]**	

Heterogeneity: Tau² = 59.59; Chi² = 1600.79, df = 21 (P < 0.00001); I² = 99%
Test for overall effect: Z = 9.96 (P < 0.00001)

Figure III3. **Forest plot.** The global forest plot of the meta-analysis is presented.

Studies with the *highest* incidence estimates were:

• Egger (2003): 60.7% (CI95%: 53.2,68.2). A study from Germany that performed prospective monitoring of all patients admitted to a geriatric ward to compare the ADR rate predicted by a computerized pharmaceutical database to that determined by direct observation.

• Zopf (2008): 35.2% (CI95%: 32.0,38.3). A Germany cohort of all patients admitted to 2 medical wards in 2 university hospitals, with intensive monitoring (daily, by a trained team of 3 physicians, 1 pharmacologist and 2 pharmacists) to characterize risk factors associated with ADRs after admission.

Studies with the lowest incidences were:

• Bates (1993): 3.6% (CI95%: 1.8,5.4). An American prospective cohort in 7 wards of a tertiary hospital, with daily chart review by a nurse and solicited reporting, to evaluate incidence and preventability of ADEs.

• Ramesh (2003): 3.7%(CI95%:3.1,4.3). An Indian study in which spontaneous, solicited notification and chart review were performed in all hospitalized patients. Intensive monitoring was performed only in patients suspects of having an ADR.

• Arulmani (2006): 3.8% (CI95%: 2.9,4.7). An Indian prospective cohort study of patients admitted to 3 wards, using solicited reporting and prospective monitoring to ascertain ADR frequency, severity and cost.

Subgroup analysis

The most relevant heterogeneity moderators were 1st: risk of bias, 2nd: population, 3rd: ward, 4st: method. We present all of the subgroup analyses' results below (figures III4-III12).

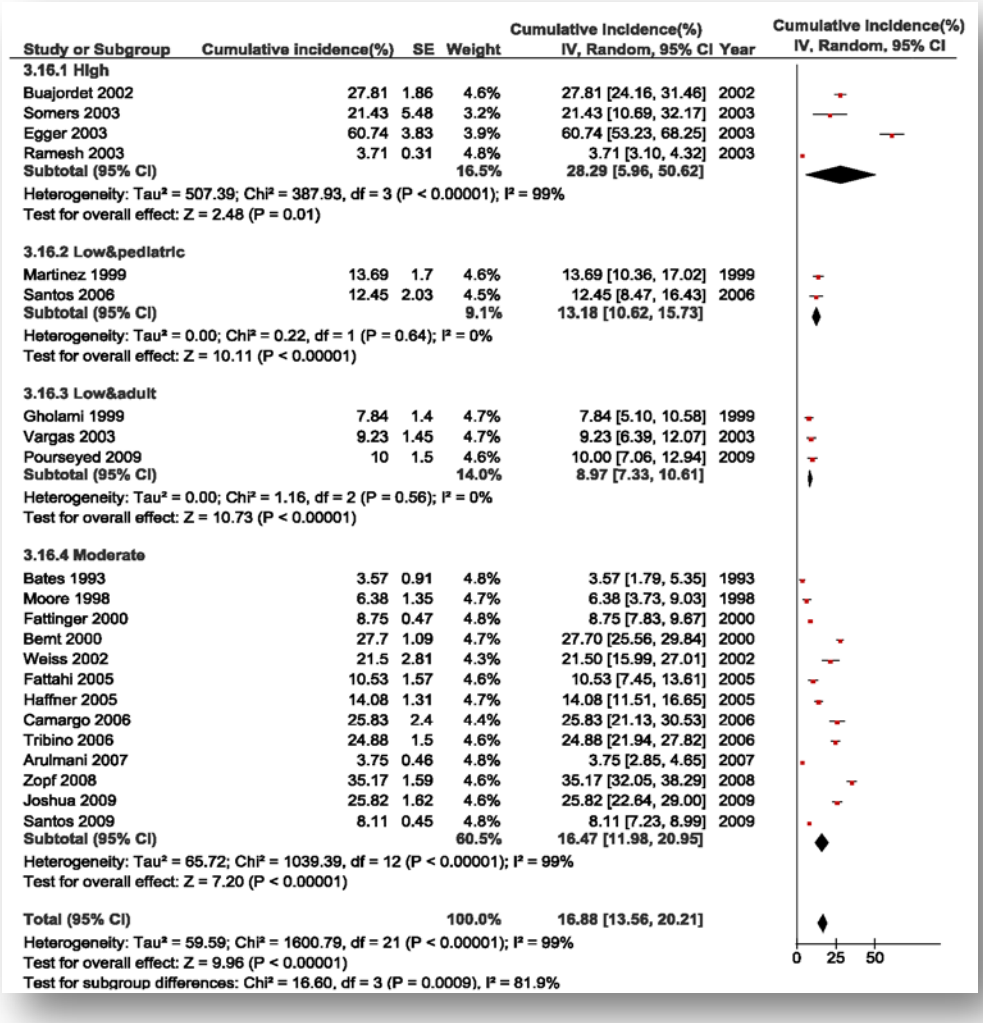


Figure III4. **Subgroup analysis based on risk of bias, according to population type (adult Vs pediatric).** Moderate and high risk of bias studies presented high heterogeneity (I^2 = 99%), that did not disappear after we adjusted for population age (pediatric versus adult). Low risk of bias studies presented low heterogeneity (I^2 = 54%) that disappeared when we adjusted for population type (I^2=0% either in adult or in pediatric group).

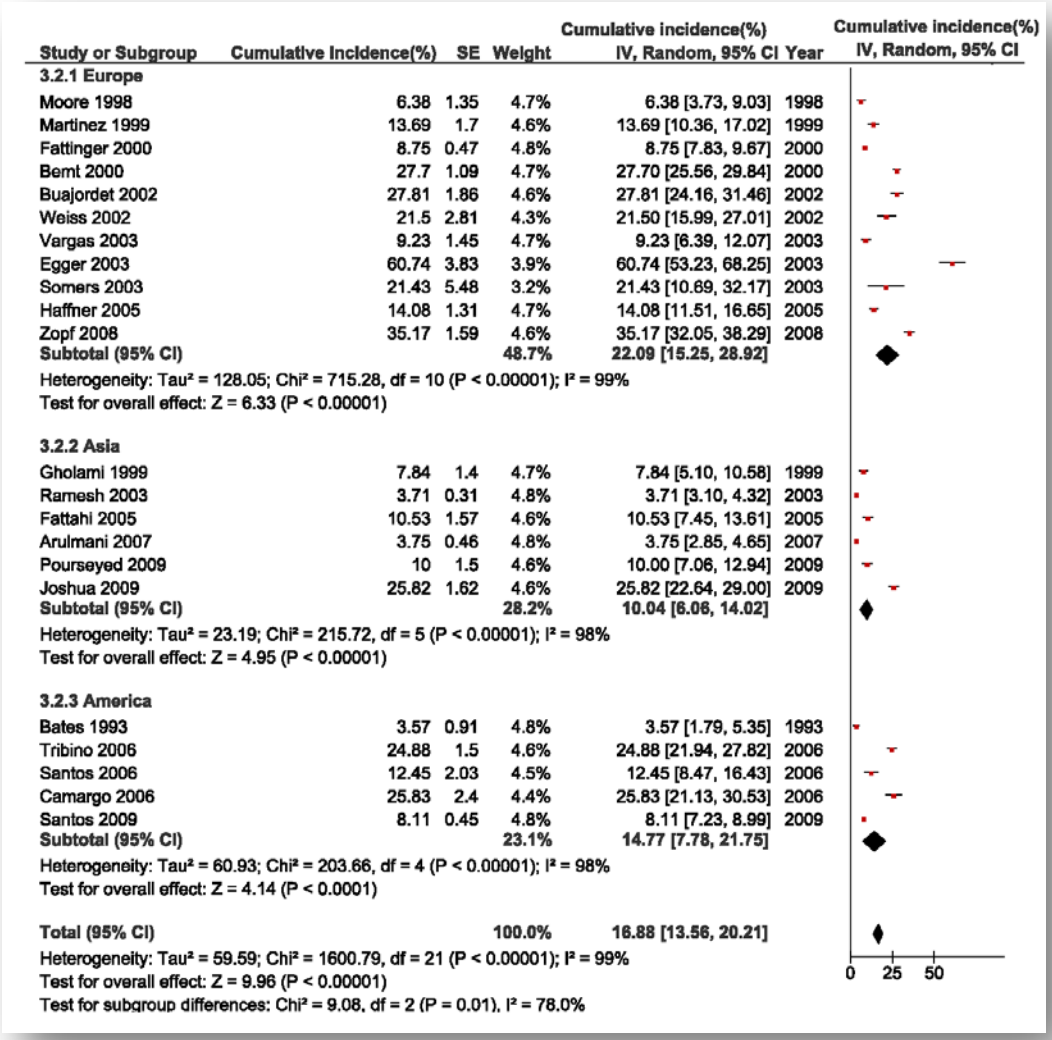


Figure III5. Subgroup analysis based on study location. There was also heterogeneity (I^2≥98%) and statistically significant difference between continents (p=0.01).

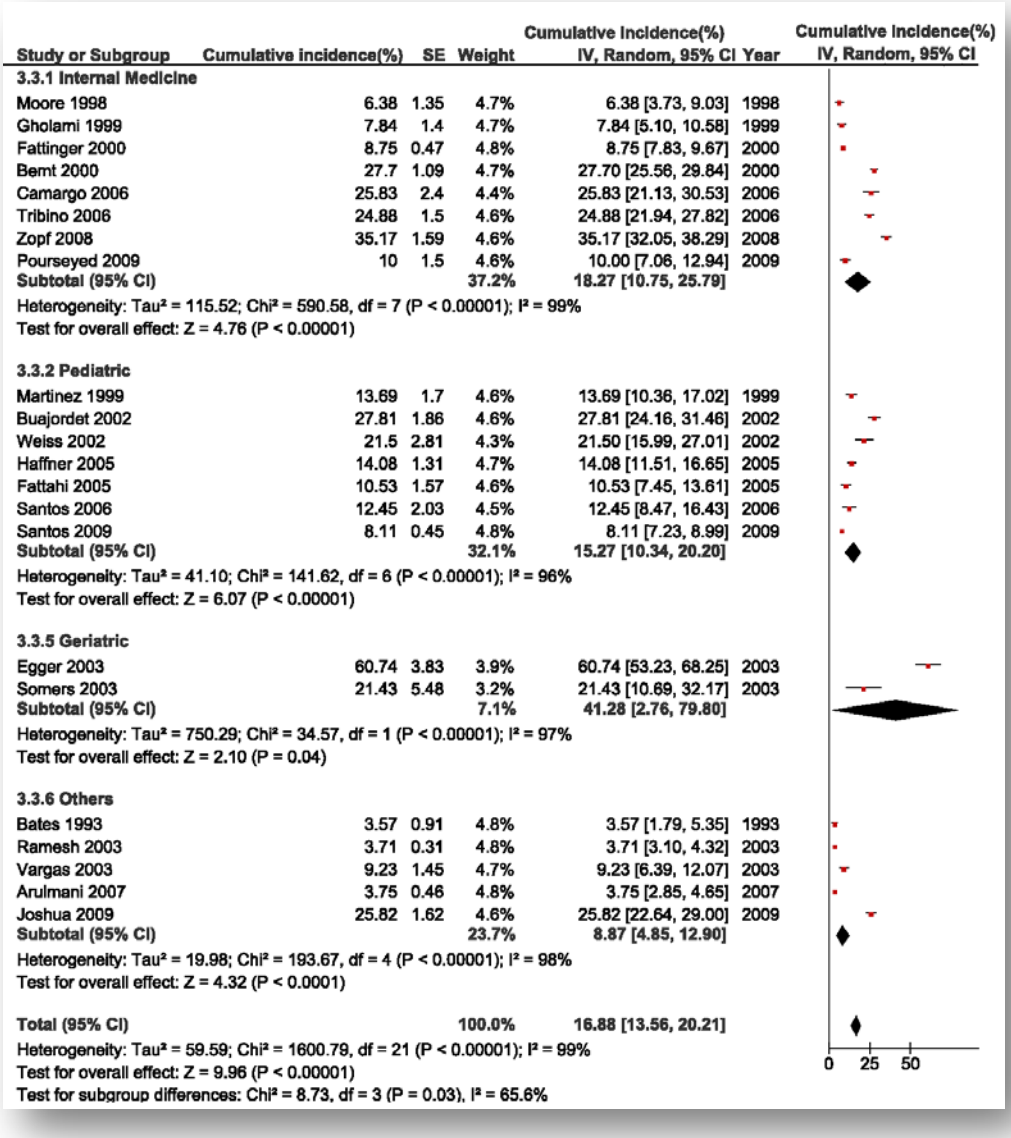


Figure III6. **Subgroup analysis of ADR frequency based on wards.** There is heterogeneity in all of them (I^2=99%), slightly smaller in the Pediatric ward (I^2=98%).

Except for the subgroup of risk of bias (adjusted to population), all subgroups presented heterogeneity. Studies with low risk of bias, adjusted to population, had no statistical heterogeneity (I^2=0%): mean incidence of ADRs in low risk of bias studies performed in adults was 8.97% (CI95%: 7.33-10.61%) and in children was 13.18%(CI95%: 10.62-15.73).

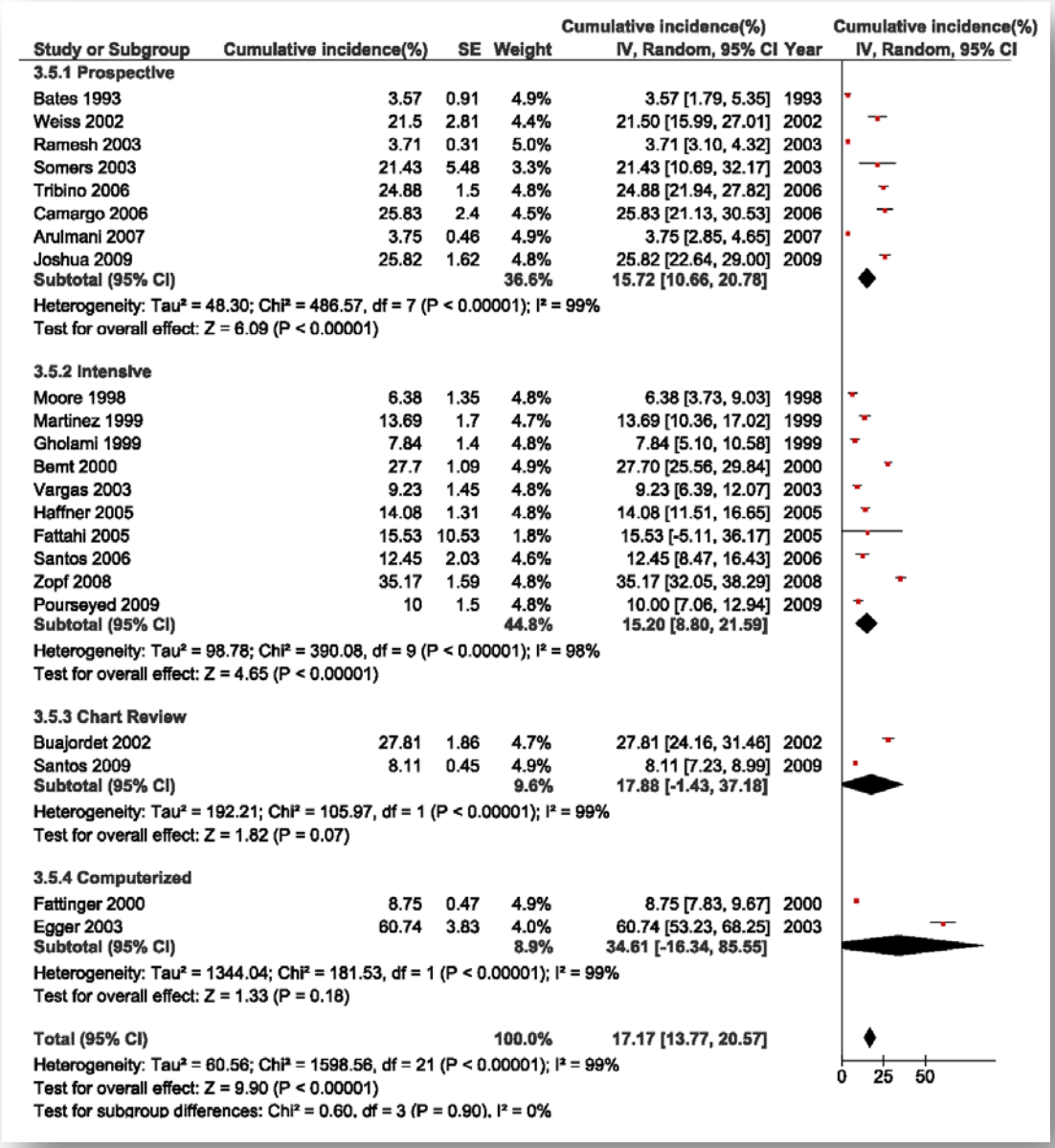


Figure III7. **Subgroup analysis according to method used to detect ADRs.** Many studies had more than one methodologies but none applied exactly to the same population (not comparable); in that case, we attributed to that study the methodology that was more comprehensive. All subgroups presented heterogeneity, slightly smaller in intensive monitoring (I2 = 98%), not statistically significant (p=0.90).

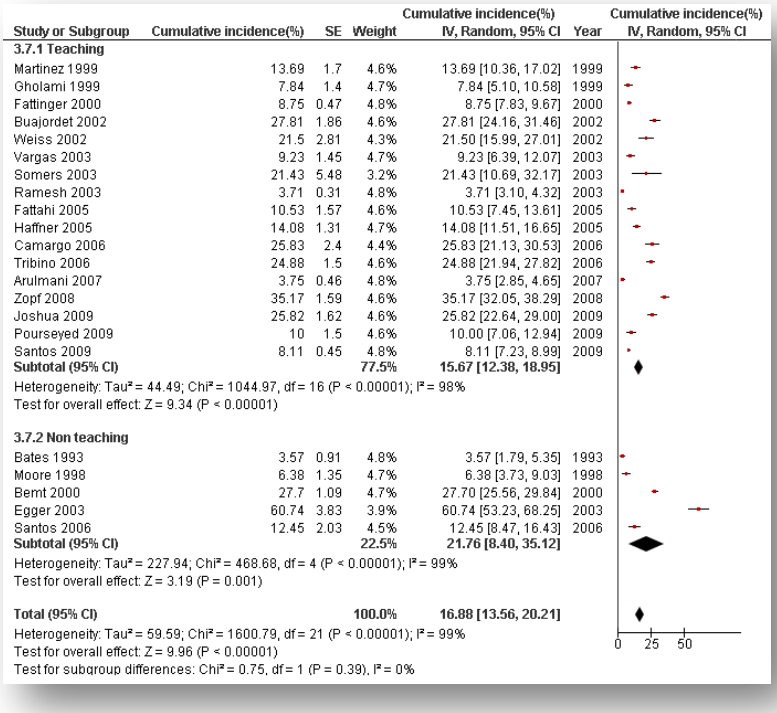


Figure III8. **Subgroup analysis according to hospital type.** There was heterogeneity in all subgroups.

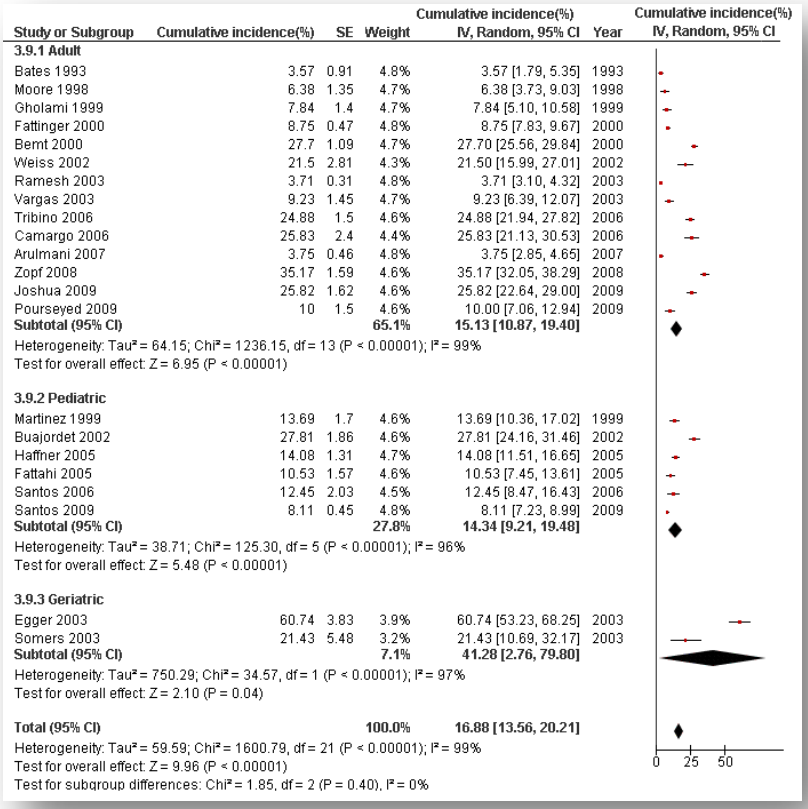


Figure III9. **Subgroup analysis according to population.** Every subgroup had heterogeneity (I^2=96%-99%); there was no statistically significant difference between subgroups of population.

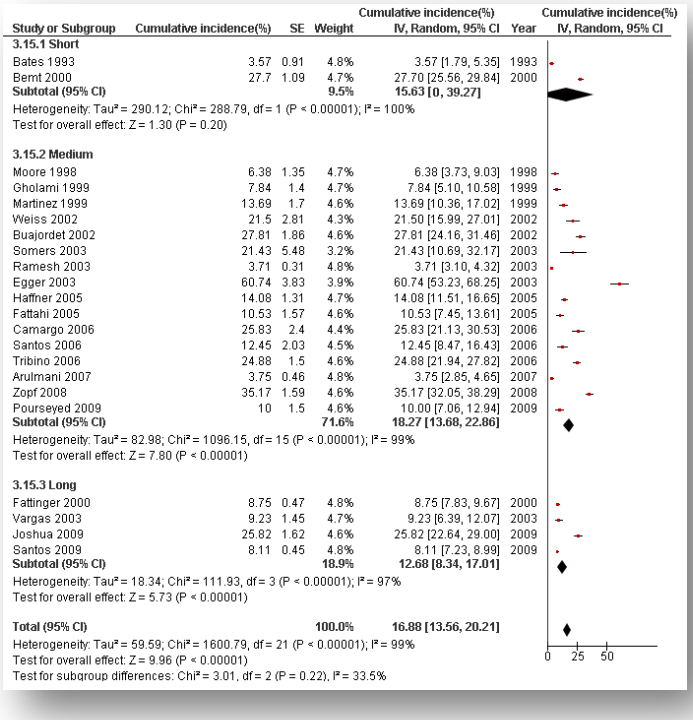


Figure III10. **Subgroup analysis according to study duration.** There was heterogeneity in all subgroups.

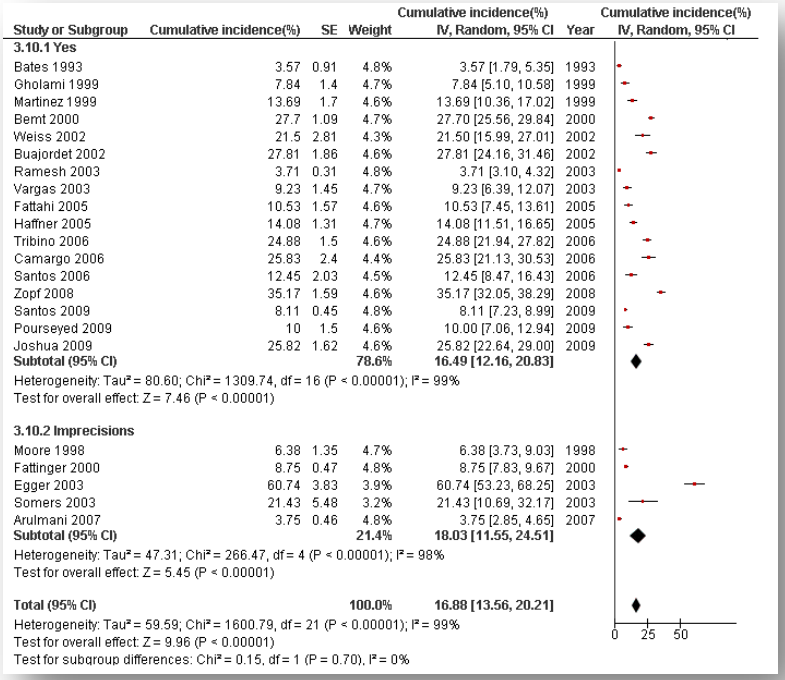


Figure III11. **Subgroup analysis according to definition of ADR.** Subgroup "Yes" for a strict application of WHO's definition of ADR; subgroup "imprecisions" for studies that had slight imprecisions for application of ADR definition. There was heterogeneity in both subgroups.

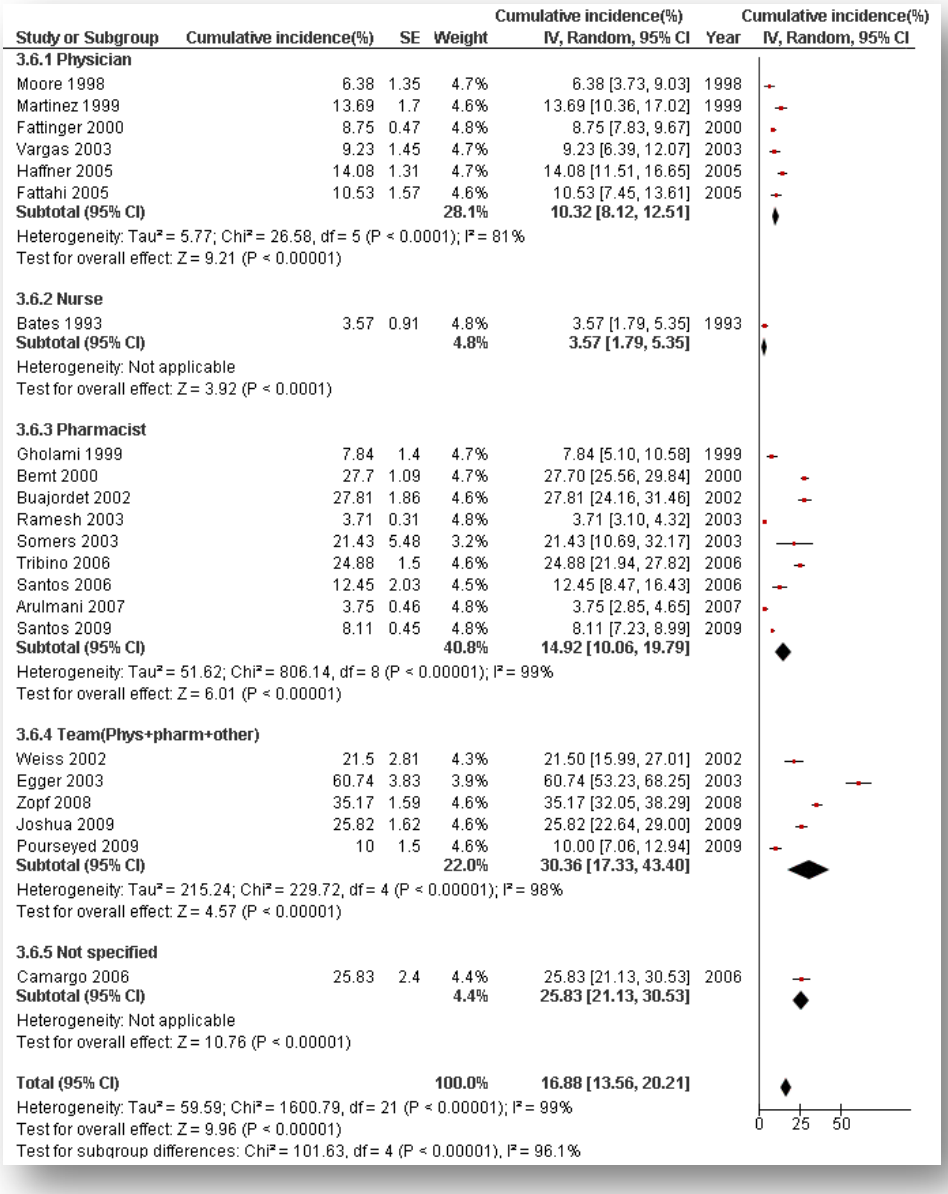


Figure III12. **Subgroup analysis according to expert that detected ADR: physician, pharmacist, nurse or team composed of several different experts.** There was heterogeneity in all subgroups, slightly smaller in physicians (I^2=81%), with statistically significant difference between subgroups (p<0.00001).

We plotted ADR incidence against study size: smaller studies tended to identify higher incidences. Our funnel plot was not completely symmetric (probably because although we emailed authors asking for unpublished data, none was supplied).

Risk of bias assessment

All studies had low risk of bias in the description of study design, while only one study calculated the intended study sample size. Most studies reported strategies to prevent selection bias (like strict intensive or prospective monitoring, applied to all patients and not just to ADR suspects), but the majority did not report strategies to prevent information bias. In figures 21 and 22 we present the summary of our quality evaluation of included studies, according to each parameter assessed - risk of bias graph and risk of bias summary.

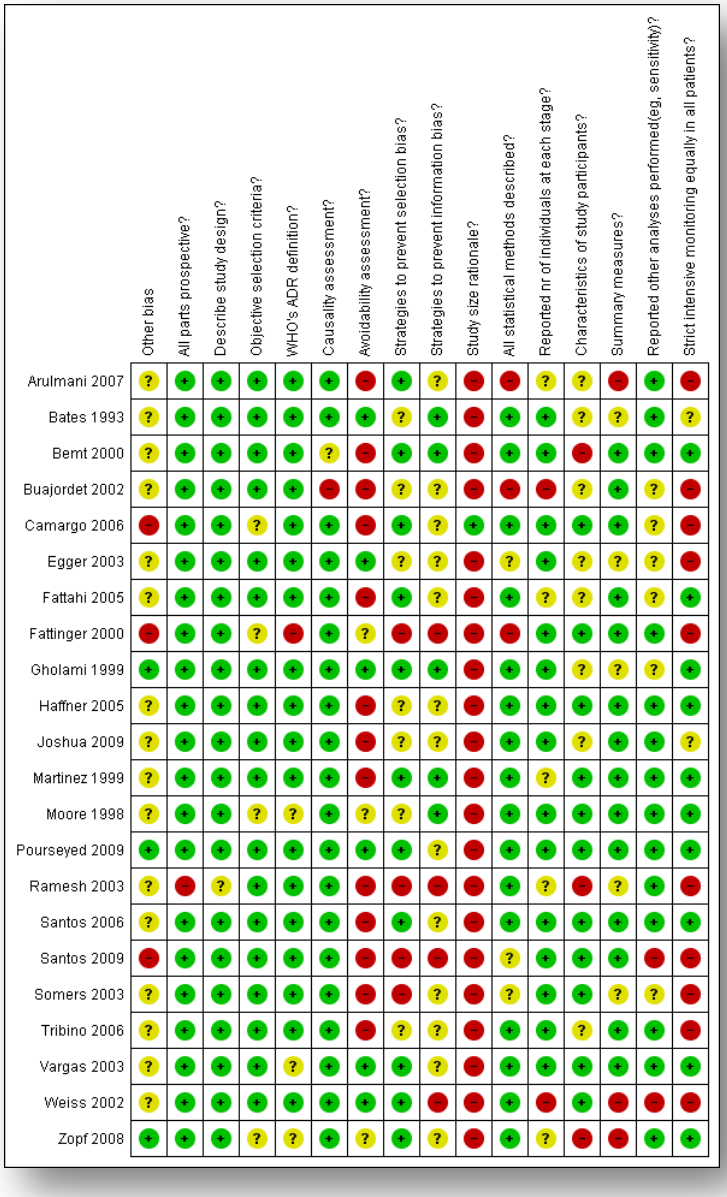


Figure III13. Risk of bias summary. Performance of major risk of bias criteria for each study. Green circles: low risk of bias. Yellow circles: moderate or unknown risk of bias. Red circles: high risk of bias.

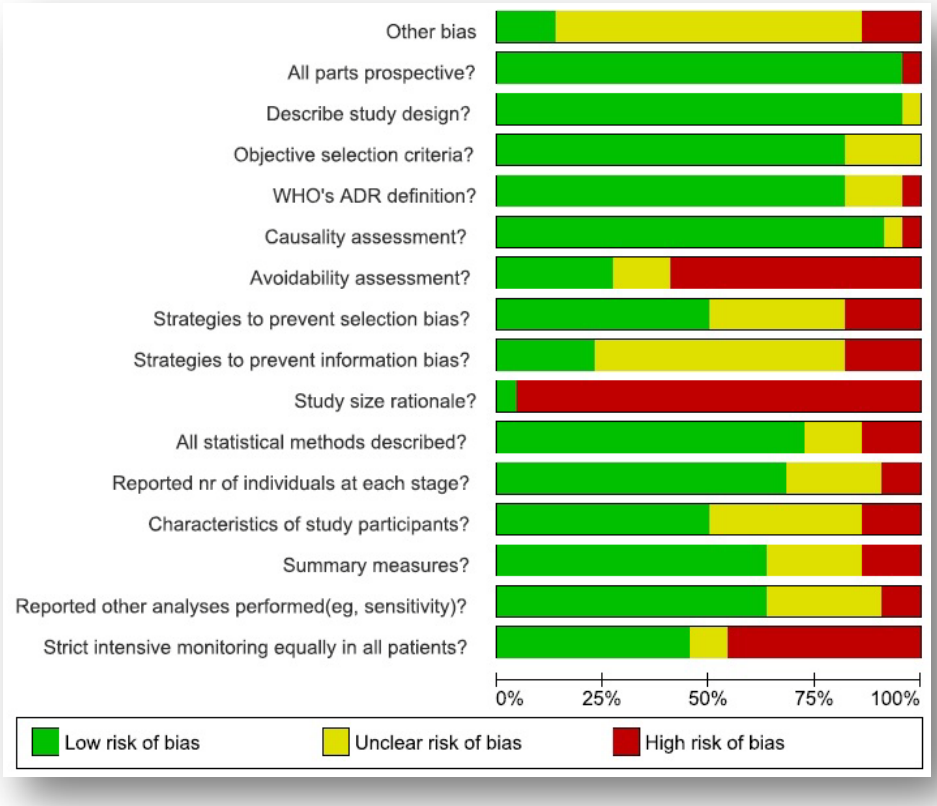


Figure III14. Risk of bias graph. Summary of global study performance for risk of bias criteria.

In summary, from 4139 studies initially found, 22 were included. Our meta-analysis indicates that ADRs may occur in 16.9% (CI95%: 13.6, 20.2%) of patients during hospitalization; however, this estimate has to be viewed with caution because there was significant heterogeneity (I^2 = 99%), as expected. The most significant moderators of heterogeneity were risk of bias, population, ward, and methodology for ADR identification. Low risk of bias studies adjusted for population (pediatric versus adult) had I^2 = 0%.

Table III2. Risk of bias assessment for every quality criteria and for each study

Study (author, year)	*Multicenter?*	*All parts prospective? Describe study desian* Objective and adequate selection criteria**	*Diagnostic criteria/ definition of ADR*	*Causality assessment*	*Avoidability assessment*	*Methods to avoid selection bias **	*Methods to avoid information bias**	*Rationale for study size**	*Describe all statistical methods**	*Report nr of individuals at each stage**	*Characterize study participants**	*Complete summary measures**	*Report other analyses performed**	*Intensive monitoring (see text)?*	*Methods to avoid other bias?*
1993 Bates	N	Y Y Y	Y (WHO)	Y (Naran-jo)	Y ("4 point scale")	U	Y	N	Y	Y	U	U	Y	U (nurse)	U
1998 Moore	N	Y Y U	U (just serious ADRs)	y	U	N	N	N	Y	Y	Y	Y	Y	Y	U
1999 Gholami	N	Y Y Y	Y (WHO)	Y (Naran-jo)	Y (Schumock)	Y	Y	N	Y	Y	U	N	U	Y	Y
1999 Martínez-Mir	N	Y Y Y	Y (WHO)	Y(Spanish Drug)	N	Y	Y	N	Y	U	Y	Y	Y	Y	U
2000 Bemt	Y	Y Y Y	Y (WHO definition)	U	N	Y	Y (adjusted Odds Ratio)	N	Y	Y	N	Y	Y	Y (pharmacist)	U
2000 Fattinger	Y	Y Y U	U:"clinically relevant"	Y (Naranjo)	U	N	N	N	N	Y	Y	Y	Y	N	N
2002 Buajordet	N	Y Y Y	Y	N	N	U	U	N	N	N	U	Y	U	N (chart review)	U
2002 Weiss	N	Y Y Y	Y (WHO)	Y (Naranjo modified)	Y	Y	N	N	Y	N	Y	N	N	N	U
2003 Egger	N	Y Y Y	Y (WHO)	Y (Schumock)	Y(Naranjo)	U	U	N	U	Y	U	U	U	N	U
2003 Ramesh	N	U Y Y	Y (WHO)	Y (WHO)	N	N	N	N	Y	U	U	U	Y	N	U
2003 Somers	N	Y Y Y	Y	Y(WHO)	U	N	U	N	U	Y	Y	U	U	N	U
2003 Vargas	N	Y Y Y	U(Karch& Lasagna)	Y (WHO)	Y	Y	U	N	Y	Y	Y	Y	Y	Y	U
2005 Fattahi	N	Y Y Y	Y (WHO)	Y (WHO)	N	Y	U	N	Y	U	U	Y	U	Y	U
2005 Haffner	N	Y Y Y	Y (WHO)	Y (WHO)	N	U	U	N	Y	Y	Y	Y	Y	Y	U
2006 Camargo	N	Y Y U	Y (WHO)	Y(Naranjo)	N	Y	U	Y	Y	Y	Y	Y	U	N	N
2006 Santos	N	Y Y Y	Y (WHO)	Y (WHO)	N	Y	U	N	Y	Y	Y	Y	Y	Y	U
2006 Tribiño	N	Y Y Y	Y (WHO)	Y (Naranjo)	N	U	U	N	Y	Y	U	Y	Y	N	U
2007 Arulmani	N	Y Y Y	Y WHO)	Y (Naranjo)	N	Y	U	N	N	U	U	N	Y	N	U
2008 Zopf	Y	Y Y U	U (WHO, imprecisions)	Y (Naranjo)	U	Y	U	N	Y	U	N	N	Y	Y	Y
2009 Joshua	N	Y Y Y	Y(WHO)	Y(WHO)	N	U	U	N	Y	Y	U	Y	Y	N	U
2009 Pourseyed	N	Y Y Y	Y (WHO)	Y (WHO)	Y (Schumock)	Y	U	N	Y	Y	Y	Y	Y	Y	Y
2009 Santos	N	Y Y Y	Y (WHO)	Y (Naranjo)	N	N	N	N	U	Y	Y	Y	N	N	N

IV.DEVELOPMENT OF NEW METHODOLOGIES IN THE DETECTION OF ADRs

Methods for ADR detection

There are several methods for ADR detection (Davies *et al,* 2007; Smith *et al*, 1996), namely: spontaneous reporting, administrative databases, chart review, computerized systems, cohort monitoring (either prospective or intensive) and trials. Figure IV1 summarizes them, including the ones that were further characterized in this thesis.

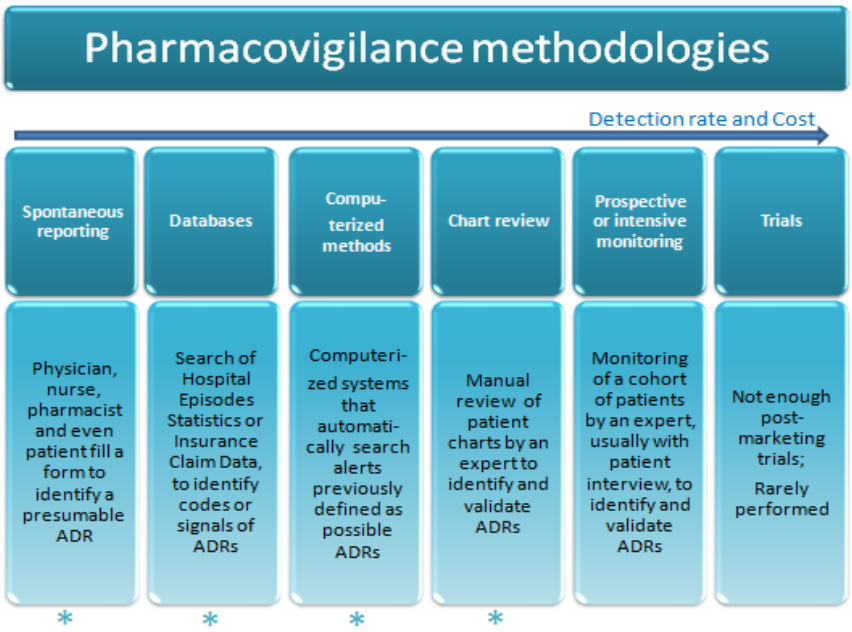


Figure IV1. Some of the main methods of Pharmacovigilance. Cost increases as detection rate grows, making several of these approaches impossible to perform as a continuous Pharmacovigilance method. Remark: these costs are merely indicative (for example, a computerized methodology may be less expensive than a chart review). Asterisks show the methods that were further explored in this thesis.

We aimed to explore four methodologies for the detection of ADRs: spontaneous reporting, database methodologies, chart review and a simple computerized method (with low computation resources to maintain respective costs low). Our original work of developing new methodologies for the detection of ADRs was based on databases and on computer-assisted chart review; we will discuss them in depth in this chapter. Also, short considerations about spontaneous reporting (assessed in one of our studies, Miguel *et al*, 2013a: appendix 2) and manual chart review (assessed in two of our studies, Miguel *et al*, 2013a: appendix 2 and Miguel *et al*, 2013b: appendix 3) will be performed in this chapter.

Spontaneous reporting

We searched the spontaneous reporting rate in Portugal in the last decade: we found an increase in the number of reports. There is also a trend of increase in the number of reports performed by Pharmaceutical Industries. However, the spontaneous reporting rate could still be markedly improved.

The number of National spontaneous notifications of ADRs from 2000 to 2009 was 13,562, corresponding to a mean prevalence of 0.001% ADRs from hospitalizations within that period of time in Portugal (more detailed in appendix 3). Furthermore, spontaneous reports that arise from hospitals should be stimulated.

Therefore, there is a need to develop a methodology that has higher detection rates than spontaneous reporting.

Chart review

Two manual chart reviews were performed: the first chart review was performed for comparison with database methodology in simple detection of ADRs, and the second chart review was performed for comparison with a computerized methodology and for deep characterization of ADRs.

2.1 First chart review - simple detection of ADRs

Methods

This work is available in appendix 2 for further detail. A retrospective chart review of hospitalized patients in CHUC (Central University Hospital of Coimbra) in 2008 was performed for ADR detection (that year was selected for enhanced comparability of the database methodology, in which most recent year with complete database information available was 2008). The number of person-hours spent in this methodology was registered. Several strict criteria were utilized (among other data to be filled in a previously built and tested formulary):

- WHO's definition of ADR (WHO 1972)
- WHO's causality assessment of ADR (WHO 2005)
- Schumock and Thornton (1992) preventability assessment
- Hartwig *et al* (1992) severity assessment

- Rawlins and Thompson (1977) classification of each ADR in: type A (predictable ADRs of *A*ugmented effect) or type B (*B*izarre unpredictable reactions).

We previously calculated sample size to independent chart review (95 patients necessary) using an online calculator (The Survey System, 2011).

Results

Of 100 random patients selected, all had prescribed drugs, and 9 suffered an ADR (9% of prevalence). Seven ADRs occurred during hospital stay and 2 were present on admission. According to WHO's causality assessment (2005), 3 ADRs were classified as certain, 3 as probable and 1 as unlikely. Four ADRs were preventable (Schumock and Thornton, 1992). Three ADRs were severe (Hartwig *et al*, 1992), 1 was moderate and 4 were mild. Eight ADRs were type A and one was type B (Rawlins and Thompson, 1977).

2.2 Second chart review - complete characterization of ADRs

Methods

This work is available in appendix 4 for further detail. A retrospective descriptive study was performed at CHUC, Portugal. From all hospitalized patients in 2010, we selected a random sample of 118 patients to perform manual chart review. We followed WHO's definition of ADR. From each patient, chart was reviewed, including: discharge note, diaries, all drugs administrated, laboratory and coding data, as well as every aspect that could constitute a symptom or sign of an ADR, even if not detected previously by responsible medical team. For complete validation, all cases were reviewed (not just the cases with a computer alert).

All ADRs were registered, described and classified according to WHO's causality assessment, preventability (Schumock and Thornton criteria, 1992) and severity (Hartwig *et al*, 1992). Associated drugs (and all administered) were registered. The reviewer also registered if ADR was previously undetected, as well as age, gender, ward, hospitalization time. Every relevant clinical information was registered.

Results

Chart review allowed the identification of 12 ADRs in 12 patients, one of them fatal (due to infection after the use of chemotherapy). 117 patients were exposed to drugs, thus ADR prevalence was 10.2% (12/117). The most frequent ADRs were hyperkalemia (16.7% of all ADRs) and warfarin leading to International Normalized Ratio levels that led to surgery delay (16.7%).

Systems more frequently affected were hematologic (33.3%), renal (25%) and cardiovascular (16.7%). Drugs more frequently involved were non steroidal anti-inflammatory drugs (NSAIDs, 25%), antibiotics (16.7%), anticoagulants (16.7%) and diuretics (16.7%).

Five ADRs were preventable (according to Schumock and Thornton classification of 1992). There were 3 severe ADRs, 5 moderate and 4 mild (Hartwig *et al*, 1992). Patients with ADRs were exposed to a higher number of drugs than patients without ADRs (Mann-Whitney test, p=0.001); there was no statistically significant difference in age, hospitalization time, number of days in intensive care units, or gender (Fisher's exact test).

Our first chart review (simpler and destined to detect ADRs) obtained a prevalence of ADRs of 9% and a cost of 35 person-hours. Our second chart review (more complete, destined to characterize ADRs and all drugs administered) obtained a prevalence of 10.2%, at a high cost of 69 person-hours. These data are illustrated in figure IV2. There is a need to develop a methodology to reduce manual chart review's resources, namely a computerized-assisted chart review.

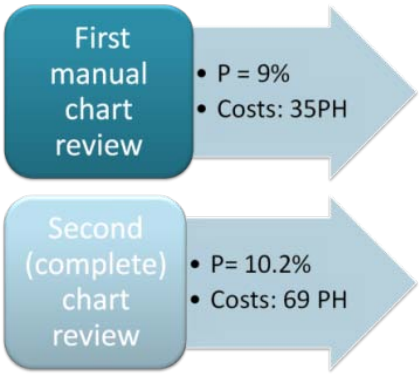


Figure IV2. Chart review results in the detection of ADRs.

P: prevalence. PH: person-hours spent in each methodology.

In summary, every methodology has its methodological issues:

Spontaneous reporting is the most used methodology (WHO, 2012; Figueiras *et al,* 2006), it is cheap, and is the only Pharmacovigilance method continuously used in the majority of countries, being the main support of WHO's International Drug Programme. However, it has the smallest detection rate of all methods.

Databases (either administrative, hospital episodes statistics, or large insurance claims data) are not widely used, but they might represent an opportunity (since they contain large amounts of patient data).

Computerized systems may be an interesting method, but attention is needed to build rules and algorithms with high specificity to avoid high costs (Ammenwerth *et al*, 2008; Bates *et al,* 2003). Other problems of this methodology are the dependency of structured data, the difficulty with using data from narrative notes and the occasional inaccuracy of ADR detection algorithms (Forster *et al*, 2012).

The *Chart review* method (either prospective or retrospective) is interesting, but too resource-consuming to be used continuously.

As for *Prospective and Intensive monitoring* (intensive monitoring has the largest detection rate, being considered by most as the *gold standard*), their resource costs are even higher, making it impossible for continuous use as a Pharmacovigilance method.

Postmarketing trials are seldom used and each of them is too specific for being developed as a Pharmacovigilance methodology.

In Portugal and in many European countries, spontaneous reporting is the only continuously applied Pharmacovigilance method, due to its low cost. Prospective monitoring is also frequently performed in several countries in Europe, but not continuously. In the United States, computerized methods and the search through large insurance databases are widely used, because in the US hospitals almost all hospitalization data is already computerized.

The limitations of spontaneous reporting, the high cost of intensive monitoring, the economic impossibility to build a computerized system in Portugal and the fact that in Portugal and many other countries there are no real and complete data about ADRs that occur during hospitalization (ADR_{In}), were the motivations of this thesis.

Our purpose was to develop and validate methodologies of ADR detection that could highly increase detection rate of ADRs, with a small increase in the resources needed to use it. We intended to assess methodological issues in each method, and to identify one or several methods that could be used as a continuous Pharmacovigilance methodology in Portugal. We also intended to estimate how many ADRs exist in Portugal in hospitalized patients.

A) ADMINISTRATIVE DATABASES: VALIDATION STUDY

Rationale for the development of an administrative databases methodology

Although the utilization of databases for ADR detection is not popular, it may have advantages if developed and validated as a methodology, such as: information of several hospitals, years and countries already available, clinical coding data from which signals of ADRs might be extracted, low resources needed and a detection rate probably higher than spontaneous reporting.

Therefore, we aimed to develop a database methodology for ADR detection. First we performed a *validation study*, in which several diagnostic codes available in the database were searched, selected and validated after manual chart review to identify the codes with highest positive predictive value (PPV). The results of this research can be found in appendix 2. Then, a *nation-wide study* was performed with the validated database methodology, to obtain the first portuguese national estimate of frequency of ADR that occurred in hospitalized patients (appendix 3).

Database methodology - validation study

In Portugal the only used Pharmacovigilance methodology is spontaneous reporting. In the central hospital selected for the validation study (Central University Hospital of Coimbra - CHUC), there are no specific methodologies currently applied for ADR detection. There is currently no specific continuous formation for physicians, pharmacists or nurses to develop prospective or intensive monitoring for ADR detection and characterization on a regular basis. Also, considering the portuguese economic crisis, it is not possible at the moment for this hospital to invest in building a computerized system for ADR detection or even for adjusting the existing computerized systems to prospectively detect ADRs in hospitalized patients. These aspects enhance the need of building a database methodology.

Methods

A retrospective study was performed for ADR detection using International Classification of Diseases 9th Revision, Clinical Modification (ICD-9-CM) diagnostic codes of an administrative database, with all hospitalizations in 2008 from CHUC-General Hospital (CHUC-HG), Portugal. This study was performed according to CHUC's Ethics Committee.

We intended to develop a methodology that allowed us to, through CHUC-HG database: to identify and characterize ADRs (namely prevalence, clinical manifestations associated, drugs more frequently involved and risk factors), to select the codes within the database with higher PPV and to validate them by chart review.

As illustrated in figure IV3, we also aimed to compare our database methodology with spontaneous reporting and with chart review. We did so in order to build a complementary methodology that could help the Portuguese Pharmacovigilance System, without increased costs.

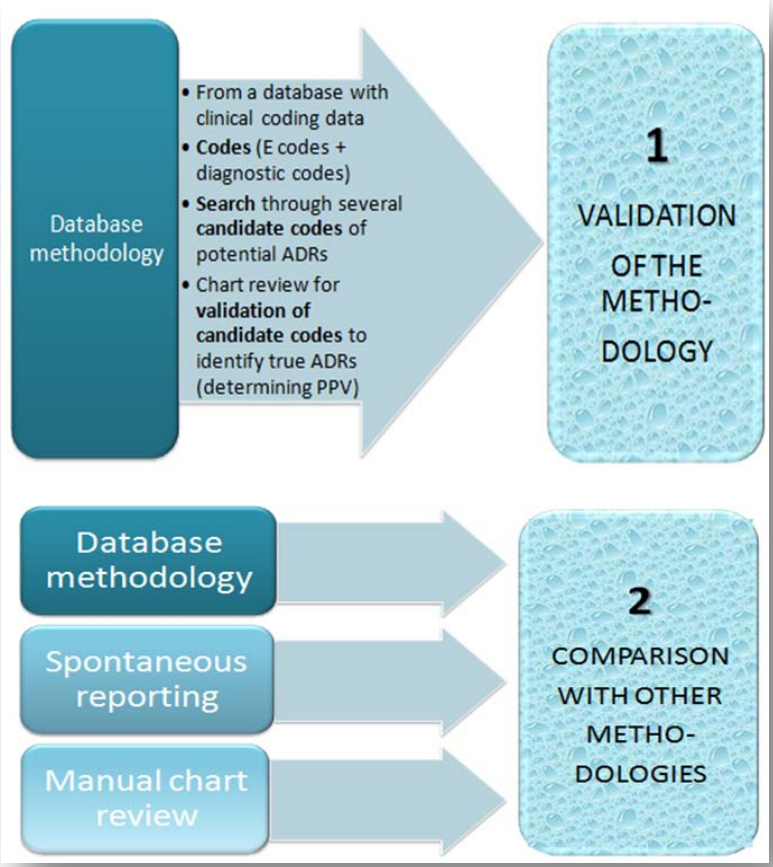


Figure IV3. Schematic representation of study design of database methodology validation study (appendix 2). First, clinical codes were selected from the CHUC database as potential signals for ADR (114 codes were tested) and validated by chart review to assess which codes corresponded to true ADRs (PPV, positive predictive value, was assessed). Then, this methodology was compared to spontaneous reporting (originated from CHUC during that period of time) and by independent chart review (of a random sample of patients, performed by the authors, in CHUC from the same period of time).

Selection and validation of clinical codes

The clinical information in our database used coding based on ICD-9-CM.

Codes searched included not only *E codes* (from E930 to E949.9, codes designed to mark ADRs, already excluding wrong doses, errors and intoxications) but also *diagnostic codes*, such as *"733.09 - Drug-induced osteoporosis"* (as reported in the literature or others considered useful). We also tested every diagnosis with the expressions: "Due to drugs", "drug-related", "*medicamentosa*" and "iatrogenic".

For validation of potential codes for ADR signals, we selected the *E codes* and the *40 diagnostic codes t*hat allowed us to identify more cases of ADR suspects which *added* information relatively to E codes, more specifically, that identified more cases of ADR suspects and didn't have an E code (this would be the result of bad coding, since ICD-9-CM instructs to use an E code with every diagnosis signaling an ADR; we wanted to detect it to increase ADR detection and improve coding).

A chart review was performed to validate ADR signals, using several strict criteria (among other data to be filled in a previously built and tested formulary). Each code was evaluated independently to calculate its PPV. Afterwards, we intended to select a few queries with the highest PPV, to build a methodology with a good global performance and easily applicable in other databases, other hospitals and other years.

Comparison with other pharmacovigilance methods

We compared database performance with *spontaneous reporting* and *chart review* (for that, a randomized group of 100 patients from the same period and hospital was selected for independent chart review). The number of person-hours spent during the application of each methodology was assessed.

Results

During the year 2008, there were 13471 hospitalizations in CHUC (10600 patients were admitted more than once during that year). Mean participant age was 64 years (standard deviation = 19.45). Forty five percent were female.

E codes generated 283 signals in the database, corresponding to 270 ADRs (in 270 patients) after validation (PPV=95%). 114 diagnostic codes were tested in the database, from which the best 40 codes generated 10752 ADR signals. For those 40 codes, 356 random ADR signals were validated through chart review, allowing the detection of 114 true ADRs with a general PPV of 32.0%. In table IV1 we represent PPV values for each of the 40 tested codes.

Diagnostic codes submitted to validation	Number of signals	Number of signals subject to validation	Signals that are true ADRs	Positive predictive value (%)
E codes	*284*	*20 (randomly selected from the 284 signals)*	*19*	*95%*
Diagnostic codes	*Signals without E code*			
Other disorders of pancreatic internal secretion including hypoglycemia	6	6	5	**83%**
Other specified aplastic anemias including due to drugs	37	16 random	8	50%
Sideroblastic anemia including due to drugs and unspecified anemia	639	20 random	1	5%
Acquired coagulation factor deficiency including due to drugs	6	6	3	50%
Second thrombocytopenia (including due to drugs)	17	17	6	35%
Drug induced neutropenia or unspecified	32	10 random	6	**60%**
Drug-induced mental disorder	4	4	1	25%
Transient mental disorders due to conditions classified elsewhere	7	7	1	14.3%
Secondary Parkinsonism (including due to drugs)	12	12	5	41.7%
Essential and other specified forms of tremor including due to drugs	12	12	3	25%
Other cerebellar ataxia including drugs	8	8	1	12.5%
Iatrogenic pulmonary embolism and infarction	17	12 random	3	25%
Phlebitis including due to drugs	41	10 random	2	20%
Mucositis (ulcerative) due to antineoplastic therapy and other drugs	1	1	0	0%
Gastric ulcer including due to drugs	74	10 random	4	40%
Hepatitis, unspecified	46	10 random	6	**60%**
Myocardial infarction	100	10 random	2	20%
Gastrointestinal bleeding, intracerebral hemorrhage	192	10 random	4	40%
Other musculary disorders including due to drugs	17	10 random	5	50%
Other anaphylactic shock including drugs	2	2	2	**100%**
Shock due to anesthesia	1	1	1	**100%**
Hypothermia due to anesthesia	2	2	0	0%
Clostridium difficile colitis pseudomembranous	22	10 random	3	30%
Acquired hypothyroidism	96	10 random	2	20%
Acid base disorders	408	10 random	2	20%
Volume depletion	547	10 random	0	0%
Disorders of fluid, electrolyte, and acid-base balance	494	10 random	3	30%
Anemia unspecified	636	10 random	3	30%
Eosinophilia	6	6	2	30%
Congestive heart failure, unspecified	756	10 random	0	0%
Iatrogenic hypotension	7	7	1	14.3%
Chronic airway obstruction	98	10 random	1	10%
Nausea and vomiting	132	10 random	0	0%
Diarrhea	39	11 random	4	36.4%
Abdominal pain	91	10 random	0	0%
Venous thrombosis and embolism including pulmonary embolism	42	10 random	1	10%
Transfer to special care	1497	10 random	1	10%
Death	832	10 random	1	10%
Transfer to another hospital	758	10 random	2	20%
Total of all queries	*10752 signals*	*356 tested signals*	*114 true ADRs*	*Global PPV of 32.0%*

Table IV1. Validation of codes and respective PPV (positive predictive values).

For a simpler global methodology with higher PPV global value, we selected the 6 queries (groups of codes) with the best PPV, from which we obtained 371 signals that corresponded to 325 true ADRs (global PPV of 87.6%, prevalence of ADRs of 2.41%).

After validation, this method required only 2 person-hours to identify and register ADRs. In table IV2, the database methodology with selected final codes is presented.

Frequency of ADRs	**Number of Signals**	**Positive predictive value (%)**
1) E codes (E930-E949)	284	95%
2) Diagnostic codes (in database records without E code, i.e., without ADR diagnosis)	**Number of signals without concomitant E code**	**Positive predictive value %**
Other disorders of pancreatic internal secretion (including hypoglycemia)	6	83%
Drug induced neutropenia or unspecified	32	60%
Hepatitis, unspecified	46	60%
Other anaphylactic shock incl. drugs	2	100%
Shock due to anesthesia	1	100%
Full algorithm (1+2)	***371 signals***	***87.6%***

Table IV2. Final database methodology. This methodology, designed to have few codes with good performances, contains E codes and 5 groups of diagnostic codes and it has a global PPV value of 87.6%.

Patients with true ADRs were older and had greater length of stay than patients without ADRs ($p<0.0001$ and $p=0.027$, respectively). There was no statistically significant difference in gender. No other risk factors for ADRs were identified.

Comparison of the database methodology with other methodologies

Seven ADRs were detected through spontaneous reporting from CHUC in 2008 (prevalence of ADR of 0.0005%). Independent chart review identified 9 ADRs (7 ADR_{In} and 2 ADR_{Ad}) from 100 patients exposed to drugs: prevalence of 9%. Only 2 ADRs had an E code. Both methodologies are compared in table IV3 in further detail.

Methodology	Database	Chart review
ADR prevalence (nr of ADRs / nr patients with drugs)	2.41% (325/13471)	9% (9/100)
% ADR during hospitalization (versus present on admission)	45.82%	77.78%
Mean person-hours required	2	35
Mean age (sd)	64 years (sd: 19.45)	60 years (sd: 20.23)
% female	45.48 %	42%
Most frequent drug groups involved	**1.** 5.9% Insulins and antidiabetic agents **2.** 2.7% Antineoplastic and chemotherapy **3.** 2.7% Anticoagulants	**1.** 33.3% NSAIDs **2.** 22.2% Diuretics **3.** 11.1% each: antibiotic, anticoagulant, chemotherapy, not specified
Most frequent manifestations associated with ADRs	**1.** 2.70% Acute renal failure **2.** 2.70% Hypoglycemia **3.** 2.43% Hepatitis	**All with 11.1%:** • Hypokalemia • Disrhythmias • Edema • Medulary aplasia • Acute renal failure • Gastrointestinal haemorrhages • Altered INR • Rash • Bronchoespasm

Table IV3. **Comparison of database methodology and manual chart review.** Abbreviations: nr=number, sd=standard deviation.

Methodological issues in the validation of the database methodology

Some of the methodological issues of the database methodology can be derived from its comparison with other methodologies, as illustrated in figure IV4:

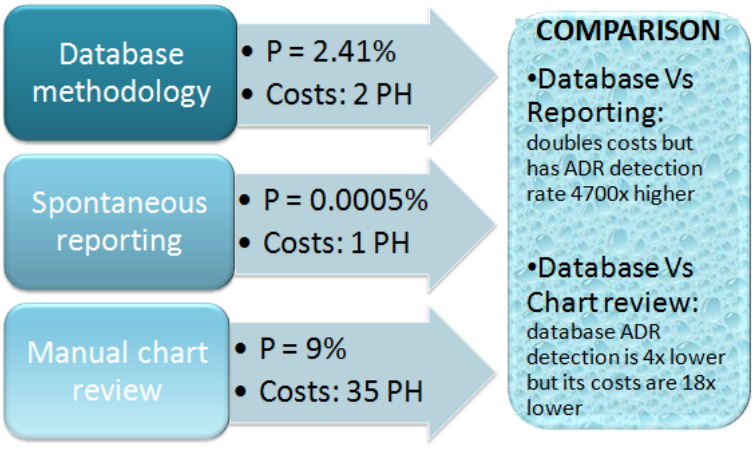


Figure IV4. Results of the comparison between database methodology, chart review and spontaneous reporting. PH: number of person-hours spent in each methodology.

This database methodology has interesting strengths in comparison with other studies that assessed ADRs in databases, such as: the fact that it identifies ADR signals beyond E codes (unlike Salmerón-García, 2010), it was validated by chart review of more than 350 signals, it identified queries that added information to E codes to complement them. The resources required (2 person-hours) were very small, allowing for a continuous application in Pharmacovigilance. It also had good a detection rate, obtaining an ADR prevalence more than 4500 times higher than the prevalence of ADR identified by spontaneous reports in that hospital.

On the other hand, there are *limitations* in the database methodology, such as: probable incomplete and wrong information that might occur in every databases, coding bias and the fact that it has a one hospital centered validation study. We chose the codes that best describe this hospital's reality, but other hospitals and countries might allow the selection of different codes. Indeed, it may be very interesting to retest all codes in other hospitals, populations, years and countries, to understand, on the one hand, which are the most universal codes, and on the other hand, which occur more in one country, or in one hospital type, or in a particular population. We are at the moment performing another database validation study in an university hospital, Hospital São João, to identify differences in the selected codes.

In conclusion, the database methodology has detection rates much higher than spontaneous reporting with an acceptable cost for continuous monitoring (much lower costs than chart review).

B) ADMINISTRATIVE DATABASES: NATION-WIDE STUDY

Rationale for a nation-wide study

After the development and validation of a database methodology with acceptable detection rates and costs (appendix 2), we intended use it to build the first national portuguese estimate of ADRs in hospitalized patients (available in appendix 3), in an attempt to complement spontaneous reporting and to help the Portuguese Pharmacovigilance System.

Methods

A retrospective study was performed for ADR identification using Hospital Episodes Statistics databases with information from all hospitals in Portugal, from 2000 to 2009, obtained from our National Health Department. These databases contained information on encrypted patient identification, episode number and process, and also information on age, sex, date of admission, date of discharge, ward(s), hospital attended (public, private), area of healthcare, district, outcome (death, discharge, transfer), payment data and International Classification of Diseases 9th Revision - Clinical Modification (ICD-9-CM) codes for: diagnoses (main diagnosis, other diagnosis up to 20), procedures (up to 20) and external causes (up to 20). Patient population included all patients hospitalized in public hospitals in Portugal, from 2000 to 2009 (we excluded ambulatory patients). Only data of the first semester of 2009 was available.

We searched E codes (from E930 to E949.9) and 5 groups of diagnostic codes selected in our validation study (table 5): disorders of pancreatic secretion, drug-induced or unspecified neutropenia, hepatitis unspecified, other anaphylactic shock including drugs and shock due to anesthesia. We excluded repeated cases basing on episode number, hospital, birthday date, sex, year, ward and hospitalization date and hour.

Statistical analyses were done with the Chi-square test for categorical variables, Student's t-test for normally distributed continuous variables and Mann-Whitney or Kruskal-Wallis for variables without normal distribution, using SPSS v20. The *a priori* level of significance was $p<0.05$.

Our main outcome was ADR detection. Secondary outcomes were: ADR related to admission (ADR_{Ad}) versus ADR during hospitalization period (ADR_{In}), age, gender, admission diagnosis, other diagnoses, hospital stay and year (2000 to 2009).

We also aimed to assess trends in ADRs from 2000 to 2009 as detected by database methodology and to compare it to trends detected by spontaneous reporting within that period of time.

Results

Study population

From 2000 to the first half of 2009, there were 9271122 hospitalizations. The mean age of hospitalized patients was 46 years (standard deviation of 28) and 56% of the patients were female. 4.4% of the hospitalizations were associated with death of the patient. Mean hospitalization period was 7.1 days (standard deviation of 3.2).

ADRs detected by the database methodology

From 2000 to 2008, there was a slight increase in number of hospitalizations in Portugal (in 2009, data refer only to first semester). 116720 ADRs were detected from 2000-2009, with a mean prevalence of 1.26%. There was a trend of increase in number of ADRs (in 2000 there were 8301 signals while in 2008 there were 14352 signals).

2.7% of the ADRs were associated with admission (ADR_{Ad}); 97.3% occurred during hospitalization (ADR_{In}). ADRs and respective signals are identified in table IV4.

Adverse drug reactions	**Value**									
Mean age	60	23.4 standard deviation (sd)								
Female Gender	63186	(54.1%)								
Death	10650	(8.8%)								
Mean hospital stay (days)	13.7	22 sd								
Years	***2000***	***2001***	***2002***	***2003***	***2004***	***2005***	***2006***	***2007***	***2008***	***2009***
Number of ADRs	8301	8769	10602	12371	12918	13444	13778	14744	14352	7440
Prevalence(%)	0.82%	0.91%	1.1%	1.25%	1.31%	1.33%	1.41%	1.53%	1.49%	1.50%

Alert type	***E code***	***Hypoglycemia***	***Neutropenia***	***Hepatitis***	***Anaphylactic shock***	***Shock due to anesthesia***
	90260	6684	17036	606	2133	1

Table IV4. Characterization of ADRs in hospitalized patients in Portugal from 2000-2009: database methodology.

ADRs detected by spontaneous reporting

The number of National spontaneous notifications of ADRs from 2000 to 2009 was 13562, corresponding to a mean prevalence of ADRs of 0.1%. Notice that the Portuguese National Pharmacovigilance department did not specify the number of spontaneous reports originating from the ambulatory setting versus hospitalizations (the number of reports originating just from hospitalizations is smaller than these estimates).

In figure IV5, we illustrate trends of hospitalization and ADRs throughout time.

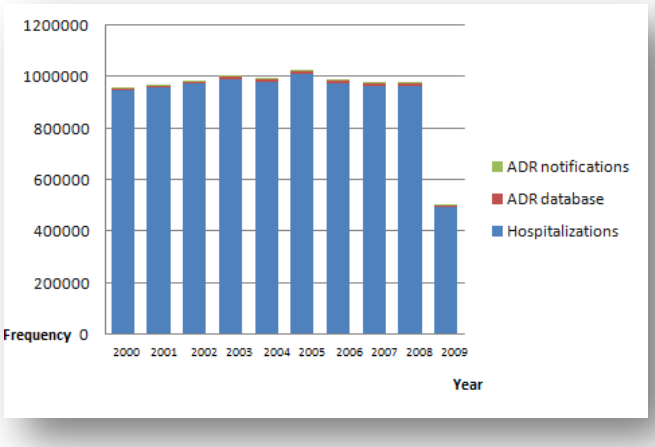


Figure IV5. Comparison of number of hospitalizations and detection of adverse drug reactions through databases and spontaneous reports. Notifications refer to spontaneous reports. Notice that 2009 refers only to the first semester of 2009 (data of second semester not available).

Risk factors of ADRs

In comparison with patients that did not suffer from an ADR, patients with ADRs were: older ($p<0.001$, Mann-Whitney test), had longer mean hospitalization period ($p<0.001$, Mann-Whitney test), more frequently of the female gender ($p<0.0002$, Fisher's exact test) and had a higher risk of death ($p<0.001$, Fisher's exact test).

We additionally verified that several comorbidities (identified also through the use of diagnostic codes) were associated with a higher risk of developing an ADR: heart failure ($p<0.0001$, Fisher's exact test), septicemia ($p<0.0001$, Fisher's exact test), dysrhythmias ($p<0.0001$, Fisher's exact test), hypotension ($p<0.0001$, Fisher's exact

test), cerebrovascular disease (p<0.0001, Fisher's exact test), stroke (p=0.0000045, Fisher's exact test), diabetes (p<0.0001, Fisher's exact test), ischemic heart disease (p<0.0001, Fisher's exact test), malignancies (p<0.0001, Fisher's exact test) and pneumonia (p=0.0000026, Fisher's exact test).

Main results of the nation-wide estimate of ADRs

In summary, in Portugal from 2000 to 2009 there were 9,271,122 hospitalizations, with 116720 hospital ADRs detected by the database methodology (prevalence of 1.26%; 97.3% of the ADRs were ADR_{In}). There were 13,562 spontaneous reports of ADRs (ambulatory and hospital) from 2000 to 2009 in Portugal (prevalence of 0.1%). The number of hospitalizations is increasing, such as the number and prevalence of ADRs throughout time.

C) COMPUTERIZED-ASSISTED CHART REVIEW

Rationale for the development of a computerized-assisted chart review

Computerized surveillance is increasingly appealing (Hassan *et al,* 2010). Many different strategies of computerized Pharmacovigilance were assessed in a recent systematic review (Forster *et al,* 2012), with different levels of complexity in implementation and integration, and consequently with a variety of costs in acquisition and maintenance.

Computerized methods are frequently used in US hospitals, in which almost all clinical data is already computerized and structured. However, in portuguese and several other countries, clinical data in hospitals is not entirely computerized, and it would be economically impossible (and not cost-effective) to build a computerized system for ADR detection with high level of automation and complexity from unstructured data.

Therefore, our purpose was to design and validate a simple computerized methodology of ADR detection that could assist manual chart review, simultaneously increasing detection and decreasing associated costs while allowing for a gold standard methodology to be routinely used. Since we live in an era of social and economic crisis, we intended to build a program that would have nearly zero costs of implementation and maintenance, and that did not require health system integration. We also intended to validate and compare this system with manual chart review.

Methods

In appendix 4, the scientific paper resulting from this research can be found.

Study setting

We selected a random sample of 118 hospitalizations in 2010 from CHUC to perform manual chart review and computerized assessment, independently, to validate our methodology and to compare: number and types of ADRs identified, risk factors for ADRs, and time spent in each methodology. The study was approved by hospital's institutional review board.

Definition of ADR

World Health Organization's definition of an ADR was applied. Previous works utilized computerized systems to identify adverse drug events (Kilbridge *et al,* 2009; Wolfstadt *et al*, 2008; Bates *et al*, 1995), but we aimed to assess specifically ADRs. The main outcomes measured were the ADR computer-detected and the ADR computer-undetected.

Comparison with chart review

Independent chart review was performed for each patient (as described above).

Development of a computerized system - Chart Helper

Considering the need of a costless computerized system, we built a program that did not require Health system integration. The main difficulty was to build manually databases with drug information in portuguese, since there were none available in our country that linked adverse drug reactions, their symptoms and signs to each drug. We used the Hospital Formulary (INFARMED 2009) and the official list of portuguese ambulatory drugs, available in the site of INFARMED (2012), the Portuguese regulatory authority of drugs, to build a database with all drugs available in Portugal. We then built an ADR database with the 10 more frequent ADRs, all ADRs that were potentially fatal for each drug, and other clinically relevant ADRs for each drug according to INFARMED and Meyler's side effects of Drugs book (Aronson, 2006). We also added to that database: the symptoms of each ADR, signs, laboratorial alterations, diagnosis and compatible coding information (for that, we used also International Classification of Diseases 9th Revision, Clinical Modification: ICD-9-CM.

We built a program, Chart Helper, with Visual Studio 2010, aiming for a simple and user-friendly interface with the reviewer. For each patient, the chart reviewer registered age, gender, chart number, hospitalization and discharge dates (duration of hospital stay was automatically calculated), and diagnosis and procedures codes (from ICD-9-CM).

All drugs administered during hospitalization were also selected from a list by the reviewer, as well as relevant symptoms, signs and laboratorial alterations. The

program used these input data, our ADR databases and some algorithms to generate two types of results:

1. Suggested ADR(s) for that patient. The program detected if a symptom, sign, diagnostic code or laboratorial alteration that the patient had, was compatible with an ADR of any of the drugs administered to him. Respective drug, ADR and alert were specified by program and then the reviewer would classify each ADR according to WHO's causality assessment (inserted in the program): certain, probable/likely, possible, conditional/unclassified, inaccessible /unclassifiable.

2. Frequent ADRs for each drug. For each drug administered to that patient, a list of frequent (and of fatal) ADRs was available for consultation by the reviewer. Therefore, this memory support tool would allow less experienced reviewers to pay more attention to certain signs and symptoms throughout the chart that could indicate an undiagnosed ADR of a drug administered to that patient.

All data (input and result data) were automatically stored in a database by Chart Helper for further analysis. Conditional and unlikely ADRs were excluded from our analysis (but also automatically registered in the database).

Statistical analysis

Statistical analyses were done with the Chi-square test for categorical variables (or Fisher's exact test whenever possible), Student's t-test for normally distributed continuous variables and Mann-Whitney or Kruskal-Wallis when dealing with variables without normal distribution, using SPSS v20. The *a priori* level of significance for all comparisons was $P<0.05$.

Results

Characteristics of participants

From the random sample of 118 patients hospitalized in 2010, mean participant age was 60 years. 40.7% were female. Table IV5 describes socio-demographic participants' characteristics.

Characteristics	*Number*	*Relative frequency (%)*
Female gender	48	40.7 %
Age *(sd: standard deviation)*	Mean: 60 years	sd: 20
Mean number of days hospitalized *(sd)*	10.1	sd: 20.0
Mean number of drugs administered per patient	5.2	sd: 3.8
Wards more frequently occupied		
Surgery	18	15.2 %
Urology	14	11.9 %
Medicine	10	8.5 %

Table IV5. **Socio-demographic characteristics of participants of the study of computerized methodology validation.**

Utilization of the computerized system for ADR detection

Program

Chart helper, the program built, requires that some data is entered as the chart review is performed, as detailed previously and illustrated in figure IV6.

Afterwards, according to each patient, two types of results are generated: list of frequent ADRs for drugs administered to each patient (figure IV7) and list of suggested ADRs considering that patient's symptoms, laboratorial alterations, diagnoses, drugs and other factors (figure IV8).

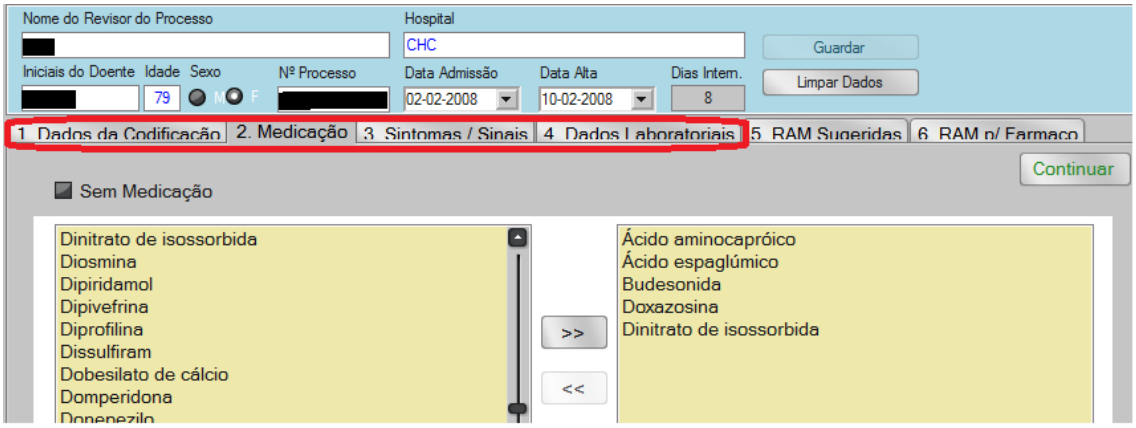


Figure IV6. **Data to be entered in Chart Helper.**

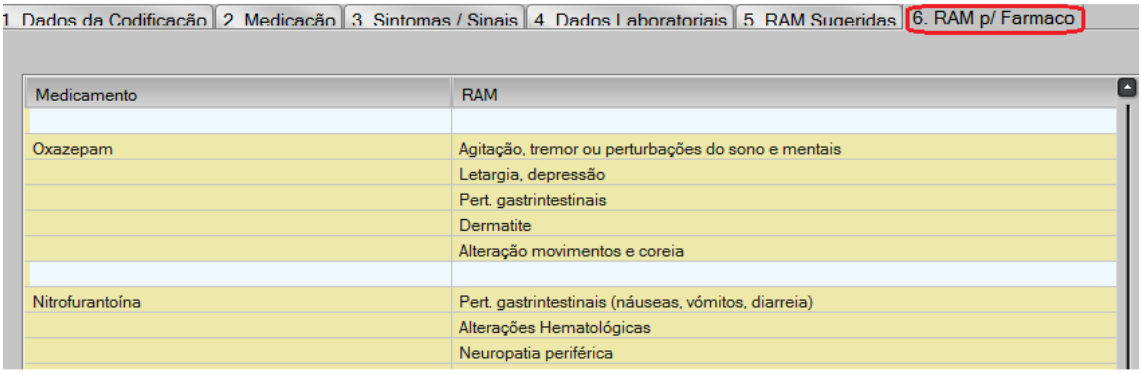


Figure IV7. Interface of Chart Helper with ADRs according to drug administered. This helps the reviewer to assess if there is a symptom or signal of a possible ADR that was not previously detected.

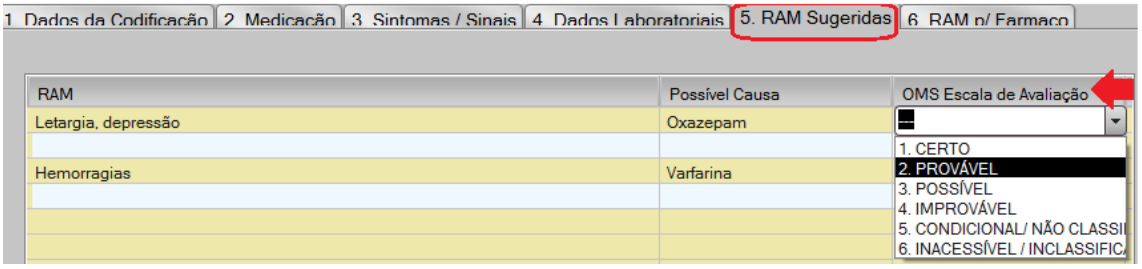


Figure IV8. Interface of Chart Helper with suggested ADRs for that particular patient. Possible ADRs are suggested according to symptoms, laboratorial alterations, drugs and coding data (rectangle). The reviewer must then perform for each of those suggestions a WHO causality assessment (arrow).

ADR detection

Sixty-five ADRs (unlikely ADRs were excluded, as recommended in ADR studies) were identified by computerized system in 29 patients, leading to a prevalence of ADRs of 24.8% (29/117; there were 117 patients exposed to drugs) and including 17 ADRs certain or probable (prevalence of 14.5%).

Two ADRs were undetected by computer (both with warfarin leading to INR levels that caused surgery delay). On the other hand, 53 ADRs were only detected by computerized system (manual chart review did not detect them).

The most frequent ADRs detected by computer were laboratorial alterations (24.3% of ADRs), agitation (14.6%) and diarrhea or constipation (13.8%). Systems more frequently affected were: hematologic (31.7%), gastrointestinal (26.0%) and renal

(16.2%). The drugs more frequently involved were: NSAIDs (15.5%), antihypertensives (14.6%) and antidepressants or antianxiety agents (14.6%).

Comparison of methodologies: manual versus computerized chart review

Table IV6 presents the comparison between manual chart review and computerized methodology. Computer-assisted chart review detected the double of ADRs with half the resources needed by manual chart review.

	Manual chart review	Computerized method
Total number of ADRs (excluding "unlikely")	12	65
Patients with ADR	12	29
ADR prevalence	10.2%	24.8%
Total number of person-hours spent (in 118 cases)	69 (mean of 35 minutes per patient)	29.5 (mean of 15 minutes per patient)
Fatal ADRs	1	1
ADRs previously diagnosed in clinical history	3	3
ADRs previously coded (E code)	1	1
Number of adverse events (including ADR)	24	77
Number of ADR associated with admission *versus* ADR that occurred during hospitalization	2 *vs* 10	2 *vs* 63
WHO's causality assessment		
Certain	4	7
Probable / likely	5	15
Possible	3	43
Unlikely or conditional/unclassified or inaccessible /unclassifiable	0	31

Table IV6. Comparison of manual and computerized chart review.

Methodological issues of computerized chart review

This methodology has a remarkable detection rate (prevalence of ADRs identified of 24.8%) with low resources needed (a mean of 15 minutes per patient), much lower than manual chart review, allowing the application of this method as a continuous method of Pharmacovigilance, unlike manual chart review. This program provides a list of ADR for each drug, as a supporting memory tool for inexperienced reviewers. It integrates validation and causality assessment during each assessment.

However, this methodology needs further validation. In spite of being resource-sparing because it has a low level of automation, it would be interesting to integrate it in the Health System and to add further automation.

In summary, Computerized chart review might be an useful Pharmacovigilance methodology with a remarkable detection rate and moderate costs. The program Chart Helper is also promising.

V. OPHTHALMIC ADVERSE DRUG REACTIONS

Ophthalmology represents a challenge in Pharmacovigilance (Fraunfelder 2007), considering the heterogeneous number of ADRs that can occur, sometimes years after administration of a drug (Hollander and Aldave, 2004), and considering the required specific ophthalmological examination for its diagnosis. The anatomy of the ocular globe is unique, which causes augmented susceptibility to the occurrence of ADRs.

Anatomy of the ocular globe

The total area of the globe is relatively small compared to the rest of the body. Nevertheless, when a drug enters the systemic circulation, it can reach a high concentration in ocular tissues through uveal or retinal circulations (American Academy of Ophthalmology, 2012; Wren, 2000). For better understanding of such a specific topic, some of the structures of the ocular globe are depicted in figure V1.

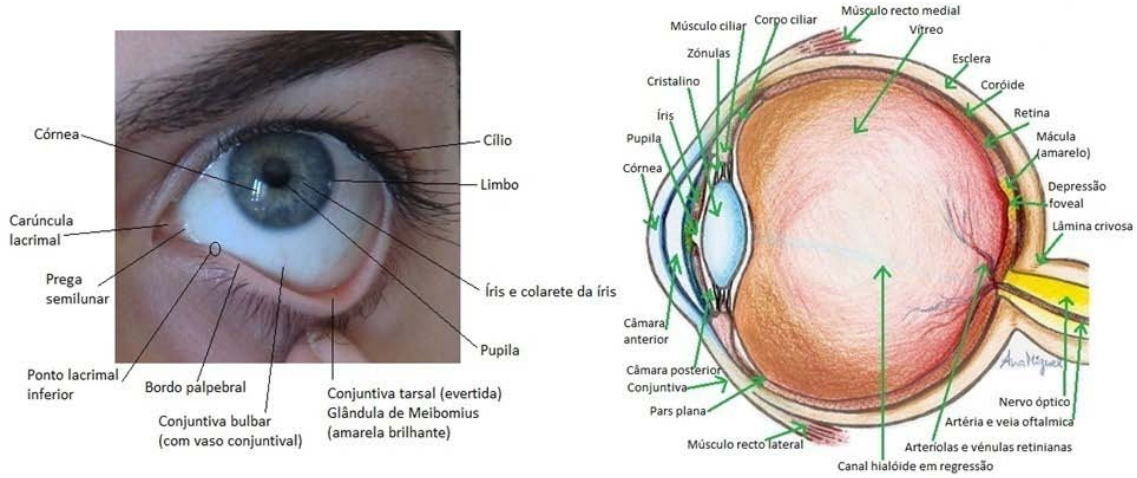


Figure V1. Anatomy of ocular globe and ocular surface. Ocular structures are depicted.

The choroid and ciliary body (which belong to the uvea) as well as the sclera have thin, fenestrated walls which allow drug molecules to pass. Small, lipid soluble molecules may pass freely into the aqueous humor, and can further diffuse into avascular

structures such as the lens, cornea, and trabecular meshwork (American Academy of Ophthalmology, 2012).

However, there are barriers that limit access of drugs to intraocular structures, namely: the intercellular tight junctions of the corneal epithelium and endothelium (which limit anterior access to the interior of the eye and belong to the blood-aqueous barrier), the vascular endothelium of the retina (non fenestrated and with tight junctions - internal blood-retinal barrier), tight junctions between the retinal pigment epithelium (which with the Bruch's membrane consist in the external blood-retinal barrier).

Drug molecules that can enter the intraocular space from the uveal circulation, may exit the eye from the Schlemm canal, ciliary body or may diffuse into adjacent anatomical structures. Drugs entering from the retinal circulation can reenter the systemic circulation, diffuse into the vitreous and anatomical structures, or get actively transported out (Wren, 2000). There are three major accumulation sites including the cornea, lens and vitreous, but a drug can be deposited in any structure of the eye.

Therefore, the ability of a drug to overcome ocular barriers determines its probability to affect ocular tissues and visual function.

Some concepts in Pharmacotherapy in Ophthalmology

Pharmacogenetics in Ophthalmology

Pharmacogenetics it the discipline that studies how genetic and heritable factors can determine how drugs are chemically metabolized in the body (Pirmohamed *et al,* 2011; Davies *et al*, 2007). Pharmacogenetic causes have also been ascribed to variations in response to ophthalmic drugs, such as the increased intraocular pressure seen in a segment of the population after prolonged use of topical corticosteroids (Danias *et al*, 2011).

Pharmacokinetics in Ophthalmology

Pharmacokinetics studies the cycle of a drug after administration, through the body, which includes absorption, distribution, metabolism, and excretion (American Academy of Ophthalmology, 2012). To achieve a therapeutic effect, a drug must reach

its site of action in sufficient concentration. Pharmacokinetics and dose together determine bioavailability or concentration of the active drug at the therapeutic site.

Pharmacodynamics in Ophthalmology

Pharmacodynamics studies the biological activity and clinical effect of a drug (American Academy of Ophthalmology, 2012).

Pharmacotherapeutics in Ophthalmology

Pharmacotherapeutics is the administration of a drug in order to reach a desired clinical effect. The therapeutic dose may vary for any patient, based on the patient's age, gender, race, other currently prescribed medications, and patient's pathologies.

Causality assessment for ADRs

Almost as important as understanding these concepts and presenting the correct definition for an ADR, is the assessment of the probability of a suspected ADR being a true ADR. The most important and widely used causality assessments are Naranjo *et al* (1981) and WHO (2005), which apply to all ADRs. In tables V1 and V2 we present both causality assessment criteria for ADRs.

Naranjo's causality assessment	Yes	No	Don't know
1. Are there previous conclusive reports of this reaction?	+1	0	0
2. Did the adverse event appear after the suspect drug was administered?	+2	-1	0
3. Did the adverse reaction improve when the drug was discontinued?	+1	0	0
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0
5. Are there alternate causes that on their own could have caused the reaction?	-1	+2	0
6. Did the reaction appear when a placebo was given?	-1	+1	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0
8. Was the reaction more severe when the dose was increased or less severe when decreased?	+1	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0
Total score*			

Table V1. Naranjo's causality assessment for ADRs (Naranjo *et al,* 1981). *Interpretation of the total score: **a)** ≥9: *Highly probable* ADR; **b)** 5-8: *Probable* ADR; c) 1-4: *Possible* ADR: d) ≤ 0: *Doubtful* ADR.

WHO's causality assessment	
1. Certain ADR	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
2. Probable ADR	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition. A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
3. Possible ADR	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear
4. Unlikely ADR	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
5. Conditional / unclassified ADR	A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.
6. Inaccessible / unclassifiable	A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

Table V2. **WHO's causality assessment for ADRs (WHO*, 2005*).**

Types of ADRs in Ophthalmology

There are three main types of ADRs in Ophthalmology:

A. Topical ADRs to a topical ophthalmic drug

These ADRs are usually easy to recognize, since the prescribing Ophthalmologist is the one who detects these ADRs in the follow-up of the patient. They can be caused either by the drug administered or by its topical conservatives. One example is ocular hyperemia frequently caused by topical prostaglandins (used in the treatment of glaucoma) (Feldman *et al,* 2003).

B. Systemic ADRs to a topical ophthalmic drug

Topical ophthalmic medications can be absorbed by the ophthalmic mucosa and in a larger dose by the nasal mucosa (the drug descends to the nasal mucosa from the lacrimal canal, and is then swallowed, with systemic absorption) (Duval *et al,* 2006) and attain significant levels in the blood, causing rare but sometimes even fatal ADRs. The most common topically administered ocular drugs causing systemic side effects are the epinephrine-like compounds used to dilate the pupil, which can be rapidly

absorbed through the mucosal membranes of the eye, leading to increased blood pressure and tachycardia. Periocular injection of anesthetics combined with epinephrine can cause the same effects quite rapidly, leading to respiratory collapse and even death (Duval *et al,* 2006).

C. Topical/ophthalmic ADRs to a systemic drug

These ADRs generally are extremely difficult to diagnose, considering that in this case a general physician prescribes a drug, but a different physician usually is required for the diagnosis (an ophthalmologist). Other difficulty is the need of obtaining a complete medical history and registering the countless systemic medications prescribed for each patient. The correlation of the symptoms and ocular signs of the patient with the suspect of an ADR caused by a particular drug is another difficulty, and confirming the ADR is by far even more difficult.

There are several isolated reports of possible ophthalmic ADRs without neither causality assessment nor systematic verification. The general frequency of ophthalmic ADRs is not known. Ophthalmic ADRs to systemic medication represent an area that lacks assessment and clarification.

Consequently, we intended to build a systematic review of ophthalmic ADRs to systemic drugs. We also intended to apply and adapt some of the previously built methodologies for the specific ADR detection in Ophthalmology, in order to assess the frequency of ophthalmic ADRs and to characterize and systematize ophthalmic ADRs.

A) Systematic review of ophthalmic ADRs to systemic drugs

As previously noted, there is a need of a recent systematic review about ophthalmic ADRs occurring after the correct prescription of a drug. From this need, the scientific article that arose and the chapter about ADRs in Ophthalmology can be consulted in appendices 6 and 9, respectively.

Methods

We performed a systematic review of studies that assessed ophthalmic ADR to systemic drugs according to the guidelines of the Cochrane Collaboration and PRISMA Statement.

We used the following definition for *adverse drug reaction:* "any noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy", according to WHO definition of 1972. We wanted to specifically assess ADRs, therefore we did not consider adverse events.

Search methods

We searched through several electronic databases (last date of search was 1/7/2012): Medline, SCOPUS, ISI web of knowledge, ISI Conference Proceedings, International Pharmaceutical Abstracts and Google scholar. We used a search query created after a pilot study to add specificity (full search query available if requested to the corresponding author) that included the terms: eye, ocular, ophthalmic, ophthalmology, adverse and reaction. We searched for grey literature and unpublished data, and hand-searched all references of included studies and relevant reviews.

Selection criteria

Studies were included if they followed all inclusion criteria listed below:

1. Studies in which the primary purpose was to assess an ophthalmic ADR to a systemic medication. Since there is a wide misuse of the terms ADR, adverse event (AE) and adverse drug event (ADE), we obtained also the full-text of studies who claimed to assess AEs or ADEs, to verify their methodology, and to include the studies that actually assessed ADRs, although they called it AEs or ADEs.
2. Studies with patient evaluation performed by an ophthalmologist.
3. Studies that specified diagnostic criteria for an ocular ADR.

We also included studies with different languages (we hired a translator), any country, experimental studies (if any). We did so to have a more thorough and complete literature search. We did not exclude systematic reviews nor narrative reviews if they added useful information about ocular ADRs, as we intended to have a general overview that, on the one hand, summarized and added further systematization to existing evidence, and on the other hand, identified areas or specific ophthalmic ADRs that lacked systematization or assessment.

Exclusion criteria:

1. Studies assessing adverse events that did not correspond to ADRs (we excluded reports of capsular rupture in phacoemulsification surgery, but we did not exclude reports of capsular rupture due to intra-operatory floppy iris syndrome, a syndrome caused by tamsulosine or other drugs).
2. Systemic ADRs to topical ophthalmic drugs or ophthalmic ADRs to topical ophthalmic drugs (they were not the purpose of our study and would increase heterogeneity and decrease clarity of our review).
3. Studies that were comments or letters, if they would not add new scientific evidence to our review. However, letters or comments that included case reports not published elsewhere about specific ocular ADRs were not excluded, in order to identify rare ophthalmic ADRs.
4. Studies assessing drugs already removed from the market.

Data collection and extraction

Two independent reviewers first examined each title and abstract to exclude obviously irrelevant reports, and then independently examined each full text report, to determine eligibility according to inclusion criteria. Disagreements were solved by consensus, recorded and analyzed using kappa statistics.

Primary outcome was the presence and type of ocular ADR and the respective causative systemic drug. We also registered: ocular structure affected, diagnosis, serious or vision-threatening ADR. All symptoms, visual acuity (VA), signals, and results of complementary examination performed at presentation were recorded, as well as after a follow-up. Attitude or treatment performed for each ADR was also registered (suspension of the causative drug, specific treatment, administration of an antidote, no treatment necessary). If VA was not recorded in the logMAR scale (Ferris 1982), it was converted.

We always assessed the drug name, identified the therapeutic drug class according to Anatomical Therapeutic Chemical Classification System of WHO (WHO 2005), and reported the number of days during which the drug was used and the administration route (if that information was available). We verified if causality was assessed in the original studies (and according to what classification, preferably WHO's or Naranjo's and respective results) as well as predictability of ADRs (using Hartwig's predictability scale, 1992), preventability (e.g.. Schumok & Thornton's preventability criteria, 1992) and types of ADRs (Rawlins and Thompson's classification, 1977). We did not intend to identify all of the ophthalmic ADRs, but to systematize the most important and the most frequent ADRs according to the results of our systematic search.

Risk of bias assessment

We performed risk of bias assessment for each included study, and recorded it in a standardized form created to assess ADR studies (in a previous work, Miguel 2012) and adapted to Ophthalmology after a pilot study. We did not use scales (discouraged by the Cochrane approach, 2008) but criteria from Cochrane, STROBE (Vandenbroucke *et al,* 2007), QUOROM (Moher *et al,* 1999) and PRISMA (Moher *et al,* 2009) adapted to

the particular scope of ophthalmic ADRs evaluation, which included: complete description of study design, description of study type (case report, case series, prospective observational study, trial,...), adequate diagnostic criteria for ophthalmic ADR, complete ophthalmologic evaluation at presentation, quantified visual acuity at presentation and follow-up, results of complementary testing described at presentation and follow-up, definition of ADR presented, rationale for study size, causality assessment of ADR, preventability assessment of ADR, description of all statistical methods, characterization of study participants, description of methods to prevent bias (information bias, selection bias and other bias), presentation of complete summary measures. The two reviewers independently assessed study quality and risk of bias; disagreements were solved by consensus. Studies were divided in low risk of bias (5 or less parameters with medium, unclear or high risk of bias), medium risk (6 to 9) and high risk (10 or more parameters evaluated as medium, unclear or high risk of bias).

Quantitative analysis

Statistical analyses were done with the Chi-square test for categorical variables, Student's t-test for normally distributed continuous variables and Mann-Whitney or Kruskal-Wallis when dealing with variables without normal distribution, using SPSS v17. Quality evaluation graphs, heterogeneity analysis, subgroup analysis and random effects meta-analysis were performed using Review Manager - version 5.0. The *a priori* level of significance for all hypothesis tests was $p<0.05$.

Results

Literature search

Pubmed search yielded 124 results; SCOPUS yielded 72 results; Google Scholar 60; ISI Web of Knowledge yielded 154; others yielded 152. From these 562 studies (corresponding to 300 distinct studies), 163 were selected to obtain full-text and then 32 studies were included (Figure V2): 1 systematic review of ADRs to a specific drug, 11 narrative reviews, 1 trial, 1 prospective study, 6 case-control or cohort or cross-

sectional studies, 6 spontaneous reports and 6 case reports or case series. Kappa agreement for study inclusion was 0.80 during the first phase and 0.82 during the full text review (good agreement).

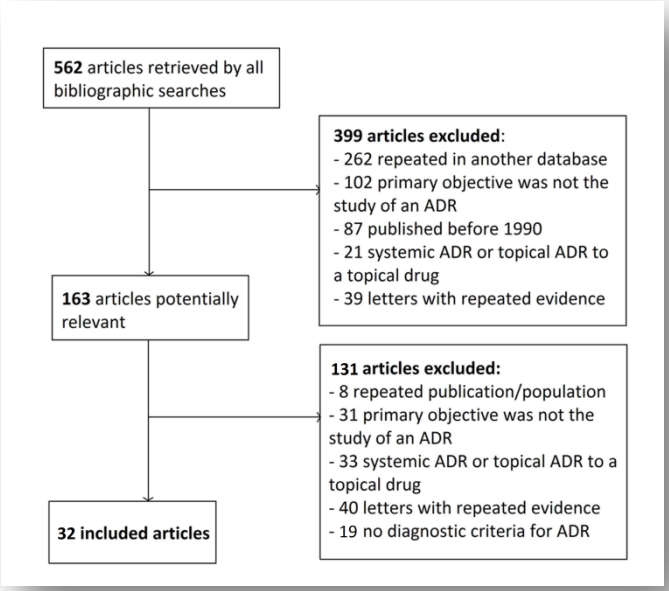


Figure V2. **Flowchart of the search strategy.**

Characteristics of included studies

Table V3 summarizes the characteristics of included studies. We identified several types of studies of ocular ADRs, most of them narrative reviews without systematic criteria nor bibliographic search.

Year, author	Study type	Drug studied	Ophthalmic ADR(s) reported*	Summary of study
1986 Davidson[32]	Narrative review	Several	Many ocular ADRs caused by: corticosteroids, chloroquine, amiodarone, phenothiazines, tamoxifen...	Narrative review without definition of ADR nor causality assessment
1989 Curran[33]	Case series	Doxorrubicin	Iritis, conjunctivitis, periorbital edema, keratitis, optic neuropathy	Case series of 4 cases of ocular ADRs to doxorrubicin
1991 Hobley[34]	Case report	Digoxin	Scintillating visual field loss (central scotoma) + dischromatopsia	Case report: visual field defect due to digoxin (therapeutic level)
1992 Malek[35]	Narrative review	Oral contraceptives	• Retinal hemorrhage or emboli, macular or papillary edema, optic neuropathy	Narrative review of ocular ADRs by oral contraceptives.
1993 Goldman[36]	Narrative review	Anticonvulsivants	• **Carbamazepine**: diplopia, paresis of extraocular muscles, nistagmus, visual allucinations • **Phenytoin**: nistagmus without oscillopsia, mydriasis • Others: paresis of extraocular muscles	Narrative review of ocular ADRs of common anticonvulsivants
1994 Macarol[37]	Spontaneous reports	Pamidronate	Scleritis, conjunctivitis, anterior uveitis	Retrospective series of spontaneous case reports
1995 Oshika[38]	Narrative review	Neuropsychiatric drugs	• **Phenothiazine**: corneal et lens deposits • **Thioridazine**: retinopathy • **Tricyclic antidepressants:** glaucoma, decreased accommodation • **Lithium**: papilledema, exophthalmia • **Chlorpromazine**: keratopathy	A narrative review of ophthalmic ADRs of neuropsychiatric drugs
1995 Fraun-Felder[9]	Letter with spontaneous reports	Leuprolide	Blurred vision	A retrospective study of series of spontaneous reports of ocular ADRs of leuprolide
1995 *b* Fraun-Felder[39]	Retrospective case-control study	Niacin	Dryness, blurred vision, diplopia, cystoid maculopathy	ADRs of patients taking niacin were compared to other dyslipidemia drugs
1997 Sweeney[40]	Prospective study	Risperidone	Eye movements affected: prolonged latency after and alteration of saccadic movements	Prospective study of patients with risperidone (4 weeks)
1999 Dulley[41]	Narrative review	Tamoxifen	• Retinopathy with deposits • Keratopathy with deposits • Colour vision defects • Foveal disfunction and ERG change	Narrative review about ocular ADRs of tamoxifen
1999 Solomon[42]	Letter with case reports	Influenza vaccine	• Case 1: anterior uveitis • Case 2: reactivation of herpetic keratitis • Case 3: left keratoplasty rejection	Letter with case reports not previously published
1999 Doughty[43]	Narrative review	Migraine drugs	Cyproheptadine, pizotyline, amitriptiline, propranolol, timolol, clonidine, flunarizine: dry eye	A narrative review of medications of headaches and their ocular ADRs
2001 Ikaheimo[44]	Observational cross-sectional study	Flecainide	• Corneal deposits • Dry eye	Observational study in which 38 flecainide medicated patients were examined.
2001 Fraunfelder[45]	Case series of spontaneous reports	Isotretinoin	• Many ADRs: abnormal meibomian glands, blepharoconjunctivitis, corneal opacities, decreased vision, keratitis, ...	Analysis of 1741 spontaneous reports with possible ocular ADRs to isotretinoin
2002 Ikaheimo[46]	Observational cross-sectional study	Amiodarone	• Corneal deposits (in 100% of the patients) • Anterior subcapsular lens deposit (22.2%) • Dry eyes (9.1%)	Observational study in which 22 patients with long term amiodarone were studied
2003 Fraun-Felder[18]	Narrative review	Several	• **Amiodarone**: cornea verticillata, periocular staining, optic neuropathy • **Cetirizine**: mydriasis, oculogyric crisis... • **Hydroxychloroquine**: corneal deposits, epiphora, extraocular paresis, ptosis • **Isotretinoin**: conjunctitivis, corneal deposits, acute myopia, optic neuritis • **Biphosphonates**: episcleritis, conjunctivitis, nerve palsy,... • **Sildenafil**: dischromatopsia, blurred vision • **Topiramate**: acute glaucoma, acute myopia, ocular pain, uveitis,...	A narrative review was performed of ocular ADRs, without systematic study search but with systematic WHO causality assessment whenever possible. Offers good guidelines and clinical implications for each drug.
2004 Fraun-Felder[47]	Retrospective series of reports	Several	• **Biphosphonates**: conjunctivitis, uveitis, blurred vision, scleritis • **Cetirizine**: blurred vision, keratoconjunctivitis sicca, oculogyric crisis • **Isotretinoin**: blurred vision • **Topiramate**: acute glaucoma, acute	A large retrospective series of spontaneous reports of ocular ADRs to different systemic drugs. WHO's definition of ADR and WHO's causality assessment were performed.

			myopia, periorbital edema, scleritis	
2006 Fraun-Felder[48]	Letter with retrospective reports of spontaneous reports of ocular ADRs	Cyclooxygenase-2 Inhibitors	Blurry vision and conjunctivitis were the most reported ADRs	Letter with large series of spontaneous reports (1006) of ocular ADRs to cyclooxygenase-2 Inhibitors (238 reports of blurry vision and 71 of conjunctivitis from celecoxib).
2007 Santaella[49]	Narrative review	Several	Several drugs were assessed, such as: pamidronate, alendronate, risedronate, topiramate	Narrative review of several retrospective case series and reports of ocular ADRs to specific systemic drugs.
2007 Sowka[50]	Case report	Sildenafil	Optic atrophy after the use of sildenafil in a 68-year old man.	Case report with a follow-up of 4 months. No causality assessment of ADR nor WHO's definition of ADR was used.
2008 Mandal[51]	Two case reports	Topiramate, >6 months, 100-150mg/day	Defects in visual field (case 1-quadrantic defects, case 2-arcuate defects)	Two case reports of visual field alterations induced by topiramate, (Naranjo's CA was performed).
2009 Bell[52]	Retrospective study	Tamsulosin	Intra-operatory floppy iris (IFIS) and related surgical outcomes	Retrospective cohort study of 96128 patients: tamsulosine was associated with IFIS and intraoperatory complications
2009 Cordel[53]	Trial	Sildenafil and tadalafil	Electroretinography (ERG) responses were the same for placebo, sildenafil and tadalafil.	Subjects were randomized to use of a placebo (n=82), tadalafil (n=85) or sildenafil (n=77) daily for 6 months.
2009 El-Domyati[54]	Case report	Sildenafil	A 48-year-old nonsmoker patient suffered from nonarteritic ischemic optic neuropathy. "Several weeks later", the visual acuity gradually improved	Case report. Causality assessment of WHO was not performed. Follow-up of "several weeks later", not specified.
2010 Richa[55]	Narrative review	Psychotropics	• Phenothiazines, lithium: keratoconjunctivitis • Chlorpromazine: periocular pigmentation • Tricyclic antidepressants, topiramate: uveitis • TCAs, typical antipsychotics, selective serotonin reuptake inhibitors: mydriasis	A narrative review was performed with several psychotropic drugs
2010 Al-Hussaini[56]	Comprehensive narrative review	Alpha-Blockers	Intra-operative Floppy Iris Syndrome (IFIS). "There is no evidence to support alpha-blocker discontinuation prior to surgery."	Review about IFIS and drugs.
2011 Lebreton[57]	Narrative review with systematic search	Corticosteroids	• Ocular hypertension • Cataract (posterior subcapsular) • Central Serous Chorioretinopathy • Ptosis • Exophthalmia	A narrative review was performed of ophthalmic ADRs of corticosteroids
2011 Azzouni[58]	Systematic review	Sildenafil	Anterior and posterior nonarteritic ischemic optic neuropathy, central retinal vein occlusion, cilio-retinal artery occlusion, acute angle closure glaucoma and optic atrophy after sildenafil use.	Systematic review of ocular ADRs by sildenafil. WHO's causality assessment was performed and of National Registry of Drug-Induced Ocular Side Effects.
2012 Seitz[59]	Case-crossover study	Antidepressants	Acute angle-closure glaucoma (AACG) (odds ratio for any antidepressant exposure in the period immediately preceding AACG was 1.62, 95% confidence interval of 1.16-2.26).	Authors searched acute angle - closure glaucoma, and investigated whether they had an exposure to antidepressants previously, using administrative databases.
2012 Saint-Jean[60]	Case series	Inhibitor of epidermal growth factor receptor (EGFR)	Multiple epithelial defects, corneal melting, ectropion and corneal perforation (requiring a penetrating keratoplasty).	Retrospective case series of 10 patients with ocular ADRs. Definition of ADR was not used.
2012 Neudorfer[61]	Retrospective study of outcomes	Isotretinoin	An association was found between isotretinoin and conjunctivitis, hordeolum, chalazion, blepharitis, eye pain, and dry eye.	Retrospective study with medical databases to identify ADRs in patients using isotretinoin.

Table V3. Included studies in this systematic review. *Ophthalmic ADRs will be described with further detail in table V4.

Ophthalmic ADRs

Many different ophthalmic ADRs exist to many systemic drugs. In table V4, we represent a summary of the main ophthalmic ADRs found in this systematic review, according to each specific drug, dose, risk factors and tried to characterize the ophthalmic ADR (if reported). Keratitis, retinopathy, glaucoma, dry eye and blurred vision were the most frequent ADRs identified.

We identified many ophthalmic ADRs to drugs that have original studies but are currently lacking a systematic review (therefore representing an opportunity for further studies). Many studies were found but only one systematic review (of ophthalmic ADRs to sildenafil) and few narrative reviews with systematic search were performed. Therefore, examples of drugs that cause ophthalmic ADRs that would benefit from a recent and specific systematic review are: tamoxifen, amiodarone, antidepressants, phenotiazines, hydroxychloroquine, oral contraceptives, etc.

Therapeutic group	Drug(s) responsible(s)	Description of ocular ADR - Patient (P), ocular segment/complaints (O) - Complementary examination (C) - Reversibility of ADR (R), follow-up time (F)	Classification of ADR - Rawlin's type A/B - Severity assessment (SA); causality assessment (CA)	- Reporting studies - Study's level of evidence (Oxford classification[62])
Acne treating agents	Isotretinoin	*Certain ADRs*: **pseudotumour cerebri, meibomian gland alterations, blepharoconjunctivitis, keratitis, myopia, corneal opacities, ocular discomfort, dry eye, photophobia, decreased vision, and teratogenic ocular abnormalities.** (Many other ADRs were reported). A recent study[61] identified a hazard ratio of 1.70 ($p<0.05$) for ocular ADRs after isotretinoin.	- Type A and B - With CA (WHO's)	Narrative review[18] and case series[45] (level 4) Retrospective study using medical databases[61] (level 2c)
Anti-allergic	Anti-histamines: cetirizine	**Pupillary changes, anisocoria, decreased accommodation** and **blurred vision. Dry eye**[47] **Oculogyric crisis**[18]: "eyes and lids are tonically elevated and the neck is hyperextended, usually without visual complaints". It is a *certain ADR*[18].	- Type B: all except oculogyric crisis (A). - WHO's causality assessment (CA) was performed[18].	Narrative reviews[18,47] (level 4)
Anti-arrhythmics	Flecainide	**Corneal deposits:** 14.5% **Dry eye:** 10.5% - 13 to 132 months of follow-up	- Type A - No CA nor SA	- Cross-sectional study[44] - Level 2c
	Amiodarone	**Corneal deposits**: 100% of the patients[32,46] Anterior subcapsular **lens deposits**[46]: 22% **Dry eye**[46]: 9% **Amiodarone-optic neuropathy**[18]: more insidious in onset and resolution, more bilateral, less involvement in visual acuity compared to non-arteritic ischaemic neuropathy. **Other**[47]**:** Photosensitivity, periocular skin pigmentation, blepharoconjunctivitis, thyroid eye disease, loss of eyelashes, pseudotumor cerebri. - 3 to 131 months of follow-up in a prospective study[46] *Certain ADRs*[18]: photosensitivity, corneal deposits, visual changes, skin pigmentation, blepharoconjunctivitis, thyroid eye disease.	- Type A: dry eye, corneal and lens deposits. Rest: type B. - WHO causality[18]	- Cross-sectional study[46] (level 2c) and narrative reviews[18,32,46] (level 4)
Anticonvulsivants	- Carbamazepine (CB) - Phenytoin(PH) - Phenobarbital(PB) and other barbiturates	**Diplopia:** caused by CB in 0.2-4% of patients[36] (if CB+ other anticonvulsivants, frequency can rise to 88%). Diplopia can be reversible with dose reduction[36]. **Nystagmus:** in 75% of patients with CB+PH[36]. Also reported after primidone and PH. **Decreased ocular movements:** by CB and PB[36] **Ophthalmoplegia:** by PB and PH **Oculogyric crisis:** by CB (in a 8-y., reversible[36]) **Blurred vision:** CB[36]; **Mydriasis**: PH[36] **Disorders of convergence, miosis:** barbiturates[36] **Papilledema:** CB[36] (C, F: not specified in any study)	- All Rawlin's type B (although diplopia may resolve with dose reduction[38]), except: Type A: decreased ocular movements, mydriasis, changes in convergence - No study with SA nor CA	- Narrative review based on case reports[36] - All studies Level 4
Antidepressants and antipsicotics	- Phenotiazine (PT) - Thioridazine - Tricyclic antidepressants (TA) - Lithium - Chlorpromazine (CP) - Monoamine oxidase inhibitors (MAOIs) - Risperidone	**Corneal and lens deposits:** by PT, CP[38], levopromazine; these deposits usually do not interfere with visual acuity **Keratopathy:** Corneal edema by PT (reversible if stopped), epitelial keratopathy by CP[38] (visual acuity remains good, may be reversible if CP is stopped) **Pigmentary retinopathy**[55]**:** by thioridazine (more frequent in high dose, may be irreversible); rarely also by CP and trifluoperazine[38] **Papilledema, exophthalmia:** lithium[38] **Alteration of saccadic eye movements:** risperidone[38,40] **Angle-closure glaucoma:** by TA, in susceptible patients with shallow anterior chamber[59,63] **Decreased accommodation:** TA, MAOIs (C, F, frequency: not specified)	- Usually type B (decreased accomodation is type A) - Na CA nor SA was performed	- Narrative reviews of case series of several psychiatric drugs[38,55] - Prospective study of risperidone[40] - Case crossover study[59] - Level 4 (low evidence) for the narrative reviews[38,55], level 2c for case crossover[59] and 2b for the prospective study[40]
Anti-erectile disfunction agents	Sildenafil	*Certain ADRs*[18,47]: **dyschromatopsia** (objects appear more blue/green), **blurred vision**, **changes in light perception**, **electrorretinogram changes, conjunctival hyperemia** and **photophobia**. Case report[50]: optic atrophy (without CA). Trial[53]: no changes in electroretinography responses for placebo, sildenafil and tadalafil (no ADR). Others[58]: Anterior and posterior nonarteritic ischemic optic neuropathy, central retinal vein occlusion, cilio-retinal artery occlusion, acute angle closure glaucoma.	- Type A and B - With CA: WHO's[18,47] and Naranjo's[58] - Without CA nor SA[50]	Narrative reviews[18,47], systematic review of case reports[58] and case report[50] (level 4) Trial[53] (level 1b)
Anti-inflammatory drugs	Cyclooxygenase-2 Inhibitors	**Blurry vision and conjunctivitis** by rofecoxib, celecoxib and valdecoxib (positive dechallenge and rechallenge tests)	- Type B - With CA	Retrospective series of spontaneous reports[48] (level 4)

	Corticosteroids	**Ocular hypertension**: Odds ratio 1.41 (CI95% 1.2-1.6)[64] Glaucoma reportedly in up to 30% of patients[32] **Cataract** (posterior subcapsular): 4.7%-15.3%[65,32] **Central serous chorioretinopathy**: OR 37(CI95% 6-222)[57] Others: **ptosis, exophthalmia** (6-8%[57])**, viral retinitis, delay in corneal cicatrization**	- Type A: cataract - Type B: other ADRs - Without CA nor SA	Narrative reviews[32,57] (level 4) Case-control studies[64,65] (level 3b)
Benign prostatic hyperplasia drugs	Alpha-blockers (e.g. tamsulosin)	More post-operatory complications (in 14 days) in patients with tamsulosine[52]: intra-operatory floppy iris Intra-operative Floppy Iris Syndrome (**IFIS**). IFIS severity is related with number of the following criteria: • iris billows with intraocular irrigation currents • iris prolapse tendency • intraoperatory pupilary constriction	- Without CA - With SA	Retrospective study[52] of 96128 patients(level 2b) Narrative review with systematic search[56]
Biphosphonates	Pamidronate Risedronate Alendronic acid Zolendronate Risedronate sodium Etidronate dissodium	**Anterior uveitis:** uni or bilateral, 24h to 17 days after medication[37], mild to severe (2 hospitalizations) **Scleritis, episcleritis:** unilateral, in 1-6 days. **Conjunctivitis:** mild, in 1-48h. **Nerve palsy, retrobulbar neuritis**, **yellow vision, blurred vision** C, F, frequency: not specified. Causality assessment[18,47]: *Certain ADR*: blurred vision, ocular irritation, conjunctivitis, pain, epiphora, photophobia, anterior uveitis, anterior scleritis, episcleritis, orbital edema. *Possible*: retrobulbar neuritis, yellow vision, diplopia, cranial nerve palsy, ptosis, visual hallucinations.	- Type B - No CA[37], but rechallenge was performed in 5 patients with uveitis (4 positive rechallenge tests) - With CA[18] performed in a narrative review	- Retrospective series of spontaneous case reports[37] and narrative reviews[18,47] - Level 4
Drugs used in heart failure	Digoxin	- 36 year-old female **Dischromatopsia + scintillating visual field** (VF) alterations, 3 months after administration of digoxin Colour test FM-100: defect on blue colour. - Reversibility, follow-up: not specified	- Rawlin's: B/idiosyncratic ADR - No SA - No CA	- Case report[34] - Level 4 (low evidence). Many other studies not included because toxic digoxin levels
Drugs used in neoplastic disorders	Imatinib	**Periorbital edema** (after CA, *certain ADR)*. **Epiphora**(*probable ADR)* Other possible ADRs: **extraocular muscle paresis, ptosis and blepharoconjunctivitis.**	- Type A: periorbital edema. Rest: type B. - With CA (WHO's)	Narrative review[18] (level 4)
	Inhibitor of epidermal growth factor receptor (EGFR)	**Multiple epithelial defects** (in 10 eyes of all cases), **corneal melting** (in 3 eyes of 2 patients), lower lid **ectropion** (2 eyes of 1 patient) and **corneal perforation** requiring a penetrating keratoplasty (in 2 eyes of 2 patients). Variable follow-ups (all > 1month).	- Type B - No CA nor SA	Retrospective series of spontaneous reports[60] (level 4)
Drugs used in Rheumatology	Chloroquine Hydroxychloroquine	**Corneal deposits, epiphora, ophthalmoplegia, ptosis** **Maculopathy:** dramatic retinopathy with macular atrophy in a bull's-eye pattern. No frequency is reported but: "approximately one million people have used hydroxychloroquine, with only 20 cases of retinal toxicity in the low dose range (< 6.5 mg/kg/day)"[18] Baseline and anual ophthalmic examinations are recommended with: visual acuity, amsler's grid, colour test, and ideally fundus photograph and visual field.	- Type A: maculopathy (related to cumulative dose), corneal deposits - Type B: ophthalmoplegia, ptosis - With CA (WHO)[18] and without[32]	Narrative reviews[18,32] (level 4)
Hormone-related therapy	Oral contraceptives	**Retinal hemorrhage or emboli, Macular edema, Papillary edema, Retrobulbar optic neuropathy** - Patient: not specified - Ocular segment: posterior (retinal alterations and papillary edema, vascular changes) - Complementary examination: angiography, CT scan - Follow-up: variable (case reports)	- Rawlin's type B - No SA - No CA	- Narrative review[35] based on few case reports (low evidence) - Level 4
	Leuprolide	**Blurred vision:** duration between 1h and 15 days, may be associated with headaches or dizziness. **Other:** papilledema, ocular pain, "ocular vascular accidents"	- Type B - No CA nor SA	- Series of spontaneous case reports[9] - Level 4
	Tamoxifen	**Crystallin retinopathy**: in the macula, may be associated with macular edema **Keratopathy** with whorl-like opacities **Colour vision** defects **Foveal disfunction** with ERG changes	- Usually type B - No CA nor SA[41] - CA(WHO causality)[47]	- Narrative review[41,47] - Level 4
	Doxorrubicin	Case 1: **iritis, conjunctivitis** Case 2: **periorbital edema** Case 3: **keratitis** Case 4: **optic neuropathy** (F, C, follow-up: not reported)	- Type B - No CA nor SA	- Case series of 4 cases[33] (level 4)
Lipid lowering agents	Niacin	**Dry eye** (Fisher exact test p=0.011), **Blurred vision**(p=0.0011) **Diplopia**(p=0.5, non statistically significant)	- Type B - No CA nor SA	- Case-control study[39] - Level 3b

		Cystoid maculopathy (2 cases)		
Migraine drugs	Cyproheptadine, pizotyline, amitriptiline, propranolol, timolol, clonidine, flunarizine	**Dry eye:** all **Diplopia:** cyproheptadine, pizotyline, amytriptiline **Mydriasis:** cyproheptadine, pizotyline, amytriptiline **Decrease in accommodation:** propranolol, timolol **Changes in intraocular pressure:** all	- Type A - No SA nor CA	- Narrative reviews[43,18] - Level 4
	Topiramate	*Certain ADRs by topiramate*: **acute angle closure glaucoma** (usually bilateral, in 1-14 days, suprachoroidal effusion), **decreased vision, headaches, hyperemia, mydriasis, uveitis, visual field defects, myopia.** *Probable ADRs by topiramate*: **blepharospasm** and **oculogyric crisis**. Case reports of others ADRs, as visual field defects[51]	- CA performed by Fraunfelder[18]	- Narrative reviews[18,51] - Level 4
Vaccines	Influenza vaccine	Case1: 41y, man, reversible **anterior uveitis** Case 2: 72 y, woman, reactivation of **herpetic keratitis** Case 3: 74 y, man, **left keratoplasty rejection**	- Type B - No CA nor SA were performed	- Letter with case reports[42] - Level 4

Table V4. **Summary of ophthalmic adverse drug reactions**.

Risk of bias assessment

Few studies had low risk of bias. Only one study performed rationale for study size. Most studies (25) performed a complete initial evaluation by an ophthalmologist, but only 11 performed a follow-up of at least 1 month. Only 13 studies performed causality assessment for ADR and only 7 applied or presented WHO's definition of an ADR. Risk of bias graph is presented in figure V3.

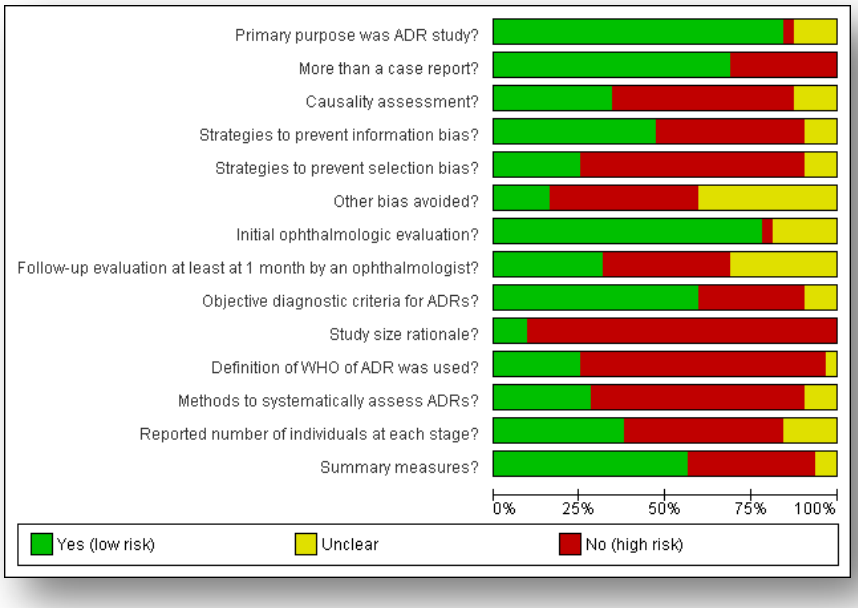


Figure V3. **Risk of bias graph**

B) Detection of ophthalmic ADRs through database methodologies

After identifying examples of specific ophthalmic ADRs and after developing general methods for ADR detection, we intended to adapt those methodologies to detect ophthalmic ADRs (the scientific paper resulting from this work is available in appendix 7).

Methods

Study design

A retrospective study was performed for ADR identification using hospital administrative databases with information from all hospitals in Portugal, from 2000 to 2009, obtained from our National Health Department. These databases contained information on encrypted patient identification, episode and process number, and also information on age, sex, admission date, discharge date, ward(s), hospital attended (public, private), area of Healthcare, district, outcome (death, discharge, transfer), payment data and International Classification of Diseases 9th Revision- Clinical Modification (ICD-9-CM) codes for: diagnoses (main diagnosis, other diagnosis up to 19), procedures (up to 20) and external causes (up to 20). Patient population included all patients hospitalized in all hospitals in Portugal, from 2000 to 2009 (inpatients and outpatients). Data from the second semester of 2009 was not available.

ADR definition and identification

We followed WHO's definition of ADR of 1972. Hospital databases included information of diagnosis. Codes searched for ADR identification were adapted to the specificities of Ophthalmology and resulted from a thorough search of: all terms of ICD-9-CM in Ophthalmology that included "drug-induced", "iatrogenic", "toxic"

and all codes that could signal an ADR, such as "362.55- toxic maculopathy" or "365.03 - steroid responsers", as detailed in the Results Section.

We also performed a search of general ADRs through the use of 'E' codes (ICD-9-CM codes from E930 to E949.9, designed to represent ADRs and already excluding wrong doses, errors and intoxications) to assess if these general ADRs could detect ocular ADRs.

In this study, we performed a query of Ophthalmology in a Nationwide study using administrative databases, including inpatients and outpatients.

Our main outcome was ADR detection. Secondary outcomes were: ADR in inpatients (ADR_I), ADRs in outpatients (ADR_O), ADR related to admission (ADR_{Ad}) versus ADR during hospitalization period (ADR_{In}), age, gender, admission diagnosis, other diagnoses, hospital stay and year (we aimed to assess trends in ADRs from 2000 to 2009).

Statistical analysis

Statistical analyses were done with the Chi-square test for categorical variables (or exact Fisher's test whenever possible), Student's t-test for normally distributed continuous variables and Mann-Whitney or Kruskal-Wallis for variables without normal distribution, using SPSS v20.The *a priori* level of significance was $p<0.05$.

Results

Study population

The baseline characteristics of the study population (n=11,944,725) are shown in table V5. The mean age of hospitalized patients was 46 years and 56% of the patients were female.

Characteristic	Value	
Mean age	48	27 sd
Female gender (%)	6598266	55.24%
District with higher number of hospitalizations	1st: Lisbon 21.2% 2nd: Porto 17.2% 3rd: Setubal 7.66%	
Mean hospital stay in inpatients (days)	7.1	3.21sd
Number of ocular ADRs	1564	

Table V5. **Socio-demographic characteristics of study population.**

From 2000, there was a slight increase in the number of hospitalizations in Portugal. 1524 specific ocular ADRs were detected through the search of codes that could represent particular ocular ADRs, as shown in table V6. Additionally, 100 episodes that could possibly correspond to an ophthalmic ADR were also detected (table V6). Therefore, a total of 1624 possible ocular ADRs were detected.

ICD-9-CM code	Diagnosis	Number of episodes
Specific ocular ADR codes		
362.55	Toxic maculopathy	1388
365.03	Steroid responders	4
365.31, 365.32	Corticosteroid-induced glaucoma	0
364.55	Miotic pupillary cyst	2
364.81	Floppy iris syndrome	2
366.45	Toxic cataract	83
367.89	Other drug-induced disorders of refraction and accommodation, Toxic disorders of refraction and accommodation	25
377.34	Toxic optic neuropathy, Toxic amblyopia	20
Possible signs of ocular ADRs		
366.46	Cataract associated with radiation and other physical influences	10
372.54	Conjunctival concretions	67
372.55	Conjunctival pigmentations, including conjunctival argyrosis	
372.56	Conjunctival deposits	
368.55	Acquired color vision deficiencies	23
368.59	Other color vision deficiencies	0
	Sub-TOTAL for specific ophthalmic ADRs	***1524***
	TOTAL	**1624**

Table V6. **Clinical codes searched and respective results in the portuguese database.**

The search of general ADRs through the use of E codes allowed us to identify 116,720 ADRs, but only 62 of them corresponded to the ocular ADRs that were identified, consequently, a specific search must be performed for ophthalmic ADRs.

Therefore, databases are a useful methodology for the detection of ocular ADRs, but require adapted diagnoses codes.

C) Systematic review of specific ophthalmic ADRs

After the general systematic review performed about ADRs, we were able to identify good targets of drugs that could benefit from a specific systematic review (if possible with meta-analysis), such as **statins** (we performed a pilot study of a Cochrane Collaboration review of ocular ADRs caused by statins: appendix 6). Other examples of drugs that have apparently good original studies but no recent systematic review to confirm respective ocular ADRs are: tamoxifen, antituberculous agents, angiotensin-converting enzyme inhibitors and cidofovir.

Ophthalmic ADRs caused by statins

To analyze the ophthalmic ADRs caused by statins, we performed a systematic review, performed as a Cochrane Collaboration Review - Eyes and Vision Group. We have finished the protocol for the pilot study and are have performed the title registration by the Cochrane Collaboration. The protocol is available in appendix 6.

Introduction

Many ophthalmic ADRs provoked by systemic drugs are known by spontaneous reporting, without systematic assessment nor definitive evidence. An ophthalmic ADR can affect every structure in the eye (Fraunfelder 2007), but some systemic drugs tend to provoke specific ophthalmic ADRs, namely amiodarone which frequently provokes cornea verticillata (Hollander 2004) and rarely provokes optic neuropathy (but with potential for irreversible blindness, Carelli 2002).

Statins are widely used for the treatment of dyslipidemia and cardiovascular pathologies (Taylor 2011). They provoke general ADRs that are well documented, such as myopathy, liver transaminases elevation and renal failure (Andrejak 2003). On the other hand, ophthalmic ADRs provoked by statins have been reported by some authors (Hermans 2011), but lack a systematic review. Specific types of ADRs that were

reported to occur after statin use include cataract formation, which is controversial, with some studies reporting an increase in the incidence of cataract (Hippisley-Cox *et al,* 2010) and others reporting a decrease (Klein *et al,* 2006). Other ADRs that have been reported are: dry eye (Smidt *et al,* 2011), diplopia (Fraunfelder *et al,* 2008), ptosis (Fraunfelder *et al,* 2008; Ertas *et al,* 2006) and ophthalmoplegia (Fraunfelder *et al,* 2008).

On the other hand, statins may have a protective role also in the delay of vitreous haemorrhage in diabetic patients (Banerjee *et al,* 2004) and in the development of age-related maculopathy (McGwin *et al,* 2003).

Statins (or HMG-CoA reductase inhibitors) are a class of drugs used to lower cholesterol levels. They inhibit the enzyme HMG-CoA reductase, which plays a central role in the production of cholesterol in the liver. They are widely used as lipid-lowering agents (Taylor 2011).

We will search ophthalmic adverse drug reactions provoked by statins systemically administered, in the correct dose, administration and indication, according to WHO's definition of ADR (WHO 2002).

Rationale

The specific ocular anatomy of the eye may facilitate the occurrence of ADRs. After a drug (namely a statin) is administered systemically, it can reach ocular tissues through uveal or retinal circulation and the fenestrated endothelium may allow the drug to pass through ocular barriers and to accumulate in ocular structures (Wren 2000). This may cause a pathological alteration of ocular structure or function and provoke an ophthalmic/ocular ADR. Nevertheless, there is controversy regarding statins: some state that its antioxidative and anti-inflammatory power may decrease the risk of cataract formation (Klein 2006), while others report an increase in the incidence of cataracts (Collins 2012, Hippisley-Cox 2010) and others report no association (Hermans 2011). Statins have been found inside the lens (Grosse 2004), and therefore may alter the lens fiber functioning, disrupting the delicate lens metabolism and consequently accelerating cataract formation. Also, the lens membrane contains cholesterol, therefore, statins can induce cataract formation because they may reduce lens cholesterol synthesis (Cenedella 1996).

In summary, the ophthalmologist should know the specific ophthalmic ADRs to systemic medication to recognize them in clinical practice. Methods of ADR detection have been explored and adapted to the specificity of ophthalmic ADRs.

VI. DISCUSSION

The fact that ADRs are so important in Public Health Care and yet are so heterogeneously and incompletely studied and detected, is a signal of the urgency of the development of methodological approaches for ADR detection. The relevance of this thesis, the methodological advantages and limitations of our studies and of these Pharmacovigilance methodologies, and our conclusions and recommendations are presented below.

A) Main findings and answers to research questions

1. What is known about the frequency of adverse drug reactions (ADRs) that occur in hospitalized patients?

After performing a systematic review which included several studies of ADRs in hospitalized patients in different hospitals in the World, we estimated the mean frequency of 17% (CI95%:14, 20%). This estimate had heterogeneity, as expected and previously reported in the literature (Lazarou *et al*, 1998). However, we were able to identify heterogeneity moderators: risk of bias, population, ward, and methodology for ADR identification. Low risk of bias studies adjusted for population (pediatric versus adult) had no statistical heterogeneity (I^2 = 0%), which is a new finding and supports our recommendations of higher methodological quality in further studies about ADRs.

2. What methodologies can be explored for the detection of ADRs besides spontaneous reporting?

Spontaneous reporting the most utilized methodology for ADR detection, because of low resources needed, but has the worse detection rate of all methodologies. The limitations of spontaneous reporting, along with the high costs of intensive or prospective monitoring, the economic impossibility to build a complete computerized system in Portugal, led us to develop two methodologies: one based in databases, and the other based on a simple computerized method that allowed computer chart-

assisted review (with low computation resources to maintain respective costs low). We compared directly our database methodology with spontaneous reporting and with manual chart review, and we compared our computerized approach with spontaneous reporting and with manual chart review. In figure VI1, we present the summary of all methodologies approached in this thesis. We believe that we have developed two methodologies that are promising. The database methodology has a detection rate (2.4%) that is many times higher than spontaneous reporting, with low resources (2PH); whereas the computerized approach has a remarkable detection rate (24.8%) with half the costs of a comprehensive manual chart review (35 PH).

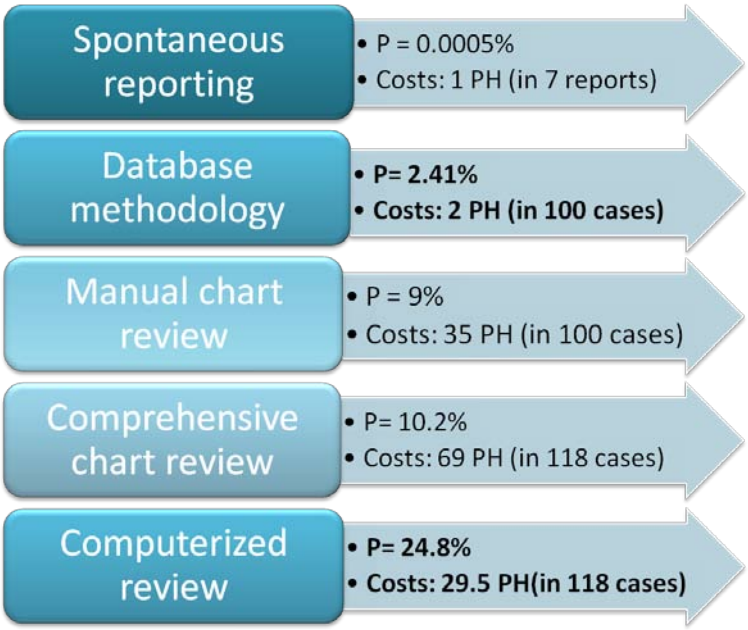


Figure VI1. Comparison of the different methodologies approached in this thesis for ADR detection. PH: Person-hours spent in the application of the methodology.

We applied the database methodology to the population hospitalized patients of public hospitals of Portugal, from 2000 to 2009, and obtained the first National estimate of ADRs. There were 9,271,122 hospitalizations, with 116,720 hospital ADRs detected by the database methodology (prevalence of 1%; 97% of the ADRs were ADR_{In}). There were 13,562 spontaneous reports of ADRs (ambulatory and hospital) from 2000 to 2009 in Portugal (prevalence of 0.1%, ten times lower). We were also able to characterize the population who suffered from ADR (all statistically significant):

they were older, had longer mean hospitalization period, more frequently of the female gender and had a higher risk of death. We additionally verified that several comorbidities may be risk factors for ADRs ($p<0.05$, Fisher's exact test in all): heart failure, septicemia, dysrhythmias, hypotension, cerebrovascular disease, stroke, diabetes, ischemic heart disease, malignancies and pneumonia. We therefore believe that the database methodology can be applied continuously, complementing spontaneous reporting.

Finally, the following table presents the comparison between all methodologies explored in this thesis. In this table the adjusted resources show that the database methodology may be the methodology with lesser costs.

Methodology	Number of ADRs identified / number of patients exposed	Prevalence (%) of ADRs detected	Resources spent (PH: person-hours)	Adjusted resources (PH per 100 ADRs detected)
Database	325 / 13471	2.41%	2 PH (per 325 ADRs)	**0.6**
Spontaneous reporting	7/13471	0.05%	1 PH (7 reports of ADRs)	**14**
Computerized	65 / 117	25%	29.5 PH (65 ADRs)	**45**
Succint chart review	9/100	9%	35 PH (9 ADRs)	**389**
Comprehensive chart review	12/117	10%	69 PH (12 ADRs)	**575**

Table VI1. **Comparison of all methodologies for ADR detection.** PH: Person-hours.

3. How can ocular ADRs be systematized and characterized?

We believe that we have contributed for the increase in the assessment and systematization of ophthalmic ADRs.

We built a general systematic review of ophthalmic ADRs (appendix 5), to add systematization and to identify specific ADRs lacking assessment. From 562 studies, we included 32 studies that summarized the most known systemic drugs causing ADRs and identified areas lacking specific systematic reviews. Then we performed a specific systematic review to systemic drugs in those areas lacking clarification and systematization, namely ophthalmic ADRs caused by statins (a Cochrane review in the protocol phase, appendix 6). Finally, we utilized the knowledge gained in the previous studies for the adaptation of our database methodology (appendix 7) to the specificities of Ophthalmology to detect ophthalmic ADRs. From all public hospitals from 2000 to 2009, 1524 specific ocular ADRs were detected through the search of codes that could represent particular ocular ADRs. Additionally, 100 episodes that could possibly correspond to an ophthalmic ADR were also detected.

We believe that the application of databases can help to increase systematization in Ophthalmology, if several adaptations are performed. Also, the increase in Ophthalmologists' education about ADRs and building protocols with other specialties if high-risk drugs are prescribed, may be of value in the further characterization and assessment of ADRs in Ophthalmology.

B) ADVANTAGES AND LIMITATIONS

We will discuss the advantages and limitations of each of the studies performed within the scope of this thesis below.

1) Frequency of ADRs in hospitalized patients

We believe that our systematic review provides an up-to-date, comprehensive assessment of the literature regarding the frequency of ADRs occurring during hospitalization with quantitative assessment and systematic evaluation of the quality of included studies. It was possible to identify multiple heterogeneity moderators, indicating the need to standardize methods and definitions used in ADR studies.

Heterogeneity sources

We were able to identify several sources of heterogeneity in studies about ADRs, particularly risk of bias and population: low risk of bias studies presented with I^2=0% either for pediatric or adult population, however in moderate and high risk of bias studies there was heterogeneity even after adjusting for age (I^2≥97%). Other heterogeneity moderators were ward and method for ADR identification.

The studies that most contributed to heterogeneity were, on one hand, studies with the highest incidences: Egger (2000) (I=60.7%) and Zopf (2008) (I=35.2%). Zopf may have overestimated ADR incidence because: they included 26 intoxications diagnosis (excluded in our analysis), there were some conflicting numbers. The same happened with Egger, that did not explicitly exclude ADR_{Ad} and studied a geriatric ward.

On the other hand, Bates (1993) (3.6% [1.8,5.4]), Ramesh (2003) (3.7%[3.1,4.3]) and Arulmani (2006) (3.8[2.9,4.7]) had the lowest incidences, which was probably due to the incomplete method used for ADR identification: Bates used prospective monitoring performed solely by a nurse; Ramesh used reporting and chart review. Arulmani reports performing intensive monitoring but did not perform daily evaluation and there are some doubts if they have performed the same follow-up to all patients.

Comparison of methodologies for ADR detection in our systematic review

Several of the included studies used different methodologies, but only four (Fattinger *et al,* 2000; Egger *et al,* 2003; Somers *et al,* 2003; Haffner *et al,* 2005) used different *concurrent* methodologies for ADR identification (there are also several reported in the literature, but they were excluded because nor validation of ADR nor intensive monitoring of all patients were applied); unfortunately we couldn't compare methodologies' performances without biasing because of insufficient data or because the population was not exactly the same for both methods.

Strengths and limitations of the systematic review

We believe that this work has several strengths, namely the complete and systematic literature search; the rigid and objective selection criteria for a good level of evidence; the subgroup analyses to identify heterogeneity factors and the risk of bias assessment of included studies. This work, however, has also some limitations, such as possible publication bias (few unpublished studies were found and the funnel plot was not completely symmetrical) and the heterogeneity found in meta-analysis and in almost all subgroup analyses (therefore, our quantitative analyses must be viewed with caution).

Conclusion

We found several studies of ADRs, but almost all had extremely different methodologies for ADR detection (even when the same methodology was reported to be used, namely intensive monitoring, the methods and criteria that were utilized in each study were highly variable) and few studies had with good methodological quality. Further studies about ADRs should be methodologically improved, methodologies for ADR detection should be standardized, definition of ADR of WHO should be always followed, and causality assessment for ADR (WHO's or Naranjo's) should be applied.

2) Methodological issues in the detection of ADRs

Several approaches for ADR detection were explored and compared in this thesis, in order to identify respective advantages, disadvantages, detection rate, resources required and other methodological issues.

2.1) Spontaneous reporting

Spontaneous reporting largely underestimates the real number of ADRs (Davies *et al,* 2007; Herdeiro *et al,* 2008): our studies found a small prevalence of ADRs detected by this method and are consistent with others (McGettigan *et al,* 1997; Smith *et al*, 1996). However, spontaneous reporting has a widespread utilization due to its low costsand is the basis for the WHO Drug Monitoring Program (WHO 2012). It is possible to increase its low detection rate (using continuous education, change in attitudes associated with underreporting and stimulating spontaneous reports) but these measures increase not only detection but also costs.

2.2) Validation study of the database methodology

We built a database methodology for ADR detection that is simple, cheap and effective, through the use of coding information available in administrative databases.
Several efforts have been performed to build a database methodology: *First,* we performed a complete test of 114 diagnostic codes' performance as well as E codes. S*econd,* there was validation of ADR code signals (through chart review of more than 350 signals), to assess positive predictive value of each code. *Third,* unlike previous literature that solely identified E codes, we identified the queries that *added* information to E codes (not queries that would generate repeated information to E codes), to decrease validation resources and to complement E codes. *Fourth,* our database method required reduced resources (2 person-hours) in ADR detection, in comparison with chart review (35 person-hours) per 100 cases. *Fifth,* there was an enhanced ability to detect ADRs, with a detection rate several times higher than the most widely used method in Pharmacovigilance: spontaneous reporting (325 *versus* 7 ADRs).

There were limitations in this study, such as the fact that we didn't validate all of the initial 10752 ADR signals. Validating all signals would be ideal but too resource-consuming, therefore this two-phase approach (of first selecting the best codes, then validating them) was a practical approach that can be used in other hospitals. The fact that this is a one hospital centered study might also be a limitation. We chose the codes that best describe this hospital's reality, but it may also be interesting to retest all codes in other hospitals, populations, years and countries, to understand on the one hand, which are the most universal codes, and on the other hand, which occur more in one country, or in one hospital type, or in a particular population.

There are also database-related limitations, namely: probable incomplete and wrong information in some cases in databases (which might occur in every large database), "*coding creep*" (this is a possible bias of all billing databases, in which more expensive codes are preferred and registered to increase the case-mix, diagnosis-related-group and consequently to increase reimbursement of that hospital) (Zuhair *et al,* 2010).

2.3) Nation-wide study of ADRs using the database methodology

In the first nationwide study of ADRs in Portugal using a methodology beyond spontaneous reporting, we identified 166,720 ADRs of 9,271,122 inpatients stays (mean prevalence of 1.3%) of all public portuguese hospitals from 2000 to the first half of 2009.

These estimates were consistent with those presented in other studies that identified risk factors of ADRs, such as comorbidities (Seiber, 2007), diabetes (Zhang *et al*, 2009), renal failure (Corsonello *et al,* 2005a), female sex (WHO, 2012) and age (Davies *et al*, 2007). They were also consistent with the frequency of ADRs identified by previous studies that used administrative databases: 0.89% in Spain (used solely E codes) (Salmerón-García, 2010), 0.9% in England (Corsonello *et al,* 2005b), 1.83% in the Netherlands (van der Hooft *et al,* 2060) and 0.8% in Australia (Wu *et al,* 2010).

The advantages of this study include its comprehensive database which contains data from all hospitalizations in every acute care public hospital in Portugal within almost a decade, as well as the validation study previously performed, a far greater detection

rate than spontaneous reporting (detecting only 12% of the ADRs identified by the database), and its reasonable costs (affordable for continuous Pharmacovigilance).

One limitation might be the use of a small one-centered validation study to a large National database; we assumed that the population was the same but we could be inducing bias if the population is different.

2.4) Chart review

From the two chart reviews performed in this thesis, a moderate detection rate was obtained (9-10.2%) but the costs were quite high (35 to 69 PH in 100-118 patients) which is consistent with other studies, namely Jha (1998) that reported costs of 55 PH. Some authors consider it as the goldstandard (Tinoco *et al,* 2011), but all agree that it is too resource-consuming to be continuously and widely used as a Pharmacovigilance methodology.

2.5) Computerized chart review

We developed and validated a computerized methodology easy and fast to apply, and costless to our National Health System, that detected five times more ADRs (65 versus 12 ADRs) than manual chart review with half the resources (69 versus 29.5 person-hours).

Unlike other expensive computerized methodologies, we started from chart review with integrated data (instead of separate laboratorial data or other indicators from health systems), and developed databases and algorithms to create automation, while leaving the ultimate decision of ADR causality assessment to the health professional reviewer, with a simple user-friendly interface.

The good detection rate and the low resources required (a mean of 15 minutes per patient), much lower than complete manual chart review, are advantages of this method. In small hospitals where it isn't feasible to implement complex computerized systems, ADR monitoring can be improved through this cheap system. The program Chart Helper also elaborates a list of frequent and fatal ADRs per drugs administered to each patient, allowing even inexperienced reviewers to detect symptoms (or signs,

laboratorial data or codes) that may constitute an ADR, working as a supporting memory tool. Another advantage is this method integrates validation and causality assessment during each assessment and the fact that we performed a validation study in all patients using chart review.

Nevertheless, further testing and validation must be performed. Although this method is resource-sparing because it has a low level of automation, it would be interesting to integrate it in the Health System and to add further automation (the costs would rise exponentially, but we believe that interesting results would be provided).

3. Application in Ophthalmology

Several ophthalmic/ocular ADRs were detected, either through the application of adapted Pharmacovigilance methodologies, and with systematic reviews of general and specific ophthalmic ADRs. We performed first a general systematic overview to summarize existing evidence and identify specific ophthalmic ADRs that were lacking systematization and meta-analysis. We then performed systematic reviews of those specific ophthalmic ADRs, as well as other studies to identify ophthalmic ADRs. We also tested and adapted database methodology for the detection of ADRs.

3.1) General systematic review of ophthalmic ADRs

There is an increasing number of studies of ophthalmic ADRs. In spite of the common belief that ADRs in Ophthalmology are rare, some ADRs might be extremely frequent (such as cornea verticillata caused by amiodarone (Hollander *et al*, 2004)), but require specific ophthalmological examination for its detection. Every ocular structure might be affected by an ADR.

Strengths of our overview lie in the comprehensive search performed, on the general increase in systematization of ophthalmic ADRs, summary of existing evidence according to WHO's causality criteria for ADR and WHO's definition of ADR, and finally in the identification of specific ophthalmic ADRs that could benefit from a specific systematic review with possible meta-analysis.

Limitations of our overview include not only the heterogeneity found in different types of ADR but also the extreme variability in the methodologies of studies of ophthalmic ADRs (from isolated case reports to retrospective series of spontaneous reports and prospective observational studies). These limitations were expected, considering that it is a general overview and that the detection of ADRs highly depends of the degree of suspicion in an ophthalmologic examination. Many ophthalmic ADRs are only detected by case reports originating from ophthalmologic examination, representing a limitation but simultaneously an opportunity to improve.

3.2) Specific ophthalmic ADRs

We performed a systematic review of specific ophthalmic ADRs caused by statins (in the phase of pilot study of a Cochrane Collaboration review).

Future studies are also needed in other drugs that have apparently good original studies reporting ophthalmic ADRs but no recent systematic review to confirm respective ocular ADRs are: tamoxifen, antituberculous agents, angiotensin-converting enzyme inhibitors and cidofovir.

3.3) Application of the database methodology in the detection of ophthalmic ADRs

The database methodology allowed the identification of 1524 specific ocular ADRs (and other 100 probable ophthalmic ADRs) in a portuguese population of all public hospitals from 2000 to the first half of 2009.

To our knowledge, this was the first Nationwide estimate of ophthalmic ADRs in Portugal. Additionally, we did not identify any other study performed internationally that used an adapted database methodology for the identification of ophthalmic ADRs, or any other method in a Nationwide level except for spontaneous reports of ocular ADRs. We also assessed a comprehensive population within almost a decade. The search of general ADRs through the use of E codes allowed us to identify 116,720 ADRs, but only 62 of them corresponded to the ocular ADRs that were identified, therefore, a specific search must be performed for ophthalmic ADRs.

Limitations of this study include possible incomplete or wrong data, which can occur in every large database, the impossibility to validate all of these alerts and the small

prevalence of ocular ADRs found, namely caused by corticosteroids (which was lower than expected). Nevertheless, this may be an interesting and new approach to identify ocular ADRs at a nationwide level. Future studies include further utilization of these codes in other countries to identify if other ADRs can be identified, and trials of educational interventions to increase detection and coding of ocular ADRs.

C) CONCLUSIONS AND RECOMMENDATIONS

Recommendations for studies about ADRs

ADRs in hospitalized patients can occur in 16.9% (CI95%:13.6, 20.2%) of patients during hospitalization, but there was heterogeneity, particularly in high risk of bias studies. Therefore, quality of ADRs studies should be improved, current methodologies for ADR detection should be standardized, and new methodologies for ADR detection should be developed and explored. Recommendations for future studies concerning ADRs include: improvement of methodological study quality (through minimization of risk of bias during the planning phase of each ADR study), standardization of methodologies (namely a standardization of intensive monitoring with strict criteria), identification of new Pharmacovigilance approaches, a clear definition of ADR (WHO) and causality assessments (Naranjo or WHO) for ADRs.

We recommend strict criteria for *intensive monitoring*, such as:

- Monitoring performed by team members specialized or experienced in ADRs
- With *daily* patient interview (and if necessary patient examination) from admission until discharge
- With *daily* chart review
- With at least weekly medical team interview (including doctor, nurse and pharmacist; clinical rounds are useful)
- With strict application of WHO's definition of ADR
- With causality assessment (from WHO or Naranjo) verified prior to discharge
- With similar follow-up for patients with and without ADR suspicion

Conclusions and recommendations regarding new methodologies for ADR detection

1. Database methodology and computerized chart review are promising

From the comparison of all methodologies, we can conclude that the methodologies developed in this thesis, database methodology and computerized chart review, are

promising and might be integrated as effective and even cheap Pharmacovigilance methodologies.

The *database methodology*, validated by us, "lies is the middle" of spontaneous reporting and chart review: it is resource-sparing enough for continuous application (it may be even more resource-sparing than spontaneous reporting, according to adjusted-resources calculation), it offers a detection rate much higher than spontaneous reporting and it has a good PPV (similar to chart review).

Computerized chart review might be an useful Pharmacovigilance methodology in the future, particularly at a time of world economic crisis, since it may allow continuous (or at least regular) surveillance with a higher ADR detection with half the resources needed by manual chart review.

2. Different methods complement each other

In our studies, we reported that chart review, database and computerized methodologies seemed to detect different types of ADRs and ADRs that occur with different drugs, complementing each other. Other studies that compared different methodologies for ADR and ADE detection also reported that each methodology tends to detect different ADRs, concluding that multiple methods for ADR detection should be used complementarily for patient safety enhancement (Petratos *et al*, 2011).

Therefore, database methodology and computerized chart review are effective Pharmacovigilance methods and should be used complementarily with spontaneous reporting.

Conclusions and recommendations in Ophthalmology

Ophthalmology represents simultaneously a challenge and an opportunity to identify ADRs. Databases are a useful methodology for the detection of ocular ADRs, but require adapted diagnoses codes.

Adapted methodologies were successful in detecting either general and specific ophthalmic ADRs and should be used continuously.

We also believe that all spontaneous reports of ophthalmic adverse drug reactions could be sent for analysis by an ophthalmologist experienced with ADRs, for further study and orientation, in an attempt of a multidisciplinary and complete analysis.

Ophthalmologists' knowledge about ophthalmic ADRs is essential for its detection and should be stimulated. Therefore, strong suggestions for the future include promoting ophthalmologists' education (to increase recognition of ophthalmic ADRs) and disseminating protocols of collaboration between Ophthalmology and other Medicine specialties whenever high-risk drugs are prescribed (such as sildenafil, biphosphonates, psychiatric medication, tamoxifen, hydroxichloroquine).

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VIII. APPENDICES

APPENDIX 1

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY (2012)
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3309

REVIEW

Frequency of adverse drug reactions in hospitalized patients: a systematic review and meta-analysis†

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ABSTRACT

Purposes To perform a comprehensive systematic review of prospective studies about frequency of adverse drug reactions (ADRs) occurring during hospitalization (ADR_{In}), including a thorough study quality assessment, meta-analysis and heterogeneity evaluation.
Methods Systematic review of several databases: Pubmed, EMBASE, CINAHL, Cochrane, ISI, International Pharmaceutical Abstracts, Scirus, NHS economic, and others, as well as manual search. Inclusion criteria were: prospective studies (assessing all patients before discharge, by a specialized team, at least once a week); with data about ADRs occurring during hospitalization, using WHO's or similar definition of ADR. Two independent reviewers assessed eligibility criteria, extracted data, and evaluated risk of bias.
Results From 4139 studies initially found, 22 were included. Meta-analysis indicate that ADRs may occur in 16.88% (CI95%: 13.56,20.21%) of patients during hospitalization; however, this estimate has to be viewed with caution because there was significant heterogeneity ($I^2 = 99\%$). The most significant moderators of heterogeneity were risk of bias, population, ward, and methodology for ADR identification. Low risk of bias studies adjusted for population (pediatric versus adult) had $I^2 = 0\%$.
Conclusions These data are useful as a broad characterization of in-hospital ADRs and their frequency. However, due to heterogeneity, our estimates are crude indicators. The wide variation in methodologies was one of the most important moderators of heterogeneity (even among studies using intensive monitoring). We suggest criteria to standardize methodologies and reduce the risk of bias. Copyright © 2012 John Wiley & Sons, Ltd.

KEY WORDS—adverse drug reactions; systematic review; meta-analysis; hospital; incidence; pharmacoepidemiology

Received 11 January 2012; Revised 29 May 2012; Accepted 30 May 2012

INTRODUCTION

Adverse drug reactions (ADRs) are frequent, important, expensive, and can be fatal.[1,2] In 1998, Lazarou estimated that ADRs were between the fourth and the sixth leading causes of death in the US[3] but there was heterogeneity.[4] ADRs are the cause of 2.7% to 15.7% hospital admissions.[5–7]

They may lead to US$1.56 billion in direct hospital costs per year in the US,[8] and drug-related morbidity may lead to US$136.8 billion in indirect costs.[9] Each ADR may represent a cost of US$2500 per patient.[10]

Although there are numerous studies about ADRs, the methods of identification and reporting ADRs vary greatly.[11–14] Some studies have assessed difficulties in building a quality systematic review of ADRs or adverse drug events,[15,16] while others have established useful recommendations.[17–19] There are several good systematic reviews about ADRs that cause hospital admission(ADR_{Ad});[20,5] however, it is still lacking in the literature a current and adequately performed systematic review regarding the frequency of ADRs occurring during hospitalization(ADR_{In}). Moreover, in systematic reviews of general ADRs, there is the need for more complete, thorough, and meticulous systematic literature search; using a single and standardized definition of ADR; and a more thorough and appropriate heterogeneity analysis.

Our primary purpose was to systematically review the literature regarding the frequency of ADR_{In}. Secondary objectives were the characterization of ADRs[3,13,21] and their identification by each pharmacovigilance method. We also aimed to undertake a thorough analysis of the methodological quality of the included studies and of factors associated with heterogeneity.

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METHODS

We performed a systematic review of studies that assessed ADR frequency among hospitalized patients. Since there is a wide variation of terms, we present some definitions.

Definition of adverse drug reactions

Adverse drug reaction: "any noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy", according to the World Health Organization (***WHO***) definition of 1972.[22] This definition is the most widely used, but there are others, like ***Karch and Lasagna's***[23] (similar but excludes therapeutic failures) and ***Edwards and Aronson's***[24]: "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".

Adverse drug events (ADE) were not the purpose of our review: "An injury related to the use of a drug, although the causality of this relationship may not be proven".[25] They include errors and ADRs.

Search methods

Our review adhered to the Cochrane approach[26] and PRISMA Statement.[27]

We searched through several electronic databases (last date of search was 2/4/2010): Medline, EMBASE, Cochrane Central, SCOPUS, EBSCO, ISI web of knowledge, ISI Conference Proceedings, International Pharmaceutical Abstracts, DARE, LILACS, Scirus, NHS economic evaluation database, other conference proceedings, clinicaltrials.gov, and Google scholar. We used a search query created after two pilot studies (full search query in supplemental material).

We emailed experts[10–12] for grey literature and unpublished data, and hand-searched all references of included studies and relevant reviews.

Selection criteria

Studies were included if they followed all **inclusion criteria** listed below:

1. Prospective studies, that followed hospitalized patients from admission to discharge, assessing in *all* patients the existence of ADRs prior to discharge, and in which investigators were able to interview physicians, patients, or nurses at least once per week. Studies assessing ADRs only at hospital entry or in emergency wards were not included.
2. Studies that previously planned and described a consistent and reproducible methodology for ADR detection, later applied to all patients in a standardized manner. These methodologies included:

   2.1. **Intensive monitoring** applied to all patients. To reduce the high methodological variability of studies that claim to perform intensive monitoring, we created strict criteria for considering a methodology as intensive monitoring:

   - Monitoring was performed by specialized team member(s) with experience in ADR identification.
   - Monitoring included a *daily* review of the chart, visiting of the ward *and* interview of the patient. If necessary, the patient was examined.
   - Monitoring included an interview of the health care team at least once a week.
   - A daily chart review without patient interview nor examination was not considered intensive monitoring (it was considered chart review).

   2.2. **Prospective monitoring** applied to all patients. This would include studies in which monitoring of patients was performed with assessment of ADRs before discharge, with patient interview or examination or health team interview at least weekly, but without fulfilling all the criteria above for intensive monitoring (even if the authors called it intensive monitoring).

   2.3. Prospective **chart review** applied to all patients, with patient interview or examination or health team interview.

   2.4. **Computerized monitoring** if another methodology (chart review, prospective, or intensive monitoring) was also applied to *all* patients. Computerized monitoring in which only computer alerts were validated were excluded, because it was not a methodology equally applied to all patients.

   2.5. **Database search** if another methodology (chart review, prospective, or intensive monitoring) was equally applied to all patients.

   2.6. **Spontaneous or solicited reporting** if another methodology (chart review, prospective, or intensive monitoring) was applied to all patients.

DOI: 10.1002/pds

3. Studies with sufficient data about frequency of ADRs (if a study focused on ADE, it needed to have separate data on ADR).
4. Studies of ADRs that occurred during hospitalization (ADR_{In}). We were not interested on ADRs as a cause of hospital admissions (ADR_{Ad}).
5. Studies that used WHO's definition of ADR.[23] Studies with other similar definitions (like Karch and Lasagna[24]) were included but analyzed separately (in order to identify if this added heterogeneity). When studies provided their own definition described in detail, we sought inconsistencies with WHO's definition (if inconsistent, they were excluded). When no definition or an imprecise definition was reported, we emailed authors. Studies that claimed to assess frequency of ADEs but provided WHO's definition and criteria of ADRs were included (they studied ADRs although they inappropriately called them ADEs). Studies with Edwards and Aronson's ADR definition[25] were not included because although it is a good definition, it is rather different from WHO's definition.

We also included studies with different languages (English, Portuguese, Spanish, French, German - we hired a translator), any country, any ward (we included pediatric wards for a comprehensive view), experimental studies (if any), and year of study (although we only included studies after WHO's definition of 1972). We did so to have a more thorough and complete literature search and to have the opportunity to analyze them as subgroups and identify sources of heterogeneity.

Exclusion criteria:

1. Studies including only patients with particular pathologies (we did not exclude studies that systematically identified ADRs in particular wards; although we planned to analyze them separately)
2. Studies for specific drug exposures (specific ADRs such as bleeding were not excluded *per se*)
3. Studies in which the primary objective was not ADR identification (like trials of drug effectiveness), in order to warrant a methodology systematically applied to assess ADRs frequency.

Outcomes assessment

Primary outcome was frequency of ADR_{In} (number of ADRs, number of patients exposed to drugs, length of hospital stay if reported). The number of patients exposed to drugs was sometimes not specified by the authors; in that case, we emailed them and if without response assumed that it was equal to number of patients included in the study (assumed data, raw data, and calculated data are all explicit in Table 1).

We calculated cumulative incidence, more adequate as a proportion than as a rate, because in a rate, we would need to know length of stay for each patient. The cumulative incidence of ADR_{In} (I) was calculated as follows:

$$I = \text{number of patients with } ADR_{In} / \text{number of patients exposed to any drug}$$

We calculated its standard error (E): $E = \text{square}(I(1\text{-}I)/N))$

Other variables of interest, if reported, were: particular diagnosis, year of study, ward and hospital type, mean age of patients, average length of hospital stay, mean number of drugs per patient. If reported which drug was used, we identified the therapeutic drug class according to Martindale's reference book,[28] number of days in which the drug was used, and administration route. We always verified if causality was assessed (and according to what classification, preferably WHO's or Naranjo's[29]) as well as predictability of ADRs (using Hartwig's predictability scale, for example),[30] preventability (e.g. Schumok and Thornton's preventability criteria)[31] and types of ADRs (Rawlins and Thompson's classification[21]); otherwise, we emailed authors.

Data collection and analysis

Two independent reviewers, AM and MA, first examined each title and abstract to exclude obviously irrelevant reports, and then independently examined each full text report, to determine eligibility according to inclusion criteria.

We performed a pilot test to evaluate the selection procedure and criteria on a sample of reports, as recommended by the Cochrane approach.[26] We then performed another pilot test with 100 random studies. We used those tests to refine criteria and train reviewers. Disagreements were solved by consensus, recorded, and analyzed using kappa statistics.

DOI: 10.1002/pds

Table 1. General characteristics on included studies of ADR_{In}

Study	*Country hospital ward*[a]	*Sample*[b] *duration*	*Method*[c] *for ADR detection*	*ADR incidence* [d]	*Summary of study*	*Remarks* [e]
1993 Bates[34]	United States.1G 7 wards: 2Med,2S, 2Ob,1ICU	420 p 1.2m	P, R, Sl	15 ADR in *15* p $I = 0.0357$ $E = 0.00901$	Prospective cohort in seven wards of a tertiary hospital, with daily chart review by a nurse and solicited reporting, to evaluate incidence and preventability of ADEs	*ADE study with separate data of frequency of ADRs * Does not explicitly report ADR_{In} but "ADR during hospitalization" *2967 patient-days (number of patients with ADR was not explicitly stated but possible to calculate)
1998 Moore[35]	France 1G 1Med	329 p 6 m	Sl, I	21 ADR in 21 p ($31ADR_T$) $I = 0.0638$ $E = 0.01345$	Prospective cohort with intensive surveillance (daily monitoring) of all patients consecutively admitted to a ward to identify "serious ADRs" (it did not identify all ADRs)	* Although they present a definition similar to WHO's definition of ADR, there were imprecisions, like: "involuntary over or underdosing were included [as ADR]. . ." *ADR incidence was calculated (modified data for further precision)
1999 Gholami[36]	Iran 1T 2 Med	370p 10m	S, I	95ADR in 29p ($102ADR_T$) $I = 0.0784$ $E = 0.0140$	Prospective study, randomized sample, with spontaneous reporting and intensive monitoring (in which a pharmacist daily reviewed patient charts, laboratory data, and interviewed patient)	* Randomized sample * "ADRs increased an average length of stay in 29.9% of patients" * "ADRs were more predictable if the reaction was hematologic"
1999 Martínez-Mir[37]	Spain 1 T 2 Ped	409p 6.7m	I, S, Sl, C, Co, R	56 ADR in *56*p ($112ADR_T$) $I = 0.137$ $E = 0.0170$	Prospective study to assess the extent, pattern and profile risk for ADRs in hospitalized patients aged 1–24 months. Records were screened daily, and there was parent interview and daily visit wards.	*Authors specify number of patients exposed to drugs: 409 * "Consistent relation between nr drugs and cumulative incidence of ADR" * Children with ADR had longer hospital stay; female had more risk of having ADR * We excluded one unlikely ADR reported by authors: modified data
2000 Bemt[38]	Netherlands 2 G 2 Med	538p 2m	S, Sl, I	248 ADR in149p $I = 0.280$ $E = 0.0193$	Prospective cohort study in a medical ward in two hospitals, to identify ADR and its risk factors, by several methods: spontaneous reporting, solicited reporting and intensive monitoring by a pharmacist, daily	*Authors say "adverse drug event" but use WHO's definition of ADR *They present adjusted odds ratio (OR) to: age, sex, no. drugs, and time of stay *Authors propose intensive monitoring if ≥7 drug/patient *Modified data
2000 Fattinger[39]	Switzerland 2 T 2 Med	3624p 36 m	P, R, Co, C	317 ADR in *317p* (461 ADR_T) $I = 0.0875$ $E = 0.00469$	Prospective cohort of two teaching hospitals in which all consecutive patients were admitted and data recorded (like symptoms, laboratorial data, ICD10 codes) to a computerized system generating alerts of ADRs, confirmed by a physician. Chart review was performed in all patients; intensive monitoring only of ADR alerts.	*From several data: possibly drug-related events, drug-related disease, unrelated, and ***clinically relevant ADRs***, we chose the last. We calculated ADR_{In} from Table 2 (text and table had some inconsistencies): 461 ADR_T - 144 ADR_{Ad} = 317 ADR_{In} (modified data) * ADR's definition of Karch and Lasagna; they did not exclude all cases of involuntary overdosing (and do not report its number) * "Clinically relevant ADRs": not all ADRs were identified.
2002 Buajordet[40]	Norway 1T 1 Ped	579 p 5m	S, Sl, R	407ADR in 161p $I = 0.278$ $E = 0.0186$	Prospective pediatric ADE study (with daily chart review) that includes frequency of ADRs	*Authors specify that all participants are taking drugs

DOI: 10.1002/pds

						*Study about ADE that has separate ADR data (however, does not specify if they are only referring to ADR_{In}) *Authors call it "intensive" but does not match our criteria
2002 Weiss[41]	Germany 1G 1Ped	214p 8m	Sl, R, C	64 ADR in 46p [68ADR_T] $I=0.215$ $E=0.0281$	An 8-month prospective study in a ten-bed pediatric ward using computerized system, chart review weekly and solicited reporting to identify ADRs	*Intensive monitoring was only applied to ADR suspects * Modified data to include only ADR_{In}
2003 Egger[42]	Germany 1G 1 Ger	163 p 4m	R, C, P	153 ADR in 99p (Computer identified 64 ADRs) $I=0.607$ $E=0.0383$	Prospective monitoring of all patients admitted to a geriatric ward to compare the ADR rate predicted by a computerized pharmaceutical database to that determined by direct observation	*They did not explicitly exclude ADR_{Ad}, but studied "ADRs during hospitalization" * "Computerized drug databases are a useful tool for detecting and avoiding ADRs." * Authors report intensive monitoring, but it does not fulfill our criteria of intensive
2003 Ramesh[43]	India 1T **R**	3717 p 7m	S, Sl, R, P	244 ADR in *138 p* (270 ADR_T) $I=0.0371$ $E=0.00310$	Spontaneous and solicited notification and chart review of all patients from one hospital. Intensive monitoring was performed in patients *suspects* of having an ADR.	*Authors say that they used WHO's causality criteria but do not report respective results *Authors do not explicitly state ADR_{In}, but possible to calculate ("3.7%"): modified data *Ward type not reported
2003 Somers[44]	Belgium 1T 1Ger	56 p *(see remarks)* 8m	P, Sl	21 ADR in *12*p $I=0.214$ $E=0.0548$	Pilot study of all patients admitted to a geriatric ward, comparing two methods of ADR identification: prospective monitoring (with patient interview at admission by pharmacist with standardized forms, and chart review three times/ week, and discussion with medical team weekly) versus solicited reporting.	* The authors call it spontaneous reporting but describe solicited reporting * "No formal causality assessment was made. . ." *12 notifications of 168 patients; 32 ADR in 22 patients of 56 interviewed. We only considered the 56 patients eligible for prospective assessment and interview. *WHO's definition of ADR was used but: "this does not exclude that some events are categorized as not related to the treatment after causality assessment"
2003 Vargas[45]	Spain 1G 1ICU	401 p 20m	Sl, I, R	39 ADR in37p $I=0.0922$ $E=0.0145$	Patients from a surgical ICU were prospectively followed to identify ADR and evaluate their effect on length of stay, daily. Authors do not report it but describe intensive monitoring.	*ADR's definition of Karch and Lasagna (which excludes lack of efficacy, unlike WHO's)
2005 Fattahi[46]	Iran 1T 1 Ped	380p 5m	S, Sl, I, R	82 ADR in 40p (94 ADR_T) $I=0.105$ $E=0.0157$	Prospective study in children < 14 years to identify ADR as a cause of admission and ADR that occurred during hospitalization (separate data). Intensive monitoring was performed with daily evaluation.	* The incidence calculated by the authors includes nr of participants (404) but only 380 patients were exposed to drugs (we used the number 380: modified data) * "Consistent relationship between number of drugs and number of ADR"
2005 Haffner[47]	Germany 1T 3 Ped	703p 3m	C, I	124 ADR in 99p (101ADR_T) $I=0.141$ $E=0.0131$	Prospective study to identify ADR in which two methods were compared: intensive monitoring (101ADR_T) versus automated search (45 ADR_T). Children were assessed daily (except weekends), there were parent and medical team interviews.	*703 participants for intensive monitoring but only 636 for computerized analysis; slightly different follow-up time (45 ADR identified by PC): modified data *Responded to email with useful data *"ADRs occur as frequently in pediatric as in adult patients."

(*Continues*)

DOI: 10.1002/pds

Table 1. (Continued)

Study	*Country hospital ward*[a]	*Sample*[b] *duration*	*Method*[c] *for ADR detection*	*ADR incidence* [d]	*Summary of study*	*Remarks* [e]
2006 Camargo[48]	Brazil 1T 5 Med	333p 9m	P, R	119 ADR in 86p $I=0.258$ $E=0.0239$	Prospective study (until discharge) with previously trained researchers that performed chart review before patient discharge	*333 participants, but only "268 were followed until discharge"(losses to follow-up) *ADR results in table do not match with text; we used data from Table 1 *One of the few studies with a randomized sample and the only included study that previously calculated sample size (data collection interrupted after an interim analysis) *Although authors refer intensive monitoring, it does not match our criteria
2006 Santos[49]	Brazil 1G 1Ped	265p 5m	I, R	47 ADR in 33p $I=0.124$ $E=0.0203$	Prospective study with intensive daily monitoring of a pediatric ward (children from 0 to 16 years) with 36 beds to identify ADEs.	*Studies ADEs but has separate data for ADRs *ADRs were more frequent with more drugs ($p<0.081$), longer hospital stay ($p<0.008$), and younger age ($p<0.020$) *"265 patients exposed to drugs from 273 participants"
2006 Tribiño[50]	Colombia 1G 1Med	836p 5m	S, SI, P, R	268 ADR in 208p $I=0.249$ $E=0.0150$	Prospective monitoring study over 5 month in a medical ward to identify ADRs and calculate its costs.	*Doubtful ADRs were excluded *"Solicited reporting, chart review, and patient exam and interview when necessary". However, does not specify daily patient evaluation *Direct costs were calculated from the perspective of the payer; calculated range of costs from ADR: USD$ 35011.92 to 45011.94
2007 Arulmani[51]	India 1G 3 wards: 1med, 1 S,1ICU	1682 p 9m	P, Sl, R	63 ADR in *63p* ($121ADR_T$) $I=0.0375$ $E=0.00463$	Prospective cohort study of patients admitted to three wards, using solicited reporting and monitoring to ascertain ADR frequency, severity, and costs.	* The authors say spontaneous reporting but describe solicited, e.g.: "during the ward rounds, these pharmacists encouraged the doctors to report suspected ADR" *Some sums of results do not match with the text (e.g. Table 1: ADR_{In}: 23 male and 43 female; total **64** ADR_{In}; in text: "**63** ADR_{In}"); we used data from the text. *"Pharmacists attended ward rounds and [. . .] encouraged doctors to report [. . .], several forms were designed. . ."
2008 Zopf[52]	Germany 2 T 2 Med	907 p 6m	I, R	566 ADR in 319p $I=0.352$ $E=0.0158$	Cohort of all patients admitted to two medical wards in two university hospitals, with intensive monitoring (daily, by a trained team of three physicians, one pharmacologist and two pharmacists) to characterize risk factors associated with ADRs after admission	*Included 26 intoxications diagnosis, which we excluded: modified data *Slight problems with table sums: "90**7** patients, from which 480 men and 42**3** women" *Does not explicitly exclude ADR_{Ad}, although mentions "ADRs *following* admission". *"The predictability of ADR depends on: raised temperature, low erythrocytes, low thrombocytes, high number of drugs and female sex"
2009 Joshua[53]	India 1T 1ICU	728p 12m	P, C	239 ADR in 188p (294 ADR_T) $I=0.258$ $E=0.0162$	Prospective study of 12 months to identify ADRs in an intensive care unit, by a team that accompanied clinicians 6 days in a week, viewed patients records. They mention intensive	*Nr of comorbidities was higher in patients with ADR: 5.7 ± 1.7 versus 4.6 ± 1.6($p<0.0001$) *Authors mention 902 participants but do not justify why only "included 728"

DOI: 10.1002/pds

					monitoring, but no patient interview nor examination is reported.		*Authors wrote "of the 222 patients with ADRs, 188 developed ADRs ($n = 239$) during hospital stay"; but in the table:"**294** ADRs"; we considered the text: modified data
2009 Pourseyed[54]	Iran 1T 1Med	400 p 3.75m	I, R	63 ADR in 40p ($47ADR_T$) $I = 0.100$ $E = 0.0150$	Prospective cohort with intensive monitoring (by a pharmacist and a pharmacologist) with two questionnaires to characterize ADRs and "all patients [. . .]were followed daily until discharge".		*Authors exclude: hospital stay <1 day, administrative errors and non compliance *3276 patient-days were studied *Explicitly mention: "patients who did not consume any drugs were omitted"
2009 Santos[55]	Brazil 1T 1Ped	1764 p 24m	R, S	302 ADR in $302p$ $I = 0.0081$ $E = 0.0045$	Chart review of all patients (children < 16 years) were performed three times a week.		*"Pharmacy interns were trained to detect and report suspected ADRs, under the supervision of pharmacists"

[a]**Second column**: **Hospital type**: Defines number of hospitals and hospital type: ***T***: teaching or university hospital; ***G***: *non teaching hospital (for example, "2T" means two teaching hospitals)*. **Wards**: Number and type of wards in which study occurred. The following abbreviations were used for ***type of ward***: Med: internal medicine, S: surgery, ICU: intensive care unit, Ped: pediatric ward, Ger: geriatric ward/unit, Ob: gynecology/obstetrics, **R**: not reported (for example, "1Ped" means the study was performed in one pediatric ward.

[b]**Third column**. **Sample size**: number of patients exposed to drugs (**p**: patients). **Duration** of study (**m**: months).

[c]**Fourth column**. **Method for ADR identification**: Every method that authors used for ADR identification is reported, according to our criteria (see text). Abbreviations used: ***S***: spontaneous reporting, ***SI***: solicited reporting, ***I***: intensive monitoring, ***P***: prospective monitoring, ***C***: computerized system with investigation of every alert to validate ADR; ***Co***: codification/codes; ***R***: chart review.

[d]**Fifth column**: **ADR incidence:** ***Number of ADRs, patients with ADRs, cumulative incidence of ADR***, and ***standard error*** are represented. For example: "21 **ADR** in 21 **p** ($31\mathbf{ADR_T}$). $\boldsymbol{I} = 0.0639$; $\boldsymbol{E} = 0.0135$" means that: 21 ADR_{In} (**ADR**) were identified in 21 patients(**p**), the number of total ADR ($\mathbf{ADR_T}$, which includes ADR_{In} and ADR_{Ad}) was 31, the calculated cumulative incidence of ADRIn(***I***) was 0.0639, and its standard error (***E***) was 0.0135. Note: when the number of patients is *italic underlined*, it means that we had to assume number of ADR was equal to number of patients that suffered an ADR, because number of patients with ADR_{In} was not supplied (just number of ADR_{In} was reported).

[e]**Remarks**: some authors' remarks for each study are presented. "Modified data" refers to studies in which we did not use raw data in order to correct inconsistencies or to exclude ADR_{Ad}.

Risk of bias assessment

We also performed two pilot studies using a standardized form to evaluate the methodological quality of included studies. We did not use scales (discouraged by the Cochrane approach[26]) but criteria from Cochrane, STROBE,[32] QUOROM,[33] and PRISMA[27] adapted to the scope of ADRs frequency evaluation, which included: complete description of study design, verification if all parts of study were prospective, number of hospitals in which study occurred, adequate selection criteria, definition of ADR, rationale for study size, causality assessment of ADR, avoidability assessment of ADR, description of all statistical methods, characterization of study participants and of number of participants at each stage, description of methods to prevent information and selection bias, intensive monitoring, description of methods to avoid other bias, presentation of complete summary measures. The two reviewers independently assessed study quality and risk of bias; disagreements were solved by consensus.

Studies were divided in low risk of bias (five or less parameters with medium, unclear, or high risk of bias), medium risk (six to nine) and high risk (ten or more parameters evaluated as medium, unclear, or high risk of bias).

Quantitative analysis

Statistical analyses were done with the Chi-square test for categorical variables, Student's t-test for normally distributed continuous variables, and Mann–Whitney or Kruskal–Wallis when dealing with variables without normal distribution, using SPSS v17. Excel was used for incidence and standard error calculations. Quality evaluation graphs, heterogeneity analysis, subgroup analysis, and random effects meta-analysis were performed using Review Manager - version 5.0. The *a priori* level of significance for all hypothesis tests was $p < 0.05$.

Subgroup analyses

High heterogeneity was expected according to previous studies. Our purpose was to identify heterogeneity sources, therefore, several subgroup analyses were planned:

- Study location - subgroups based on continent or country
- Methodology for ADR detection
  1. *Intensive monitoring*
  2. *Prospective monitoring*
  3. *Chart review*

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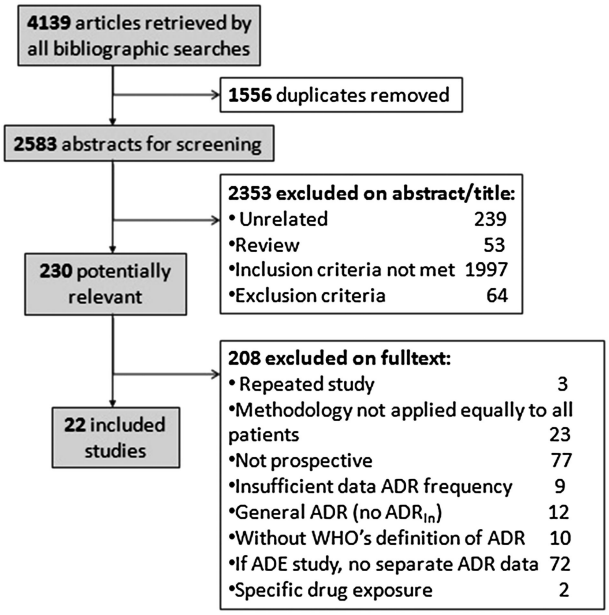

Figure 1. Flowchart of search strategy

4. *Computerized monitoring* that generated ADR alerts (included only if alerts were validated by team and if other methodology was also applied to all patients, such as chart review or prospective or intensive monitoring)
5. *Database monitoring* (included only if other concurrent methodology applied to all patients)
6. Spontaneous or solicited *reporting* (included only if other methodology was concurrently used in all patients)
7. *If several methodologies were concurrently applied in a study, we planned to compare them (only if the population was strictly the same).*

- Ward type - internal medicine, general surgery, intensive care unit, pediatric, geriatric, obstetric, or other as reported by authors. We registered if the study was performed on several wards without specifying number of patients for each, and also if ward was not reported.
- Hospital type - teaching/university versus non teaching hospital - as reported by authors (if conflicting or unreported, we searched the internet).

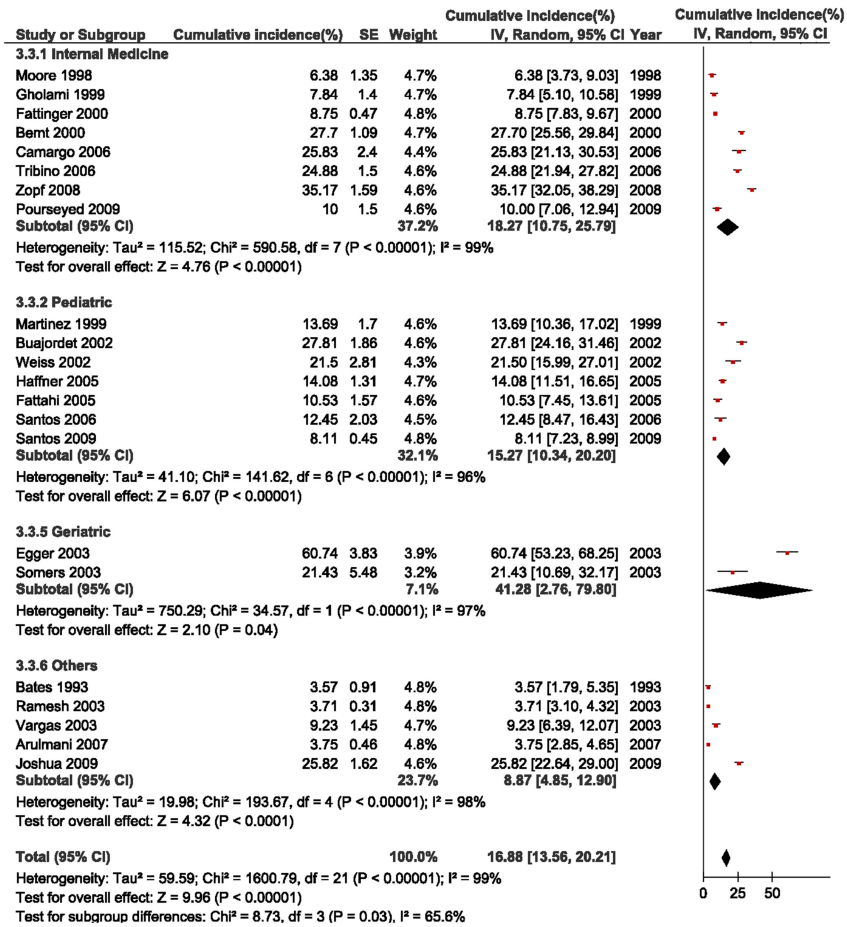

Figure 2. Subgroup analysis based on wards

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- Risk of bias
- Adult Vs pediatric (<18 years) versus geriatric (>64years) population.
- ADR definition - WHO's strict definition[23] versus Karch and Lasagna's[24] or WHO's definition with slight imprecisions in application
- Study duration (short follow-up studies <3 months; medium: 4–11 months; long ≥ 12months)

RESULTS

Literature search and selection process

Pubmed search yielded 1124 results; EMBASE yielded 653 results; CINAHL 173; Cochrane 7; ISI Conference Proceedings 95; ISI Web of Knowledge 573; International Pharmaceutical Abstracts 887; Google Scholar 60; Scirus 61; NHS economic evaluations database 14; others yielded 492. From these 4139 studies (corresponding to 2853 distinct studies), 230 were selected to obtain full text and then 22 studies were included[34–55] (Figure 1). A list of exclusions can be obtained from the corresponding author. During the first phase, Kappa agreement for study inclusion was 0.77; during the full text review, was 0.89 (good agreement).

Characteristics of included studies

Table 1 summarizes the characteristics of included studies; within these, there were 18 818 hospitalized patients exposed to drugs; 2458 of them suffered an ADR while hospitalized; 3553 ADR_{In} were identified.

ADR incidence

The pooled ADR cumulative incidence estimated in the meta-analysis was 16.88 (CI95% of 13.56,20.12); however, there was heterogeneity: $I^2 = 99\%$.

Studies with the *highest* incidence estimates were:

- Egger[42]: 60.74% (CI95%: 53.23,68.25). A study from Germany that performed prospective monitoring of all patients admitted to a geriatric ward to compare the ADR rate predicted by a computerized pharmaceutical database to that determined by direct observation.
- Zopf[52]: with 35.17% (CI95%: 32.05,38.29). A Germany cohort of all patients admitted to two medical wards in two university hospitals, with intensive monitoring (daily, by a trained team of three physicians, one pharmacologist, and two pharmacists) to characterize risk factors associated with ADRs after admission.

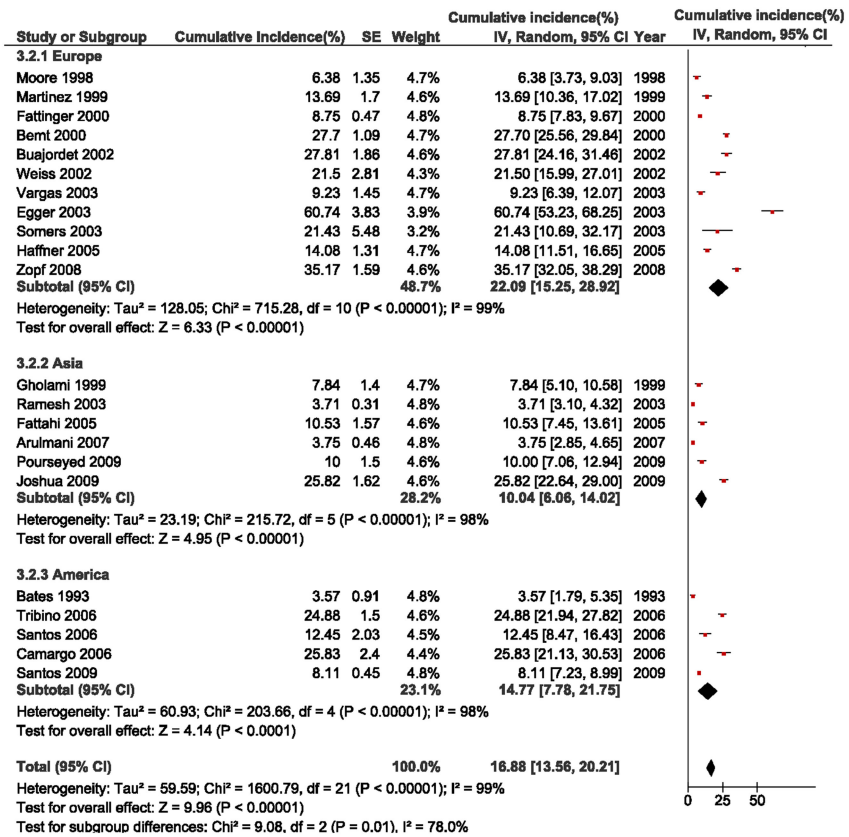

Figure 3. Subgroup analysis based on study location

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Studies with the *lowest* incidences were:

- Bates[34]: 3.57% (CI95%: 1.79,5.35). An American prospective cohort in seven wards of a tertiary hospital, with daily chart review by a nurse and solicited reporting, to evaluate incidence and preventability of ADEs.
- Ramesh[43]: 3.71%(CI95%:3.10,4.32). An Indian study in which spontaneous, solicited notification, and chart review were performed in all hospitalized patients. Intensive monitoring was performed only in patients suspects of having an ADR.
- Arulmani[51]: 3.75% (CI95%: 2.85,4.65). An Indian prospective cohort study of patients admitted to three wards, using solicited reporting and prospective monitoring to ascertain ADR frequency, severity, and cost.

Subgroup analysis

The most relevant heterogeneity moderators were 1st: risk of bias, 2nd: population, 3rd: ward, 4st: method.

Ward (Figure 2): there was significant heterogeneity in every ward ($I^2 \geq 96\%$), and statistically significant difference between wards ($p = 0.03$).

Study location (Figure 3): there was also heterogeneity ($I^2 \geq 98\%$) and statistically significant difference between continents ($p = 0.01$).

Risk of bias (Figure 4): Moderate and high risk of bias studies presented high heterogeneity ($I^2 = 99\%$), that did not disappear after we adjusted for population age (pediatric versus adult). Low risk of bias studies presented low heterogeneity ($I^2 = 54\%$) that disappeared when we adjusted for population type ($I^2 = 0\%$ either in adult or in pediatric group).

Method for ADR identification (Figure 5):Many studies had more than one methodologies but none applied exactly to the same population; therefore, none was truly comparable; in that case, we attributed to that study the subgroup of the methodology that was more comprehensive. All subgroups presented heterogeneity, slightly smaller in intensive monitoring ($I^2 = 98\%$), non statistically significant ($p = 0.90$).

Other subgroup analyses performed (in supplemental material) revealed also heterogeneity: hospital type

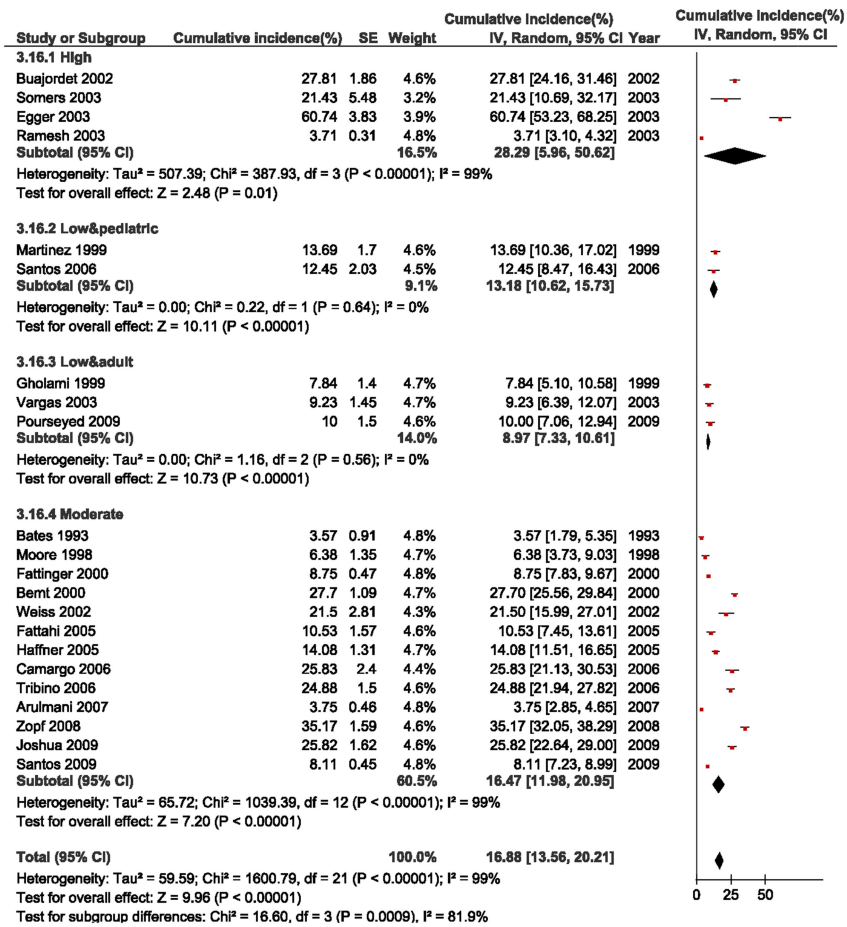

Figure 4. Subgroup analysis of risk of bias adjusted for population age

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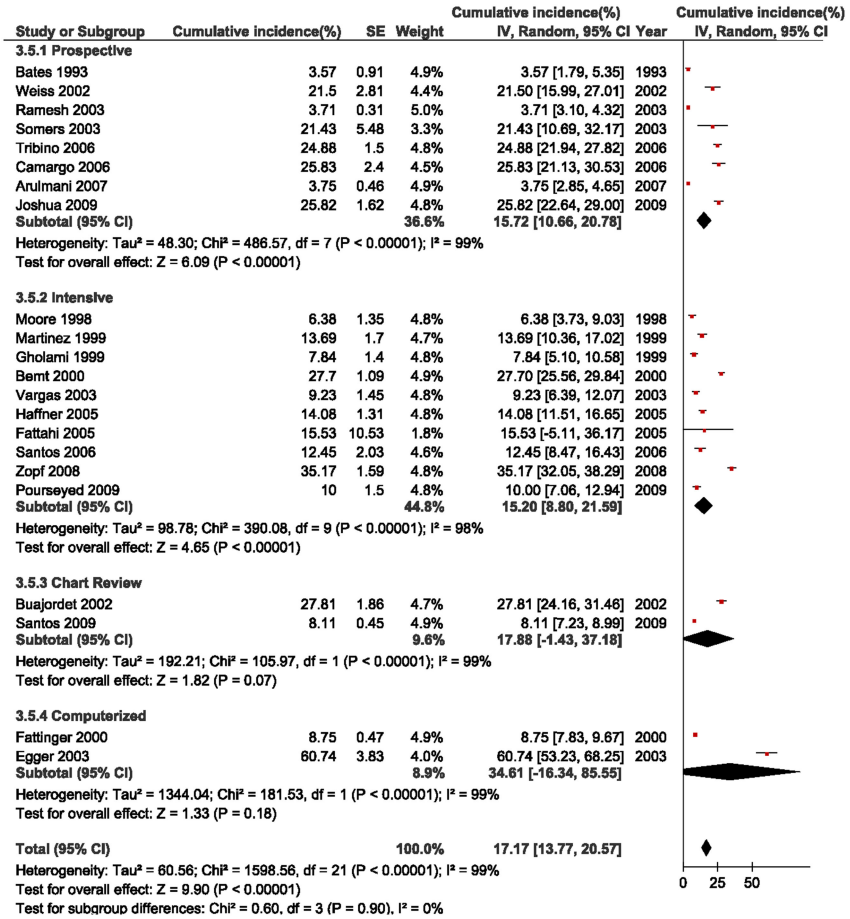

Figure 5. Subgroup analysis of methodology for ADR identification

($I^2 = 99\%$ in teaching and non teaching hospitals, no difference between subgroups $p = 0.41$), population (adult $I^2 = 99\%$, pediatric $I^2 = 96\%$ and two geriatric studies that presented $I^2 = 97\%$, $p = 0.42$), study duration (small studies $I^2 = 100\%$, medium $I^2 = 99\%$, long $I^2 = 97\%$, $p = 0.19$), strict definition of ADR ($I^2 = 99\%$ for all subgroups, $p = 0.76$). We also performed a *post-hoc* subgroup analysis according to team member responsible for ADR detection during the study; all had heterogeneity: physician $I^2 = 88\%$, pharmacist $I^2 = 99\%$, and multidisciplinary team $I^2 = 98\%$, $p < 0.00001$.

We plotted ADR incidence against study size[56]: smaller studies tended to identify higher incidences. Our funnel plot was not completely symmetric (probably because although we emailed authors asking for unpublished data, none was supplied).

Risk of bias assessment

In Figure 6, we present the summary of our quality evaluation of included studies, according to each parameter assessed - risk of bias graph. All studies had low risk of bias in the description of study design, while only one study calculated the intended study sample size. Most studies reported strategies to prevent selection bias (like strict intensive or prospective monitoring, applied to all patients and not just to ADR suspects), but the majority did not report strategies to prevent information bias.

Table 2 shows the performance of each study in each quality criteria. Few studies had low risk of bias,[36,37,45,49,54] and several had moderate risk.[34,35,38,39,41,46–48,50–53,55]

DISCUSSION

What this study adds

This systematic review provides an up-to-date, comprehensive assessment of the literature regarding the frequency of ADRs occurring during hospitalization with quantitative assessment and systematic evaluation of the quality of included studies. It was

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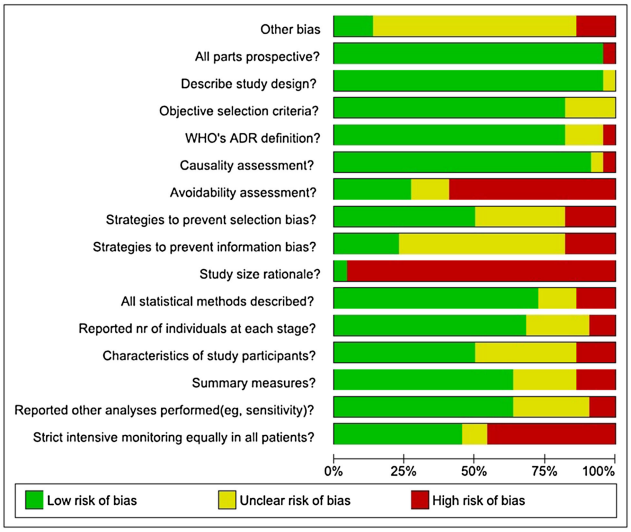

Figure 6. Risk of bias graph

possible to identify multiple heterogeneity moderators, indicating the need to standardize methods and definitions used in ADR studies.

The **objective** of this study was to estimate ADR_{In} frequency and to identify and explore sources of heterogeneity. Because there was significant heterogeneity in almost all analyses, quantitative data must be viewed with caution.

Several **sources of heterogeneity** were identified; however, adjusting for them surprisingly did not change significantly the results except for ***risk of bias and population***: low risk of bias studies presented with $I^2 = 0\%$ either for pediatric or adult population; however, in moderate and high risk of bias studies, there was heterogeneity even after adjusting for age ($I^2 \geq 97\%$). This reveals the absolute importance of creating specific quality criteria for studies about ADRs, as well as following guidelines and definitions of ADRs, and standardizing methodologies for ADR

Table 2. **Risk of bias assessment**. We report risk of bias assessment criteria and results for all included studies

Study (author, year)	*Multicenter?*	*All parts prospective?*	*Describe study design**	*Objective and adequate selection criteria**	*Diagnostic criteria/ definition of ADR*	*Causality assessment*	*Avoidability assessment*	*Methods to avoid selection bias **
1993 Bates	N	Y	Y	Y	Y (WHO)	Y (Naran-jo)	Y ("4 point scale")	U
1998 Moore	N	Y	Y	U	U (just serious ADRs)	y	U	N
1999 Gholami	N	Y	Y	Y	Y (WHO)	Y (Naran-jo)	Y (Schumok)	Y
1999 Martínez-Mir	N	Y	Y	Y	Y (WHO)	Y(Spanish Drug)	N	Y
2000 Bemt	Y	Y	Y	Y	Y (WHO definition)	U	N	Y
2000 Fattinger	Y	Y	Y	U	U (just included "clinically relevant")	Y (Naranjo)	U	N
2002 Buajordet	N	Y	Y	Y	Y	N	N	U
2002 Weiss	N	Y	Y	Y	Y (WHO)	Y (Naranjo modified)	Y	Y
2003 Egger	N	Y	Y	Y	Y (WHO)	Y (Schumok)	Y(Naranjo)	U
2003 Ramesh	N	U	Y	Y	Y (WHO)	Y (WHO)	N	N
2003 Somers	N	Y	Y	Y	Y	Y(WHO)	U	N
2003 Vargas	N	Y	Y	Y	U(Karch and Lasagna)	Y (WHO)	Y	Y
2005 Fattahi	N	Y	Y	Y	Y (WHO)	Y (WHO)	N	Y
2005 Haffner	N	Y	Y	Y	Y (WHO)	Y (WHO)	N	U
2006 Camargo	N	Y	Y	U	Y (WHO)	Y(Naranjo)	N	Y
2006 Santos	N	Y	Y	Y	Y (WHO)	Y (WHO)	N	Y
2006 Tribiño	N	Y	Y	Y	Y (WHO)	Y (Naranjo)	N	U
2007 Arulmani	N	Y	Y	Y	Y WHO)	Y (Naranjo)	N	Y
2008 Zopf	Y	Y	Y	U	U (WHO, imprecisions)	Y (Naranjo)	U	Y
2009 Joshua	N	Y	Y	Y	Y(WHO)	Y(WHO)	N	U
2009 Pourseyed	N	Y	Y	Y	Y (WHO)	Y (WHO)	Y (Schumok)	Y
2009 Santos	N	Y	Y	Y	Y (WHO)	Y (Naranjo)	N	N

Abbreviations and symbols used: *: Adapted from STROBE criteria, **N**: no, **Y**: yes, **U**: unclear, **WHO**: definition of WHO used for ADR

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detection. The biggest ***heterogeneity moderator*** was risk of bias, followed by population, ward, and method for ADR identification.

We included surprisingly few studies from the US,[34] which is related to our strict inclusion criteria. Many US studies used computerized methods of ADR identification for patient screening but followed just ADR suspects, not *all* hospitalized patients, therefore not assessing equally in all patients the existence of ADRs. On the one hand, it is clear that the present and future of pharmacovigilance involves computer systems; on the other hand, we wanted to include only computerized studies that used a concurrent systematic validation by evaluating *all* patients (either with chart review or prospective or intensive monitoring), to obtain a more valid estimate of ADR incidence. Since many American hospitals use electronic health records, computerized approach could replace manual chart review; however, all of the chart review included studies perform concurrently patient examination and ward visit of all patients, which is still lacking in computerized approaches for us to consider computerized approach enough *per se* as an inclusion criteria in this review in particular.

Asian studies showed a tendency to have smaller incidences of ADRs (10.04[6.06,14.02]) (Figure 3), and Europe higher (22.09[15.25–28.92]), with statistically significant differences between all continents; however, since there was heterogeneity in all, we do not know it this tendency is real.

The studies that most contributed to heterogeneity were, on one hand, studies with the **highest incidences**: Egger[42] ($I = 60.74\%$) and Zopf[52] ($I = 35.17\%$). In our sensitivity analysis, Zopf added most heterogeneity (smaller standard error). Zopf may have overestimated ADR incidence because: they included 26 intoxications diagnosis (excluded in our analysis), there were some conflicting numbers (for example, on page 792: "907

*Methods to avoid information bias**	*Rationale for study size**	*Describe all statistical methods**	*Report nr of individuals at each stage**	*Characterize study participants**	*Complete summary measures**	*Report other analyses performed**	*Intensive monitoring (see text)?*	*Methods to avoid other bias?*
Y	N	Y	Y	U	U	Y	U (nurse)	U
N	N	Y	Y	Y	Y	Y	Y	U
Y	N	Y	Y	U	N	U	Y	Y
Y	N	Y	U	Y	Y	Y	Y	U
Y (adjusted Odds Ratio)	N	Y	Y	N	Y	Y	Y (pharmacist)	U
N	N	N	Y	Y	Y	Y	N	N
U	N	N	N	U	Y	U	N (daily chart review)	U
N	N	Y	N	Y	N	N	N	U
U	N	U	Y	U	U	U	N	U
N	N	Y	U	U	U	Y	N	U
U	N	U	Y	Y	U	U	N	U
U	N	Y	Y	Y	Y	Y	Y	U
U	N	Y	U	U	Y	U	Y	U
U	N	Y	Y	Y	Y	Y	Y	U
U	Y	Y	Y	Y	Y	U	N	N
U	N	Y	Y	Y	Y	Y	Y	U
U	N	Y	Y	U	Y	Y	N	U
U	N	N	U	U	N	Y	N	U
U	N	Y	U	N	N	Y	Y	Y
U	N	Y	Y	U	Y	Y	N	U
U	N	Y	Y	Y	Y	Y	Y	Y
N	N	U	Y	Y	Y	N	N	N

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patients were intensively followed [. . .] comprising 480 males and 423 females"[which gives only 903]), and did not clearly exclude ADR_{Ad} (although they refer to "ADRs *following* hospital admissions"). The same happened with Egger, that did not explicitly exclude ADR_{Ad}, but studied "occurrence of ADRs *during* hospitalization"; if ADR_{Ad} were included, this might explain the high incidence reported. Also, Egger studied a geriatric ward, and ADRs tend to occur more frequently in the elderly.

On the other hand, Bates[34] (3.57% [1.79,5.35]), Ramesh[43] (3.71%[3.10,4.32]), and Arulmani[51] (3.75 [2.85,4.65]) had the **lowest** incidences. This was probably due to the method used for ADR identification: Bates used prospective monitoring performed solely by a nurse without latter pharmacist or physician validation; Ramesh did not use intensive monitoring (he used reporting and chart review). Arulmani reports performing intensive monitoring, but does not specify daily patient evaluation ("patient exam and interview when necessary"), and there are some doubts if they have performed the same follow-up to all patients.

Several of the included studies used **different methodologies**, but only four used different ***concurrent*** methodologies for ADR identification[39,42,44,47] (there are also several reported in the literature, but they were excluded because nor validation of ADR nor intensive monitoring of all patients were applied); unfortunately, we could not compare methodologies' performances without biasing because of insufficient data or because the population was not exactly the same for both methods.

Several studies claimed to have performed intensive monitoring but used extremely different methodologies; consequently, we recommend **strict criteria for intensive monitoring**, such as:

- Monitoring performed by team members specialized or experienced in ADRs
- With *daily* patient interview (and if necessary patient examination) from admission until discharge
- With *daily* chart review
- With at least weekly medical team interview (including doctor, nurse, and pharmacist; clinical rounds are useful)
- With strict application of WHO's definition of ADR
- With causality assessment (from WHO or Naranjo) verified prior to discharge
- With similar follow-up for patients with and without ADR suspicion

The **strengths** of this systematic review are: *first*, a complete and systematic literature search; *second*, a choice of studies within rigid and objective selection criteria for a good level of evidence; *third*, planning several subgroup analysis to identify heterogeneity factors; *fourth*, objective quality evaluation of included studies.

The **limitations** of this study include possible publication bias because few unpublished studies were found (none through email response of experts and some through bibliographic search) and the funnel plot was not completely symmetrical.

The biggest limitation of this study is its heterogeneity and the inability to surpass it and to estimate the real ADR incidence. This heterogeneity is also present in the other systematic reviews of ADRs, since Lazarou's[3](the reason for criticism[4]) to more recent studies, either about ADRs associated with hospital admissions[5–7] or ADRs during hospitalization.

There are many studies about ADRs but almost all add heterogeneity; therefore, attention must be directed to several methodological aspects of ADRs studies. The frequency, relevance, and impact of ADR_{In} clearly indicate the need for further studies of this nature in the future. Improvement of methodological study quality (through minimization of risk of bias during the planning phase of each ADR study), standardization of methodologies (namely, a standardization of intensive monitoring with strict criteria), a clear definition of ADR (WHO), causality(Naranjo), and preventability assessments are **suggestions for studies in the future**.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

KEY POINTS

- Hospital adverse drug reactions(ADRs) are frequent, important, expensive, and can be fatal.
- Meta-analysis of available studies indicates that ADRs may occur in 16.88% (CI95%: 13.56-20.21) of patients during hospitalization (however, this estimate has to be evaluated with caution because there is high heterogeneity among studies).
- The most significant moderators of heterogeneity were the study methodological quality (risk of bias), population, ward studied, and method used for ADR identification.
- Few studies regarding frequency of ADRs in hospitalized patients have low risk of bias, thus improvement of study quality is highly recommended.

DOI: 10.1002/pds

ACKNOWLEDGEMENT

The authors would like to thank MSD for obtaining the fulltext of 14 articles.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article:

Table supplemental. Reasons for exclusion

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DOI: 10.1002/pds

APPENDIX 2

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2013; **22**: 98–102
Published online 1 October 2012 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3348

BRIEF REPORT

Methodologies for the detection of adverse drug reactions: comparison of hospital databases, chart review and spontaneous reporting

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ABSTRACT

Purpose To evaluate a methodology for adverse drug reactions (ADRs) detection through hospital databases.
Methods A retrospective analysis was conducted to identify ADRs using diagnostic codes from databases, later validated by chart review. An independent chart review was performed for comparison, as well as assessment of spontaneous reports.
Results 325 ADRs were identified (prevalence of 2.41%, positive predictive value of 87.6%). Independent chart review identified 9% of ADRs at a cost of 35 person-hours (versus two person-hours in databases). There were seven spontaneous reports of ADRs.
Conclusions Although not frequently used, the detection of ADRs through databases is a relatively less expensive, fast and effective methodology that can improve current pharmacovigilance systems. Copyright © 2012 John Wiley & Sons, Ltd.

KEY WORDS—adverse drug reactions; hospital; prevalence; databases; pharmacovigilance; pharmacoepidemiology

Received 3 May 2012; Revised 17 August 2012; Accepted 23 August 2012

INTRODUCTION

Adverse drug reactions (ADRs) represent an important burden in Health Care[1]: they are between the fourth and the sixth leading causes of death in the US[2] and lead to US$1.56 to US$4 billion in direct hospital costs per year in the US. [3]

The **methodology** of ADR detection and monitoring varies widely, and in the last decades, several approaches to pharmacovigilance have been developed[1]:

1. Spontaneous reporting of a potential ADR by a health team member is the main method used in Europe, but underreporting[4] is a problem. The World Health Organization (WHO) Programme for International Drug Monitoring relies on spontaneous reports from more than 100 countries including Portugal and builds a global database to identify possible relationships between the use of a drug and adverse effects and ADRs.
2. Intensive monitoring is the *gold standard*, in which an expert team prospectively examines hospitalized patients and applies criteria to identify and classify ADRs; however, it is extremely resource and time consuming for routine use. [5]
3. Chart review (prospective or retrospective) is reasonable but also resource and time consuming. [6]
4. Computerized systems generate ADR signals in several groups of patients, later validated by an expert team. [7] This is an interesting method, but attention is needed to build rules and algorithms with high specificity, otherwise it may also be resource consuming. Other problems of this methodology are the dependency of structured data and the difficulty with using data from narrative notes.
5. Administrative databases are not widely used, but they may have some advantages. [8]

In many European countries including Portugal, spontaneous reporting is the only continuously applied pharmacovigilance method due to its low cost. Prospective monitoring is also frequently performed in several countries in Europe. In the United States, computerized methods and the search through large insurance databases are widely used.

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In our hospital (Hospital University Centre of Coimbra, General Hospital - HUCC-HG), there are no specific methodologies currently applied for ADR detection. There is currently no specific formation for physicians, pharmacists or nurses to develop prospective or intensive monitoring for ADR detection and characterization on a regular basis. Also, considering the Portuguese economic crisis, it is not possible at the moment for this hospital to invest in building a computerized system for ADR detection or even for adjusting the existing computerized systems to prospectively detect ADRs in hospitalized patients.

The limitations of spontaneous reporting, the high cost of intensive monitoring, the economic impossibility to build a computerized system in our hospital and the fact that in Portugal and many other countries there are no real data about ADRs that occur during hospitalization (ADR_{In}) were the motivations of this project.

Our **purpose** was to develop and validate a methodology of ADR detection through diagnostic codes of administrative databases, allowing us to identify and characterize ADRs. We also intended to evaluate this methodology, comparing it with chart review and with spontaneous reporting.

METHODS

Study design

A retrospective study was performed for ADR detection using International Classification of Diseases 9th Revision, Clinical Modification (ICD-9-CM) diagnostic codes of an administrative database, with all hospitalizations in 2008 from HUCC, Portugal. This Hospital Centre is composed of eight hospitals in Coimbra (three psychiatric hospitals, two maternities, one pediatric hospital, one university hospital and one general hospital). The study was performed in the General Hospital of HUCC -HUCC-HG, a tertiary hospital in Coimbra, with 341 beds and a mean number of 12 500 hospitalized patients per year. This study was performed according to HUCC's Ethics Committee.

Development of a methodology

We intended to develop a methodology that allowed us to, through HUCC-HG's database: identify and characterize ADRs (namely prevalence, clinical manifestations associated, drugs more frequently involved and risk factors), select the codes within the database with higher predictive positive value (PPV) and validate them by chart review. We also aimed to compare our database methodology with spontaneous reporting and with chart review. We did so in order to build a complementary methodology that could help the Portuguese pharmacovigilance system without increased costs.

Database and coding information

The clinical information in our database used coding based on ICD-9-CM. **Codes searched** included not only ***E codes*** (from E930 to E949.9, codes designed to mark ADRs, already excluding wrong doses, errors and intoxications) but also ***diagnostic codes***, such as "*733.09 - Drug-induced osteoporosis*" (as reported in the literature[6,8–10] or others considered useful). We also tested every diagnosis with the expressions: "Due to drugs", "drug-related", "*medicamentosa*" and "iatrogenic".

For validation, we selected the ***E codes*** and the 40 ***diagnostic codes*** that allowed us to identify more cases of ADR suspects which *added* information relatively to E codes, more specifically, that identified more cases of ADR suspects and did not have an E code (this is the result of bad coding, since ICD-9-CM instructs to use an E code with every diagnosis signaling an ADR; we wanted to detect it to increase ADR detection and improve coding).

Methodology validation

A chart review was performed to **validate ADR signals** by an experienced team member (AM), using several strict criteria (among other data to be filled in a previously built and tested formulary):

- WHO's definition of ADR: "any noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy". [11] Adverse drug events, which include ADRs and errors, were not the purpose of our study; an adverse drug event is: "an injury related to the use of a drug, although the causality of this relationship may not be proven".[12]
- WHO's causality assessment of ADR[11]
- Schumok's preventability assessment[13]
- Hartwig's severity assessment[14]
- Rawlin's type A and B classification of each ADR[15]

Each query was evaluated independently to calculate its PPV. Afterwards, we intended to select a few queries with the highest PPV, to build a methodology with a good global performance and easily applied in other databases, other hospitals and other years.

Comparison with other pharmacovigilance methods

We compared database performance with *spontaneous reporting* and *chart review* (for that, a randomized

DOI: 10.1002/pds

group of 100 patients from the same period and hospital was selected for independent chart review).

The number of person-hours spent during the application of each methodology was assessed.

Statistical analysis

We previously calculated sample size to independent chart review (95 patients necessary) using an online calculator. [16] Statistical analyses were done with the Chi-square test for categorical variables, Student's *t*-test for normally distributed continuous variables and Mann–Whitney or Kruskal–Wallis for variables without normal distribution, using SPSS v20. The *a priori* level of significance was $p < 0.05$.

RESULTS

During the year 2008, there were 13 471 hospitalizations in HUCC-HG (10 600 patients were admitted more than once during that year). Mean participant age was 64 years (sd = 19.45). Forty five percent were female.

E codes generated 283 signals in the **database**, corresponding to 270 ADRs (in 270 patients) after validation (PPV = 95%). 114 additional diagnostic codes were tested in the database, from which the best 40 codes generated 10 752 ADR signals (data in supplementary Table 1). For those 40 codes, 371 random ADR signals were validated through chart review, allowing the detection of 114 true ADRs with a general PPV of 32.0% (supplementary Table 2).

For a simpler methodology with higher PPV global value, we selected the six queries with the best PPV, from which we obtained 371 signals that corresponded to 325 true ADRs (global PPV of 87.6%, prevalence of ADRs of 2.41%). After validation, this method required only two person-hours to identify and register ADRs. In Table 1, the database methodology is described.

Patients with true ADRs were older and had greater length of stay than patients without ADRs ($p < 0.0001$

Table 1. ADR identification through a simple methodology of six selected codes in administrative databases

Frequency of ADRs	**Number of signals**	**Positive predictive value**
1) E codes (E930-E949)	284	95%
2) Diagnostic codes (in database records without E code, i.e. without ADR diagnosis)	**Number of signals without concomitant E code**	**Positive predictive value**
Other disorders of pancreatic internal secretion (including hipoglicemia)	6	83%
Drug-induced neutropenia or unspecified	32	60%
Hepatitis, unspecified	46	60%
Other anaphylactic shock incl. drugs	2	100%
Shock due to anesthesia	1	100%
Full algorithm (1 + 2)	***371 signals***	***87.6%***

Table 2. Comparison of methodologies: administrative database versus chart review. Abbreviations: nr = number, sd = standard deviation

Methodology	Database	Chart review
ADR prevalence (nr of ADRs / nr patients with drugs)	2.41% (320/13 471)	9% (9/100)
% ADR during hospitalization (versus present on admission)	45.82%	77.78%
Mean person-hours required	2	35
Mean age (sd)	64 years (sd: 19.45)	60 years (sd: 20.23)
% female	45.48 %	42%
Most frequent drug groups involved	1. 5.9% Insulins and antidiabetic agents 2. 2.7% Antineoplastic and chemotherapy 3. 2.7% Anticoagulants	1. 33.3% NSAIDs 2. 22.2% Diuretics 3. 11.1% each: antibiotic, anticoagulant, chemotherapy, not specified
Most frequent manifestations associated with ADRs	1. 2.70% Acute renal failure 2. 2.70% Hypoglycemia 3. 2.43% Hepatitis	All with 11.1%: •Hypokalemia •Disrhythmias •Edema •Medulary aplasia •Acute renal failure •Gastrointestinal haemorrhages •Altered INR •Rash •Bronchoespasm

DOI: 10.1002/pds

and $p = 0.027$, respectively). There was no statistically significant difference in gender. No other risk factors for ADRs were identified.

During the year of 2008, there were seven ADRs detected through **spontaneous reporting** that were generated from HUCC-HG (prevalence of ADR of 0.0005%).

Independent chart review identified nine ADRs (seven during hospital stay and two present on admission): prevalence of 9%. Only two ADRs had an E code. Both methodologies are compared in Table 2.

According to OMS's causality assessment[11], three ADRs were classified as certain, three probable and one unlikely. Four ADRs were preventable. [13] Three ADRs were severe[14], one was moderate and four were mild. Eight ADRs were type A and one was type B (according to Rawlins and Thomson classification of ADRs[15], type A are Augmented, predictable and dose-related adverse reactions, while type B are Bizarre, rare and unpredictable ADRs).

DISCUSSION

What this study adds

This work allowed us to build a methodology of ADR detection that is simple, cheap and effective, through the use of coding information available in administrative databases. We identified 325 ADRs of 13 471 inpatients stays (prevalence of 2.41%).

The **strengths** of this work are: *First*, we performed a complete test of 114 diagnostic codes' performance as well as E codes. S*econd*, there was validation of ADR code signals (through chart review of more than 350 signals), to assess PPV of each code. *Third*, unlike previous literature, we identified the queries that *added* information to E codes (not queries that would generate repeated information to E codes), to decrease validation resources and to complement E codes. *Fourth*, our database method required reduced resources (two person-hours) in ADR detection, in comparison with chart review (35 person-hours). *Fifth*, there was an enhanced ability to detect ADRs, with a detection rate 46 times higher than the most widely used method in pharmacovigilance: spontaneous reporting (325 versus seven ADRs).

The **limitations** of this study may include: probably incomplete and wrong information in some cases in databases (which might occur in every large database), "*coding creep*" (this is a possible bias of all billing databases, in which more expensive codes are preferred and registered to increase the case-mix, diagnosis-related group and consequently to increase reimbursement of that hospital[17]) and the fact that we did not validate all of the initial 10 752 ADR signals. Validating all signals would be ideal but too resource consuming; therefore, this two-phase approach (of first selecting the best codes, then validating them) was a practical approach that can be used in other hospitals. The fact that this is a one hospital centred study might also be a limitation. We chose the codes that best describe this hospital's reality, but other hospitals and countries, where coding systems have either changed to ICD-10 or may still employ ICD-9 but with different coding considerations or payment structures, might represent other realities. Therefore, other hospitals and countries might allow the selection of different codes. Indeed, it may be very interesting to retest all codes in other hospitals, populations, years and countries, to understand, on the one hand, which are the most universal codes, and on the other hand, which occur more in one country, or in one hospital type, or in a particular population. Consequently, **suggestions for studies in the future** include not only further validation of this methodology in other hospitals, years and countries, but also a nation-wide study for detection of ADRs using databases.

We believe that the smaller prevalence of ADRs identified by the database methodology compared to independent chart review (2.41% versus 9%) is not a limitation, considering the small resources utilized (two person-hours versus 35 person-hours) and the high PPV obtained (87.6%). On the one hand, chart review, prospective and intensive monitoring have good detection rates but are too resource consuming for continuous application; on the other hand, spontaneous reports grossly underestimate ADRs. Therefore, we validated a database methodology that "lies is the middle": it is resource sparing enough for continuous application, with a detection rate much higher than spontaneous reporting and with a good PPV. In addition, in our work, we noticed that chart review and database seemed to detect different types of ADRs and with different drugs, complementing each other. Other studies that compared different methodologies for ADR and ADE detection also reported that each methodology tends to detect different ADRs, concluding that multiple methods for ADR detection should be used complementarily for patient safety enhancement. [18,19]

In conclusion, the use of national or administrative databases to identify ADRs is not a widely validated approach, but it may have advantages, such as:

1. Information already available about inpatient stays, with different useful clinical and demographic data, available in almost every hospital and in most countries.

DOI: 10.1002/pds

2. Nearly no cost added. This factor is increasingly important in an era of economic crisis.
3. Few human resources necessary to validate ADRs.
4. The possibility of a national perspective.
5. Coding information including not only E codes (specifically referring to ADRs: E930-E949.9) but also diagnostic codes (that can improve ADR detection and further coding).

Therefore, we believe that this methodology should be embraced as an effective methodology of pharmacovigilance. The identification of ADRs through databases can complement other established pharmacovigilance methodologies and increase our knowledge about ADRs, leading to their detection and ultimately prevention.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

KEY POINTS

- There are several methods for detection of adverse drug reactions (ADRs). Among them, spontaneous reporting is the most widely used, but insufficient.
- We validated a methodology of ADR detection through hospital databases, in a retrospective study, using clinical information and ICD-9-CM to build search queries that included and complemented E codes. We compared this methodology with independent chart review and spontaneous reporting.
- Using the above mentioned methodology, during 2008, in a university hospital, we identified 325 ADRs from 13 471 hospitalized patients (prevalence of 2.41%, positive predictive value of 87.6%), with low resources needed (two person-hours in all patients). Independent chart review identified a prevalence of ADRs of 9% in that period, but needed 35 person-hours per 100 patients. There were seven ADRs identified by spontaneous reporting in 2008 in that hospital (prevalence of 0.05%).

ACKNOWLEDGEMENTS

The authors would like to thank the support given by the research project HR-QoD - Quality of data (outliers, inconsistencies and errors) in hospital inpatient databases: methods and implications for data modeling, cleansing and analysis (project PTDC/SAU-ESA/75660/2006).

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article.

Supplementary Table 1. In this table, we report all tested codes in our database

Supplementary Table 2. Validation of the selected codes and respective results

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APPENDIX 3

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2013
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3468

BRIEF REPORT

Detection of adverse drug reactions using hospital databases—a nationwide study in Portugal

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ABSTRACT

Purpose This study aimed to detect and characterize adverse drug reactions (ADRs) that occurred during hospitalization (ADR_{In}) and ADRs associated with admission (ADR_{Ad}) in Portugal from 2000 to 2009. We also intended to compare the results of this methodology with spontaneous reporting.

Methods We conducted a nationwide study using a hospital administrative database that included all acute care public hospitalizations in Portugal, from 2000 to 2009. We used International Classification of Diseases—9thRevision—Clinical Modification coding data for the detection of ADRs. Codes searched included "E" codes (E930 to E949.9, codes that exclude poisonings and errors) and five groups of diagnoses codes associated with high prevalence of ADR as found in a previous study: hypoglycemia, drug-induced neutropenia, hepatitis unspecified, anaphylactic shock due to drugs, and shock due to anesthesia.

Results From 9 271 122 hospitalizations within that period, 116 720 ADRs were detected through the database methodology, representing 1.26% from all hospitalizations. Of the ADRs, 97.3% occurred during hospitalization (ADR_{In}), whereas 2.7% were associated with admission. Age, female sex, and comorbidities such as pneumonia, heart failure, diabetes, and malignancies were associated with ADRs (all with differences statistically significant). There were 13 562 spontaneous reports from 2000 to 2009.

Conclusions Several methods have been used for the detection of ADRs, but they are difficult to apply at a national level. Spontaneous reporting is widely used but grossly underestimates the frequency of ADRs. The database methodology can be very useful to estimate ADRs frequency and to perform a simple characterization of ADRs nationwide.

KEY WORDS—adverse drug reactions; prevalence; databases; pharmacovigilance; hospital administrative databases; pharmacoepidemiology

Received 25 August 2012; Revised 25 April 2013; Accepted 6 May 2013

INTRODUCTION

Adverse drug reactions (ADRs) are a major health care and patient safety problem, being responsible for significant morbidity, mortality, and costs in health care systems.[1–3] It is estimated that they occur in a mean of 16.88% of patients during hospitalization (95%CI: 13.56–20.21)[4] and that they are associated with an overall median of 5.3% of hospital admissions (interquartile range 2.7–9.0%).[5] The cost of drug-related problems, which include ADRs, may be higher than the total cost of cardiovascular or diabetes care.[6] Therefore, the identification and prevention of ADRs is increasingly important.

Pharmacovigilance is the science and activities related to the detection, assessment, understanding, and prevention of all ADRs and of any other drug-related problem.[7] Several methods can contribute to pharmacovigilance, from spontaneous reporting to intensive monitoring, but all have methodological issues:

Spontaneous reporting (reports of a health care member whenever there is a suspicion of an ADR) is a cheap method, good at the identification of new ADRs, and is the basis of the International Monitoring Program.[7] The limitations of spontaneous reporting include underreporting,[8] heterogeneous report quality,[9] and risk of bias.[10]

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The utilization of *administrative databases* and hospital episodes statistics has been performed by a few authors to identify ADRs.[11–14] Although not widely used, it may have advantages if developed and validated as a methodology, such as follows: information of several hospitals, years and countries already available, clinical coding data from which signals of ADRs might be extracted, low resources needed, and a detection rate higher than spontaneous reporting.[15]

Computerized methodologies are interesting and have good detection rates,[16] but need to be performed in hospitals where patient data is computerized, which is not possible in many countries. Other difficulty is related to the low specificity of some algorithms, causing an override of alerts and making them less effective and more costly.[17]

Manual chart review for ADR detection consists of retrospectively or prospectively reviewing patient charts to identify ADRs, generally by experts in ADRs.[18,19] However, it is time and personnel costly: some studies estimated a cost of 55 person-hours per week.[19]

Prospective and intensive monitoring[20] refer to studies performed prospectively in hospitalized patients, with patient interview or examination and health team members interview, performed by experts, to detect ADRs before discharge. They usually have the highest detection rate (intensive monitoring is considered the gold standard) but the highest cost,[21] not allowing a nationwide study.

These methods were developed for different purposes and thus not all are eligible for a nationwide measurement of the frequency of a disease as an epidemiological tool. In fact, spontaneous reporting is used frequently to estimate frequency of ADRs, but inappropriately (one would need the number of patients receiving drugs, details of administration, and other data).

Our purpose was to identify and characterize ADRs in a nationwide study, using hospital databases with clinical information. Secondarily, we aimed to assess trends in hospitalization and in the frequency of ADRs throughout the years of 2000 to 2009.

METHODS

Study design

A retrospective study was performed for ADR identification using hospital administrative databases with information from all episodes in acute care public hospitals in Portugal, from 2000 to 2009, obtained from Administração Central do Sistema de Saúde (ACSS), the Ministry of Health's Central Authority for Health Services. This national database is built by ACSS, which aggregates data from each hospital. The hospital database is first built and maintained at each hospital (using a standardized national approach), and then centrally by ACSS.[22] To enable this, every hospital uses the same software to store patient information. Coders input data after reading the discharge note and all clinical data, and then attribute a clinical code according to International Classification of Diseases 9th Revision—Clinical Modification (ICD-9-CM). Unlike other countries, all coders in Portugal are physicians, who perform a standardized national course and examination, to assure repeatability (so that the same information recorded by different coders in different hospitals is coded similarly). There are also auditors (internal within the hospital and external at the national level of the ACSS) that perform routine verification to detect and correct errors and to assure quality; currently, they all use the same program for that purpose, "Auditor". If ACSS has any doubt when aggregating the hospital databases into one national database, they contact each hospital, which will review the processes to standardize the information and clarify that issue.

Therefore, the national database (that we obtained from ACSS) contains information on anonymized patient identification, episode, and process number, and also information on age, sex, admission date, discharge date, ward(s), hospital attended (tertiary, university), district, outcome (death, discharge, transfer), payment data (Diagnosis Related Groups), and ICD-9-CM codes for the following: diagnoses (principal diagnosis and secondary diagnoses up to 19), procedures (up to 20), and external causes (up to 20). Patient population included all patients hospitalized in all acute care public hospitals in Portugal, with discharges between 2000 and 2009 (we excluded outpatient episodes). At the time of execution of this work, hospital administrative data from the second semester of 2009 was not available.

ADR definition and identification

We followed WHO's definition of ADR: "any noxious, unintended, and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy."[21] We were not interested in adverse effects nor medication errors, considering that they are excluded by this definition.

The database of public hospitals in Portugal included information of diagnoses in the form of codes of ICD-9-CM. Codes searched for ADR identification included "E" codes and diagnostic codes. "E" codes belong to a chapter in ICD-9-CM that aims to classify external causes of injury; "E" codes from E930 to E949.9 are already designed to represent ADRs and

DOI: 10.1002/pds

exclude wrong doses, errors, and poisonings. The five diagnostic codes searched in this study were selected after a validation study previously performed.[15]

In that study, "*E*" *codes* and 114 *diagnostic codes* were tested in a hospital database. Those 115 groups of codes included every code in the ICD-9-CM that contained the expressions: "Due to drugs", "drug-related", "*medicamentosa*", "iatrogenic", and "drug-induced"; others considered useful as "bleeding", "diarrhea", "dysrhythmias"; and others reported in the literature.[11–14] A list of all tested codes can be requested from the corresponding author. From those 115 tested codes (which generated thousands of signals), the 40 codes with the highest numbers of signals were selected for chart review (we selected the signals that *added* information to the E codes and were not already detected in the E codes). However, considering that the 40 code groups generated more than 10 000 ADR signals, 10–20 random patient charts for each code were selected (more than 350 patient processes were reviewed) for validation. Chart review was considered the gold standard for the assessment of the positive predictive value for each code. Finally, the six groups of codes with higher PPV (positive predictive value) were selected to build a simple database methodology, with a global PPV value of 87.6%, and included the following:

(1) "E" codes (ICD-9-CM codes of E930 to E949.9; PPV of 95%).
(2) Other disorders of pancreatic internal secretion including hypoglycemia (ICD-9-CM codes: 251.0–2251.9; PPV of 83%).
(3) Drug-induced or unspecified neutropenia (ICD-9-CM codes 288.00, 288.03, 288.09; PPV of 60%)
(4) Hepatitis unspecified (ICD-9-CM 573.3; PPV of 60%).
(5) Other anaphylactic shock including drugs (ICD-9-CM codes 995.0 to 995.3; PPV of 100%).
(6) Shock due to anesthesia (ICD-9-CM code 995.4; PPV of 100%).

In this study, we applied those six previously validated codes for ADR detection as a simple and fast methodology,[15] in a nationwide study using administrative databases, through a simple query to detect ADR episodes. We excluded repeated cases on the basis of episode number, hospital, birthday date, sex, year, ward, and hospitalization date and time.

Our main outcome was ADR detection. Secondary outcomes were the following: ADR related to admission (ADR_{Ad}) versus ADR during hospitalization period (ADR_{In}), age, sex, admission diagnosis, other diagnoses, hospital length of stay, and year (we aimed to assess trends in ADRs from 2000 to 2009).

Spontaneous reporting

The number of spontaneous reporting of ADRs in hospitalized patients from 2000 to 2009 was not available in the database and was obtained from Portuguese National Authority of Medicines and Health Products (INFARMED).

Statistical analysis

Statistical analyses regarding frequency of ADRs were carried out with the Chi-square test for categorical variables (or exact Fisher's test whenever possible), Student's *t*-test for normally distributed continuous variables and Mann–Whitney or Kruskal–Wallis for variables without normal distribution, using SPSS v20 (IBM Corp., Armonk, NY, USA). The *a priori* level of significance was $p < 0.05$. For the identification of a trend throughout the years, we performed a simple linear regression, using the ADR frequency as the dependent variable and the year as the independent variable.

RESULTS

Study population

The baseline characteristics of the study population ($n = 9\,271\,122$) are shown in Table 1, in comparison with the demographic characteristics of the subgroup of patients that suffered an ADR. The mean age of all hospitalized patients was 46 years, and 56% of the patients were female.

From 2000 to 2008, there was a slight increase in the number of hospitalizations in Portugal (in 2009 data refer only to first semester). There were 116 720 ADRs detected from 2000 to 2009, with a mean prevalence of 1.26%. There was an increase trend in the incidence of ADRs, statistically significant ($p < 0.001$) in linear regression analysis; in 2000, there were 8301 signals, whereas in 2008, there were 14 352 signals. Of the ADRs, 2.7% were associated with admissions, and 97.3% occurred during hospitalization.

Each alert of ADR identified through the database is characterized in Table 2.

The number of national spontaneous notifications of ADRs from 2000 to 2009 was 13 562, corresponding to a mean prevalence of 0.1%. In Table 3, we illustrate trends of hospitalization, spontaneous notifications, and ADRs identified in databases throughout time.

Risk factors of ADRs

In comparison with patients that did not suffer from an ADR, patients with ADRs were older ($p < 0.001$, Mann–Whitney test), had higher mean length of stay ($p < 0.001$, Mann–Whitney test), were more frequently

DOI: 10.1002/pds

Table 1. Socio-demographic characteristics of study population compared with subgroup of patients that suffered from ADRs

	General population		Subgroup of ADRs		
Characteristic	Value	% or SD	Value	% or SD	*p*-value
Total number	9 271 122	NA	116 720	NA	NA
Mean age	46	28.04 SD	60	23.4 SD	<0.001
Female sex	5.152.684	56 %	63 186	54.1%	<0.0002
Death	410.253	4.4%	10 650	8.8%	<0.001
Mean hospital length of stay (days)	7.1	3.21 SD	13.7	22 SD	<0.001

Abbreviations: SD, standard deviation; NA, not applicable.

Table 2. Characterization of adverse drug reactions identified through the hospital database

		Type of ADRs					
ADR alerts	Total number	ADR at admission	ADR during hospitalization	Mean age	Number of female gender (%)	Mean hospital length of stay	Number of deaths (%)
E codes	90 260	252	90 008	62	49 628 (55.0%)	14	6906
Hypoglycemia	6684	1273	5411	55	3611 (54.0%)	10	1187
Neutropenia	17 035	1515	15 521	47	8140 (47.8%)	14	1968
Hepatitis	606	60	546	48	605 (99.8%)	6	4
Anaphylactic shock	2133	356	1777	47	1201 (56.3%)	12	0
Shock due to anesthesia	1	0	1	0	1(100%)	88	0

Table 3. Trends in hospitalizations, spontaneous reports and ADRs identified in databases

				ADRs database—type of alert					
Year	Number of hospitalizations	Spontaneous reporting	ADRs identified by the database (%)	E codes	Hypoglycemia	Neutropenia	Hepatitis	Anaphylactic shock	Shock due to anesthesia
2000	949 427	641	8301 (0.82%)	5750	829	1338	49	335	0
2001	959 895	1342	8769 (0.91%)	6184	699	1576	62	248	0
2002	973 328	1251	10 602 (1.1%)	8073	709	1573	92	155	0
2003	991 804	1097	12 371 (1.25%)	9853	731	1574	52	161	0
2004	982 627	1623	12 918 (1.31%)	10 423	727	1545	85	138	0
2005	1 013 770	1259	13 444 (1.33%)	9987	698	2443	86	230	0
2006	973 887	1284	13 778 (1.41%)	10 855	656	2002	69	195	1
2007	965 576	1424	14 744 (1.53%)	11 686	689	2042	48	279	0
2008	965 463	1603	14 325 (1.49%)	11 452	601	2000	44	255	0
2009*	495 345	2038	7440 (1.50%)	5997	345	942	19	137	0
Total	9 271 122	13 562	116 720 (1.26%)	90 260	6684	17 035	606	2133	1

Types of alerts identified in the databases are also identified.
*For the year of 2009, only the first semester data was available.

of the female sex ($p < 0.0002$, Fisher's exact test), and had a higher risk of death ($p < 0.001$, Fisher's exact test).

Additionally, we verified that several comorbidities (identified also through the use of diagnostic codes) were associated with a higher risk of developing an ADR: heart failure ($p < 0.0001$, Fisher's exact test), septicemia ($p < 0.0001$, Fisher's exact test), dysrhythmias ($p < 0.0001$, Fisher's exact test), hypotension ($p < 0.0001$, Fisher's exact test), cerebrovascular disease ($p < 0.0001$, Fisher's exact test), stroke ($p = 0.0000045$, Fisher's exact test), diabetes ($p < 0.0001$, Fisher's exact test), ischemic heart disease ($p < 0.0001$, Fisher's exact test), malignancies ($p < 0.0001$, Fisher's exact test), and pneumonia ($p = 0.0000026$, Fisher's exact test).

DISCUSSION

To our knowledge, this was the first estimate of the frequency of ADRs in a nationwide level in Portugal. We identified 166 720 ADRs of 9 271 122 inpatients stays (prevalence of 1.26%); if we applied respective

DOI: 10.1002/pds

PPV values (PPV values were estimated in the validation study[15]), this would detect 104 015 true ADRs.

We identified an increase in the number of hospitalizations from 2000 to 2009 (as expected along the evolution of the National Health Care) and in the number and percentage of ADRs. The reported increase in the frequency of ADRs is also expected, considering the higher number of drugs available, the tendency of prescribing multiple drugs per patient, improved register of clinical conditions in databases, improvement of clinical coding, and even population ageing. Each prescribing physician should consider the risk of ADRs carefully before prescribing an additional drug to a patient.

Our results were consistent with those presented in other studies that identified risk factors of ADRs, such as comorbidities,[14] diabetes,[23] renal failure,[23] female sex,[24] and age.[1,24] They were also consistent with the frequency of ADRs identified by previous studies that used administrative databases for a nationwide estimate: 0.89% in Spain,[11] 0.9% in England,[25] 1.83% in the Netherlands,[12] and 0.8% in Australia.[26] The Spanish study[11] identified a smaller frequency of ADRs, 0.89%, perhaps because the authors utilized solely E codes, in opposition to our work, in which we used E codes and other validated diagnostic codes. Whitstock and colleagues[26] utilized a methodology beyond databases, linking clinical trial data with administrative health data, but tested it solely for newly released drugs and older population in Australia, consequently identifying a smaller frequency of ADRs, 0.8%. Wu and colleagues[25] searched several codes using the ICD-10 coding system, but estimated only the frequency of ADRs associated with hospital admission, which might explain the slightly inferior estimate in comparison with us, 0.9%. However, a higher frequency of ADRs was found by Hooft *et al.*[12] (1.83%) although they were only referring to ADRs associated with hospital admission (including ADRs that directly caused admissions and ADRs that did not cause but were present at admission) and although they only searched E codes. This higher estimate might be related to the fact that in the Netherlands (unlike Portugal and many other countries), the coding is independent of reimbursement;[12] therefore, there is no tendency to omit a "negative" code (which could lead to bias, usually known as "coding creep"[27]).

The strengths of our study include our comprehensive database, which contains data from all hospitalizations in every acute care public hospital in Portugal within almost a decade. Another strength comes from the validation study previously performed,[15] which has enabled us to add measures of error to our estimate, identify diagnostic codes that may represent signals for ADRs other than "E" codes, and identify the error associated with "E" codes (the PPV for "E" codes was just 95% because several drug-related errors were erroneously coded as ADRs). The database methodology has a far greater detection rate than spontaneous reporting (detecting only 12% of the ADRs identified by the database), which is perhaps the greatest advantage of this methodology considering the purpose for which it was built: to obtain a good detection rate with reasonable costs (affordable for continuous pharmacovigilance). Therefore, spontaneous reporting can be used for the identification of new ADRs, and the database methodology can be used for a fast and large-scale estimate of incidence of ADRs.

Limitations of our work are inherent to the use of administrative databases, which often contain incomplete or wrong information because of its purpose. If on one hand, reimbursement databases assure comprehensive data, on the other, they might lead to coding bias ("code creep", in which coders select a different code to increase reimbursement to their hospital[27]). It is not possible to estimate the error caused by these biases. Another limitation is related to the fact that we applied the PPV value of a small one-centered validation study to a large national database; for that, we had to assume that the population was the same. We could be inducing bias if the population is different. If we use the methodology of previous database studies (in which they assume that all "E" codes represent an ADR and simply search "E" codes), we would have 90 260 ADRs ("E" codes), with a prevalence of 0.97%, which is a prevalence somewhat similar to the one that we obtained. Nonetheless, we believe that this methodology is more comprehensive and enables us to identify codes that add information to "E" codes and therefore to identify ADRs previously undetected. Additionally, we suggest multi-centered validation studies in different countries to select specific diagnostic codes associated with ADRs within each country and to build an estimate of error associated with each methodology.

Although the database methodology allows us to obtain a higher frequency of ADRs than spontaneous reporting, it is low in comparison with prospective monitoring and intensive monitoring (the main methodologies used in the included studies of the systematic review that estimated a mean of 16.88% of ADRs in hospitalized patients[4]). Nevertheless, these methodologies have the highest costs, making them impossible to use in a large-scale study such as our own.

Additionally, several studies report that different methods tend to identify different types of ADRs,[15,16] and many authors suggest the simultaneous use of several methodologies to enhance ADR detection.[28,29]

DOI: 10.1002/pds

Therefore, future studies should include a complete estimate and characterization of ADRs, nationwide, prospectively to allow the use of different methods complementarily, with causality assessment of each ADR and ideally with cost analysis.

CONCLUSION

In conclusion, this is the first nationwide estimate of ADRs in Portugal throughout almost a decade: a mean prevalence of 1.26% of ADRs (2.7% of which were associated with admission) was detected. The database methodology has flaws and underestimates the real number of ADRs, but it should be used continuously as a methodology that can complement (but not replace) other pharmacovigilance methodologies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

KEY POINTS

- Spontaneous reporting is the only pharmacovigilance method continuously used in Portugal. This method grossly underestimates the number of adverse drug reactions (ADRs). Chart review, computerized methods, and intensive monitoring are too resource-consuming to be utilized in a nationwide level in Portugal.
- Using hospital administrative databases, we have built a nationwide estimate of ADRs in Portuguese hospitals, from 2000 to 2009. We detected 116 720 ADRs (97.3% of which occurred during hospitalization and 2.7% were the cause of admission), with a prevalence of 1.26% of all hospitalizations. Throughout this time, there were only 13 562 spontaneous reports of ADRs in Portugal (prevalence of 0.1%).
- Databases are not widely used as a pharmacovigilance methodology, but have many potential advantages, such as a moderate ADR detection rate and relatively low resources needed.

ACKNOWLEDGEMENTS

The authors would like to thank the support given by the research project HR-QoD—quality of data (outliers, inconsistencies and errors) in hospital inpatient databases: methods and implications for data modeling, cleansing and analysis (project PTDC/SAU-ESA/75660/2006), and ACSS for providing access to the data.

The authors would also like to thank the INFARMED, Portuguese National Authority of Medicines and Health Products, for the data provided about spontaneous reporting in Portugal.

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APPENDIX 4

ISSN: 0975-766X
CODEN: IJPTFI
Available Online through
www.ijptonline.com
Research Article

RESOURCE-SPARING COMPUTERIZED TOOL FOR DETECTION OF ADVERSE DRUG REACTIONS

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Received on 31-12-2012 *Accepted on 20-01-2013*

Abstract

Aims: To develop and validate a computerized methodology of adverse drug reactions (ADRs) detection that could assist manual chart review (CR), with low costs of implementation and maintenance.

Methods: A computerized clinical decision support tool (CT) was built, as well as drug databases and algorithms that allowed to identifying ADRs from few input data obtained through chart review. A retrospective study of 118 random patients was performed for validation.

Results: CT detected 65 ADRs in 29 patients (versus 12 ADRs in 12 patients in CR) with low resources needed (29.5 versus 69 person-hours), allowing to identify a prevalence of 24.8% ADRs (versus 10.2%). CT suggested ADRs and also described frequent ADRs for each drug (allowing inexperienced reviewers to identify previously unsuspected ADR signs).

Conclusions: CT is a promising Pharmacovigilance methodology, particularly at a time of world economic crisis, since it allows continuous surveillance with five times greater detection and half the resources needed by CR. It may be of use in hospitals without electronic records.

Keywords: adverse drug reactions, pharmacovigilance, chart review, computers.

Introduction:

Adverse drug reactions (ADRs) are frequent, costly, often preventable and are responsible for many deaths in hospitalized patients. ADRs are among the most frequent causes of death in developed countries[1]. It is estimated that they occur in a mean of 16.88% of patients during hospitalization (CI95%:13.56-20.21)[2] and that they are associated with an overall median of 5.3% of hospital admissions (interquartile range 2.7-9.0%)[3]. The costs of

drug-related problems (which include ADRs) may be higher than the total cost of cardiovascular or diabetes care[4]; while the mean additional cost attributable to an ADR is estimated to be US$3332[5].

Consequently, the identification and ultimately the prevention of ADRs is one of the few ways to simultaneously increase quality in Health Care and decrease its costs. There are several methods of ADR identification[6]. Manual chart review has good detection rates and is considered by some as the "gold standard" to identify adverse drug reactions in health care organizations[7], but it is time and personnel costly: some studies estimated a cost of 55 person-hours per week[8]. This makes it impossible to use as a methodology of continuous detection of ADRs in all hospitalized patients.

On the other hand, computerized surveillance is increasingly appealing[9,10]. Many different strategies of computerized Pharmacovigilance were assessed in a recent systematic review[11], with different levels of complexity in implementation and integration, and consequently with a variety of costs in acquisition and maintenance. However, this type of surveillance requires that all patient information is computerized, which is not possible in many hospitals, such as ours.

Therefore, our purpose was to design and validate a computerized tool for ADR detection that would assist chart review, simultaneously increasing detection and decreasing associated costs for the detection of ADRs. Since we live in an era of social and economic crisis, we wanted to build a program that would have low costs of implementation and maintenance, and that did not require health system integration.

Materials and methods

Study setting

A retrospective study was performed at Central University Hospital of Coimbra, Portugal. From all hospitalized patients in 2010, we selected a random sample of 118 patients to perform manual chart review and computerized assessment, independently, to validate our methodology and to compare: number and types of ADRs identified, risk factors for ADRs, and time spent in each methodology. The study was approved by hospital's institutional review board.

Definition of ADR

World Health Organization's definition of an ADR was applied: "any noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy"[12]. Previous works utilized

computerized systems to identify adverse drug events ("an injury resulting from medical intervention related to a drug")[13-16], but we aimed to assess specifically ADRs.

Outcome assessment

The primary outcome was frequency of ADRs (including ADRs that led to admission, ADR_{Ad}, and ADRs that occurred during hospitalization, ADR_{In}). We assessed: number of ADRs, number of patients that suffered from an ADR, number of patients exposed to drugs, length of hospital stay. We registered number of ADRs computer-detected and number of ADRs computer-undetected. Secondary outcomes included: particular diagnosis, ward, age, gender, length of hospital stay, number and name of drugs administered to each patient, and other clinical data as detailed below.

Manual chart review

From each patient, chart was reviewed, including: discharge note, diaries, all drugs administered, laboratory and coding data, as well as every aspect that could constitute a symptom or sign of an ADR, even if not detected previously by responsible medical team. For complete validation, all cases were reviewed (not just the cases with a positive computer alert).

All ADRs were registered, described and classified according to WHO's causality assessment[17], preventability (Schumock criteria[18]) and severity (Hartwig[19]). ADRs classified as conditional or unlikely were excluded from the analysis (but registered). Associated drugs (and all administered) were registered. Reviewer also registered if ADR was previously undetected, as well as age, gender, ward, hospitalization time, and other relevant clinical information.

Computerized system - Chart Helper

Considering the need of a costless computerized system, we built a program that did not require Health system integration. The main difficulty was to build manually databases with drug information in portuguese, since there were none available in our country that linked adverse drug reactions, their symptoms and signs to each drug. We used the Hospital Formulary[20], and the official list of portuguese ambulatory drugs, available in the site of INFARMED[21], the Portuguese Regulatory Authority of Drugs, to build a database with all drugs available in Portugal. We then built an ADR database with the 10 more frequent ADRs, all ADRs that were potentially fatal for each drug, and other clinically relevant ADRs for each drug according to INFARMED[21] and Meyler's side

effects of Drugs book[22]. We also added to that database: the symptoms of each ADR, signs, laboratorial alterations, diagnosis and compatible coding information (for that, we used also International Classification of Diseases 9th Revision, Clinical Modification: ICD-9-CM[23]).

We built a program, Chart Helper, with Visual Studio 2010, aiming for a simple and user-friendly interface with the reviewer. For each patient, the user of Chart Helper (the chart reviewer) registered age, gender, chart number, hospitalization and discharge dates (duration of hospital stay was automatically calculated), and diagnosis and procedures codes (from ICD-9-CM[23]). Some data must be input manually because in most of portuguese hospitals, not all patient data is computerized (most data is stored in paper records).

All drugs administered during hospitalization were also selected from a list by the reviewer, as well as relevant symptoms, signs and laboratorial alterations. The user could input symptoms and signs not previously present in the database, but detected in the chart review, therefore increasing overall detection of ADRs.

We intended to take advantage of two types of input data: first, already existing coding and administrative data with useful clinical information, and second, manual chart review to identify symptoms or other alterations missing in coding data but detected by the user. The program tool used all of these input data, our ADR databases and some algorithms to generate two types of results:

1. Suggested ADR(s) for that patient. The program detected if a symptom, sign, diagnostic code or laboratorial alteration that the patient had, was compatible with an ADR of any of the drugs administered to him. Respective drug, ADR and alert were specified by program as a decision support tool, and then the reviewer would decide if the suggested ADR really occurred and would classify it according to WHO's causality assessment[17] (available in the program): certain, probable/likely, possible, conditional/unclassified, inaccessible /unclassifiable.
2. Frequent ADRs for each drug. For each drug administered to that patient, a list of frequent (and of fatal) ADRs was available for consultation by the user. Therefore, this memory support tool would allow less experienced users to pay more attention to certain signs and symptoms throughout the chart that could indicate an undiagnosed ADR of a drug administered to that patient.

All data (input and result data) were automatically stored in a database by Chart Helper for further analysis. Conditional and unlikely ADRs were excluded from our analysis (but also automatically registered in the

database).

Data analysis

We calculated sample size (to identify ADR prevalence of 10%) using an online calculator (100 patients were necessary)[24]. Statistical analyses were done with the Chi-square test for categorical variables (or Fisher's exact test whenever possible), Student's t-test for normally distributed continuous variables and Mann-Whitney or Kruskal-Wallis when dealing with variables without normal distribution, using SPSS v20. The *a priori* level of significance for all comparisons was $p<0.05$.

Results

Characterization of sample

From the random sample of 118 patients hospitalized in 2010, mean participant age was 60 years. 40.7% were female.

Table-1: Describes socio-demographic participants' characteristics.

Characteristics	***Number***	***Relative frequency (%)***
Female gender	48	40.7 %
Age *(sd: standard deviation)*	Mean: 60 years	sd: 20
Mean number of days hospitalized *(sd)*	10.1	sd: 20.0
Mean number of drugs administered per patient	5.2	sd: 3.8
Wards more frequently occupied		
Surgery	18	15.25 %
Urology	14	11.86 %
Medicine	10	8.48 %

Demographic characteristics of participants

Chart review

Chart review allowed the identification of 12 ADRs in 12 patients, one of them fatal (due to infection after the use of chemotherapy). 117 patients were exposed to drugs, thus ADR prevalence was 10.2% (12/117).

The most frequent ADRs were hyperkalemia (16.7% of all ADRs) and warfarin leading to International Normalized Ratio levels that led to surgery delay (16.7%).

Systems more frequently affected were hematologic (33.3%), renal (25%) and cardiovascular (16.7%). Drugs more frequently involved were non steroidal anti-inflammatory drugs (NSAIDs, 25%), antibiotics (16.7%), anticoagulants (16.7%) and diuretics (16.7%).

Five ADRs were preventable (according to Schumok's classification). There were 3 severe ADRs, 5 moderate and 4 mild (Hartwig classification). Twenty-four adverse events were identified.

Patients with ADRs were exposed to a higher number of drugs than patients without ADRs (Mann-Whitney test, p=0.001); there was no statistically significant difference in age, hospitalization time, number of days in intensive care units, or gender (Fisher's exact test).

Computerized clinical decision tool

1. Program

Chart helper, the program built, requires that some data are entered as the chart review is performed, as detailed in the Methods section and illustrated in *figure 1a*. Afterwards, according to each patient, two types of results are generated: list of frequent ADRs for drugs administered and list of suggested ADRs (*figure 1b and 1c*).

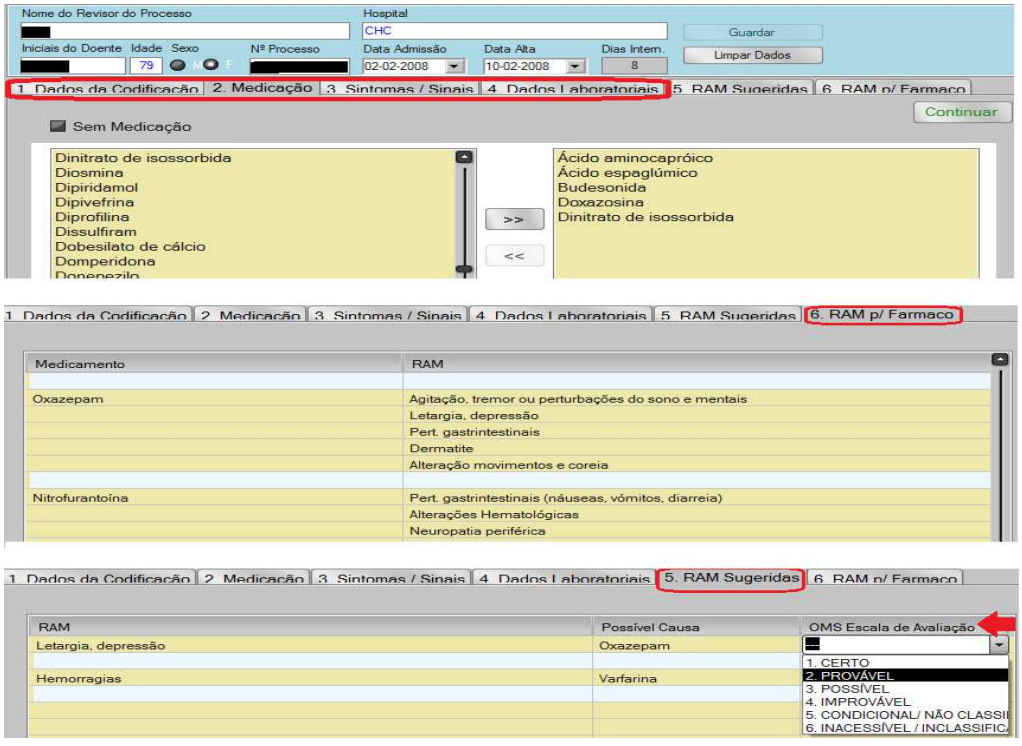

Figure-1: Some examples of Chart Helper interface.

1a. Data input (above)

Some of the data that must be entered by reviewer (red square): coding data (if available), drug names administered to that patient, symptoms and signs and laboratorial data. **1b. List of ADRs (middle)** List of frequent and fatal ADRs for the drugs administered to that patient, working as a "memory enhancer". This allows less experienced reviewers to pay more attention to certain symptoms (or other alterations) that may represent an ADR in that patient. **1c Suggested ADRs (below)** If the patient had symptoms, signs, codes or any laboratorial alteration that is compatible of an ADR to a drug administered to that patient, the program suggests an ADR and respective drug (an ADR alert). In the example above, there are 2 ADRs suggested for that patient (hemorrhage by warfarin and lethargy or depression by oxazepam). These must be classified according to WHO's causality of ADRs (red arrow) by the reviewer.

2. ADR detection

Sixty-five ADRs (unlikely ADRs were excluded) were identified by computerized system in 29 patients, leading to a prevalence of ADRs of 24.8% (29/117) and including 17 ADRs certain or probable (prevalence of 14.5%). Two ADRs were undetected by computer (both with warfarin leading to INR levels that caused surgery delay). On the other hand, 53 ADRs were only detected by computerized system (manual chart review did not detect them), all of which were validated by further manual chart review to identify if they were true ADRs. From 81 alerts, 65 were true ADRs (positive predictive value of 80%).

Most frequent ADRs detected by computer were laboratorial alterations (24.29% of ADRs), agitation (14.63%) and diarrhea or constipation (13.82%). Systems more frequently affected were: hematologic (31.71%), gastrointestinal (26.02%) and renal (16.23%).

The drugs more frequently involved were: NSAIDs (15.45%), antihypertensives (14.63%) and antidepressants or antianxiety agents (14.63%).

Discussion

Our work allowed us to develop and validate a computerized methodology easy and fast to apply, and nearly costless to our National Health System. This effective computerized methodology detected five times more ADRs (65 versus 12 ADRs) than manual chart review with approximately half the resources (69 versus 29.5 person-hours).

Our approach is new, because we started from chart review with integrated data (instead of separate laboratorial data or other indicators from health systems), and developed databases and algorithms to create automation, while leaving the ultimate decision of ADR causality assessment to the health professional reviewer (the user of the system), with a simple user-friendly interface.

Methodology comparison

Table-2: Presents the comparison between manual chart review and computerized methodology.

	Manual chart review	**Computerized method**
Total number of ADRs (excluding "unlikely")	12	65
Patients with ADR	12	29
ADR prevalence	10.2%	24.8%
Total number of person-hours spent	69	29.5
Fatal ADRs	1	1
ADRs previously diagnosed in clinical history	3	3
ADRs previously coded (E code)	1	1
Number of adverse events (including ADR)	24	77
Number of ADR associated with admission *versus* ADR that occurred during hospitalization	2 *vs* 10	2 *vs* 63
WHO's causality assessment		
Certain	4	7
Probable / likely	5	15
Possible	3	43
Unlikely or conditional/unclassified or inaccessible /unclassifiable	0	31

Comparison of ADR detection by each methodology.

Strengths of this study

We believe our work has several strengths. The greatest strength of this study lies in its results, showing a clear superiority over manual chart review, with a prevalence of ADRs identified of 24.8%.

Second, the low resources required, much lower than manual chart review, allows the application of this method as a continuous method of Pharmacovigilance, which was not previously possible for chart review. Even in small hospitals where it isn't feasible to implement complex computerized systems, ADR monitoring can be improved through this resource sparing system. In fact, we believe that this solution might be interesting for those hospitals in which patient information is not computerized.

Third, this program elaborates a list of frequent and fatal ADRs per drugs administered to each patient, allowing even inexperienced reviewers to detect symptoms (or signs, laboratorial data or codes) that may constitute an ADR, working as a supporting memory tool.

Fourth, it does not need *a posteriori* validation, since it integrates validation and causality assessment performed by a reviewer during each assessment.

Last, unlike the previously published studies that reviewed only charts of ADR alerts, we intended to identify also ADRs undetected by this computerized methodology and to perform a true validation, therefore we performed chart review to all patients.

Limitations of this work and suggestions for future work

This work has also several limitations. Further testing and validation should be performed, namely in other hospitals, other countries, and with a higher number of patients. This validation study had a retrospective design, but it would be interesting to test this computerized approach prospectively, to enhance ADRs detection and treatment. It is a resource-sparing tool because it has a low level of automation, however, it would be interesting to integrate it in the health system and to add further automation: although the costs would rise exponentially, we believe that interesting results would be provided. This program also allows us to compare different reviewers, therefore a study in which we compare ADR detection with this computerized system among different reviewers could reveal subjectivity factors unknown so far.

Finally, although one of the biggest difficulties was building it in portuguese language, translation into English (and the adaptation of all databases of drugs and ADRs) for validation in other countries is relatively easy and could also show interesting results.

Conclusions

This computerized clinical decision support tool for ADR detection might be an useful Pharmacovigilance

methodology in the future, particularly at a time of world economic crisis, since it allows continuous surveillance with a higher ADR detection (five times greater) and half the resources needed by manual chart review. It is a promising method that requires further studies.

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APPENDIX 5

Pharmacoepidemiology and Drug Safety - Decision on Manuscript ID PDS-13-0102.R1

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09-Dec-2013

Dear Ms Miguel,

It is a pleasure to accept your manuscript entitled "Ophthalmic adverse drug reactions to systemic drugs: a systematic review" in its current form for publication in Pharmacoepidemiology and Drug Safety. You will be contacted by our typesetters/copyeditors soon.

If your paper is an Original Manuscript or a Review, it will appear on the Early-View website ahead of its appearance in the print version of the journal. The online appearance constitutes formal publication and the paper can then be cited, using the DOI number. If your manuscript is a Letter to the Editor or a Commentary, it will appear online in a compiled monthly issue of the journal. All accepted manuscripts will appear in a print issue of the journal.

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Thank you for submitting your interesting and valuable manuscript to the journal. Please accept my congratulations on this acceptance and extend my good wishes to your co-authors.

Yours sincerely,

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Title: Ophthalmic adverse drug reactions to systemic drugs: a systematic review

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Keywords: adverse drug reactions, clinical pharmacology, pharmacoepidemiology, Ophthalmology

Competing interests: none

Word count: 2009

Figure and table count: 0 figures, 2 tables

Keypoints:

- Ophthalmology is perhaps one of the medical specialties in which there are the few assessed ADRs, but the eye is a complex organ in which minimal impairment can produce a substantial functional effect.
- We performed a systematic review regarding ophthalmic ADRs to systemic drugs, to systematically summarize evidence and to identify specific areas that lacked systematization or assessment.
- From 562 studies initially found, only 32 were included, and few studies had low risk of bias. Drugs frequently involved included amiodarone, sildenafil, hydroxychloroquine and biphosphonates.
- Many ophthalmic ADRs are frequent but remain unnoticed, therefore the systematization of specific ophthalmic ADRs, the increase of knowledge and the dissemination of protocols of collaboration are suggested.

Prior postings and presentations: none

Abstract:

Purpose: To perform a comprehensive and systematic review regarding ophthalmic ADRs to systemic drugs to: 1) systematically summarize existing evidence, 2) identify areas, ophthalmic ADRs or drugs that lacked systematization or assessment (namely drugs with original studies characterizing specific ophthalmic ADRs but without causality assessment nor without meta-analysis).

Methods: Systematic review of several electronic databases (last search 1/7/2012): Medline, SCOPUS, ISI web of knowledge, ISI Conference Proceedings, International Pharmaceutical Abstracts and Google scholar. Search query included: eye, ocular, ophthalmic, ophthalmology, adverse and reaction. Inclusion criteria were: 1. Primary purpose was to assess an ophthalmic ADR to a systemic medication; 2. Patient evaluation performed by an ophthalmologist; 3. Studies that specified diagnostic criteria for an ocular ADR. Different types of studies were included and analyzed separately. Two independent reviewers assessed eligibility criteria, extracted data, and evaluated risk of bias.

Results: From 562 studies found, 32 were included (1 systematic review to sildenafil, 11 narrative reviews, 1 trial, 1 prospective study, 6 transversal studies, 6 spontaneous reports and 6 case series). Drugs frequently involved included amiodarone, sildenafil, hydroxychloroquine and biphosphonates. Frequent ophthalmic ADRs included: keratopathy, dry eye and retinopathy.

Conclusions: To increase evidence about ophthalmic ADRs, there is a need for performing specific systematic reviews, applying strictly the World Health Organization's (WHO) definition of ADR and WHO causality assessment of ADRs.

Some ophthalmic ADRs may be frequent, but require ophthalmological examination, therefore ophthalmologists' education and protocols of collaboration between other specialties whenever they prescribe high-risk drugs are suggestions for the future.

Introduction

Ophthalmology is perhaps one of the medical specialties in which there are the fewest assessed ADRs, representing a particular challenge in Pharmacovigilance[1]. However, the eye is a complex organ in which minimal impairment can produce a substantial functional effect[2]. Ophthalmic ADRs are usually not continuously detected, although they might be either frequent or specific of a drug or drug group, such as acute angle-closure glaucoma and myopic shift caused by topiramate[3], cataracts provoked by corticosteroids[4], floppy iris syndrome caused by tamsulosine[5] and uveitis caused by rifabutin[6].

Some ADRs are rare but can cause irreversible blindness (such as in optic atrophy provoked by ethambutol)[7], while others are extremely frequent but usually harmful (namely *cornea verticillata* caused by amiodarone)[8].

There are reports that suggest ophthalmic ADRs provoked by a systemic drug, but remain unsupported because no systematic review has been performed. Many ophthalmic ADRs have been identified solely due to spontaneous reports, namely blurred vision caused by leuprolide[9], or other ophthalmic ADRs caused by different drugs such as biphosphonates, cetirizine or isotretinoin[2]. Therefore, on the one hand, prospective studies or trials should be performed to study the causality of each drug to each ophthalmic ADR; on the other hand, a systematic review should be performed to clarify and assess what ophthalmic ADRs can occur after the correct prescription of each drug. A systematic review would be useful not only to identify drugs in which ophthalmic ADRs are frequent or serious, but also to increase knowledge of physicians (prescribing physicians and ophthalmologists), enabling a greater detection of ophthalmic ADRs after a ophthalmic examination and enabling the construction of multi-disciplinary protocols whenever a high-risk drug is prescribed.

General ADRs are estimated to cause of 2.7% to 15.7% hospital admissions and to occur in 16.9 % of hospitalized patients (confidence interval 95%: 13.6%, 20.2%)[11]. In a study performed in the United States (US) it was estimated that more than 100000 people die every year as a consequence of fatal ADRs, placing fatal ADRs between the fourth and sixth leading causes of death in the US[12]. However, the specific frequency of ophthalmic ADRs is not known.

Although there are several studies about ophthalmic ADRs, this theme presents with specific difficulties[13,14], and the methods of identification and reporting ADRs vary greatly[15,16]. Some studies have established recommendations[17,18], and others offer guidelines to performing systematic reviews of studies of ophthalmic ADRs[19,20].

We intended to perform a general systematic review about ophthalmic ADRs to systemic drugs in order to, on the one hand, systematically summarize existing evidence, and on the other hand, identify areas of specific ophthalmic ADRs or drugs that lacked systematization or assessment. This includes the identification of drugs that cause specific ophthalmic ADRs which are well described in original studies but without systematic review nor meta-analysis (therefore, opportunities for specific systematic reviews with meta-analysis in the future are also identified).

Methods

We performed a systematic review of studies that assessed ophthalmic ADRs to systemic drugs according to the guidelines of the Cochrane Collaboration[19] and PRISMA Statement[21], adapted to this theme.

Definitions

We used the following definition for *adverse drug reaction:* "any noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy", according to the World Health Organization (WHO) definition[22] of 1972.

An adverse event is: "an injury related to medical management, in contrast to complications of disease"[23]. Medical management includes all aspects of care, including diagnosis and treatment, failure to diagnose or treat, and the systems and equipment used to deliver care[23]. Therefore, to increase specificity, we wanted to assess only adverse drug reactions.

Search methods

We searched through several electronic databases (last date of search was 1/7/2012): Medline, SCOPUS, ISI web of knowledge, ISI Conference Proceedings, International Pharmaceutical Abstracts and Google scholar. We used a search query

created after a pilot study to add specificity (full search query available if requested to the corresponding author) that included the terms: eye, ocular, ophthalmic, ophthalmology, adverse and reaction. We searched for grey literature and unpublished data, and hand-searched all references of included studies and relevant reviews.

Selection criteria

Studies were included if they followed all **inclusion criteria** listed below:

1. Studies in which the primary purpose was to assess an ophthalmic ADR to a systemic medication. Since there is a wide misuse of the terms ADR, adverse event (AE) and adverse drug event (ADE), we obtained also the full-text of studies who claimed to assess AEs or ADEs, to verify their methodology, and to include the studies that actually assessed ADRs, although they called it AEs or ADEs.

2. Studies with patient evaluation performed by an ophthalmologist.

3. Studies that specified diagnostic criteria for an ocular ADR.

We also included studies with different languages (we hired a translator), any country and experimental studies (if any). We did so to have a more thorough and complete literature search. We did not exclude systematic nor narrative reviews if they added useful information about ocular ADRs, as we intended to have a general overview that summarized and added further systematization to existing evidence, and to identify areas or specific ophthalmic ADRs that lacked systematization or assessment.

Exclusion criteria:

1. Studies assessing adverse events that did not correspond to ADRs (for example, we excluded reports of capsular rupture in phacoemulsification surgery, but we did not exclude reports of capsular rupture due to intra-operatory floppy iris syndrome, a syndrome that is an ADR provoked by tamsulosine or other drugs).

2. Systemic ADRs to topical ophthalmic drugs, or ophthalmic ADRs to topical ophthalmic drugs (they were not the purpose of our study and would increase heterogeneity and reduce clarity of our study).

3. Studies that were comments or letters, if they would not add new scientific evidence to our review. However, letters or comments that included case reports not

published elsewhere about specific ocular ADRs were not excluded, in order to identify rare ophthalmic ADRs.

4. Studies assessing drugs already removed from the market.

Data collection and extraction

Two independent reviewers, AM and FH, first examined each title and abstract to exclude obviously irrelevant reports, and then independently examined each full text report, to determine eligibility according to inclusion criteria. Disagreements were solved by consensus, recorded and analyzed using kappa statistics.

Primary outcome was the presence and type of ocular ADR and the respective causative systemic drug. Secondary outcomes included: ocular structure affected, diagnosis, serious or vision-threatening ADR. All symptoms, visual acuity (VA), signals, and results of complementary examination performed at presentation were recorded, as well as after a follow-up. Attitude or treatment performed for each ADR was also registered (suspension of the causative drug, specific treatment, administration of an antidote, no treatment necessary). If VA was not recorded in the logMAR scale[24], it was converted.

We always assessed the drug name, identified the therapeutic drug class according to Anatomical Therapeutic Chemical Classification System of WHO[25], and reported the number of days during which the drug was used and the administration route (if that information was available). We verified if causality was assessed in the original studies (and according to what classification, preferably WHO's[23] or Naranjo's[26], and respective results) as well as predictability of ADRs (using Hartwig's predictability scale, for example)[27], preventability (eg. Schumok & Thornton's preventability criteria)[28] and types of ADRs (Rawlins and Thompson's classification[29]). We did not intend to identify all of the ophthalmic ADRs, but to systematize the most important and the most frequent ADRs according to the results of our systematic search.

Risk of bias assessment

We performed risk of bias assessment for each included study, and recorded it in a standardized form created to assess ADR studies (in a previous work[10]) and adapted

to Ophthalmology after a pilot study. We did not use scales (discouraged by the Cochrane approach[20]) but criteria from Cochrane, STROBE[30], QUOROM[31] and PRISMA[21] adapted to the particular scope of ophthalmic ADRs evaluation, which included: complete description of study design, description of study type (case report, case series, prospective observational study, trial,...), adequate diagnostic criteria for ophthalmic ADR, complete ophthalmologic evaluation at presentation, quantified visual acuity at presentation and follow-up, results of complementary testing described at presentation and follow-up, definition of ADR presented, rationale for study size, causality assessment of ADR, preventability assessment of ADR, description of all statistical methods, characterization of study participants, description of methods to prevent bias (information bias, selection bias and other bias), presentation of complete summary measures. The two reviewers independently assessed study quality and risk of bias; disagreements were solved by consensus.

Studies were divided in low risk of bias (5 or less parameters with medium, unclear or high risk of bias), medium risk (6 to 9) and high risk (10 or more parameters evaluated as medium, unclear or high risk of bias).

Results

Literature search

Pubmed search yielded 124 results; SCOPUS yielded 72 results; Google Scholar 60; ISI Web of Knowledge yielded 154; others yielded 152. From these 562 studies (corresponding to 300 distinct studies), 163 were selected to obtain full-text and then 32 studies were included[9,17,32-61] (Figure 1): 1 systematic review of ADRs to a specific drug, 11 narrative reviews, 1 trial, 1 prospective study, 6 case-control or cohort or cross-sectional studies, 6 spontaneous reports and 6 case reports or case series. Kappa agreement for study inclusion was 0.80 during the first phase and 0.82 during the full text review (good agreement).

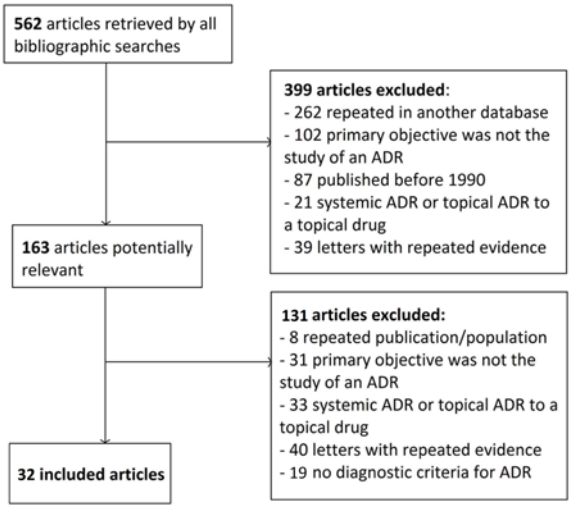

Figure 1. Flowchart of search strategy.

Characteristics of included studies

Table 1 summarizes the characteristics of included studies. We identified several types of studies of ocular ADRs, most of them narrative reviews without systematic criteria nor bibliographic search.

Table 1 (end of manuscript)

Ophthalmic ADRs

Many different ophthalmic ADRs exist to many systemic drugs. In table 2, we represent a summary of the main ophthalmic ADRs found in this systematic review, according to each specific drug, dose, risk factors and tried to characterize the ophthalmic ADR (if reported). Keratitis, retinopathy, glaucoma, dry eye and blurred vision were the most frequent ADRs identified.

Table 2 (end of manuscript)

We identified many ophthalmic ADRs to drugs that have original studies but are currently lacking a systematic review (therefore representing an opportunity for further studies, as described in the Discussion Section, below). Many studies were found but only one systematic review (of ophthalmic ADRs to sildenafil[56]) and few narrative reviews with systematic search were performed. Therefore, examples of drugs that cause ophthalmic ADRs that would benefit from a recent and specific

systematic review are: tamoxifen, amiodarone, antidepressants, phenotiazines, hydroxychloroquine, oral contraceptives, etc.

Risk of bias assessment

In figure 2 we present the summary of our quality evaluation of included studies, according to each parameter assessed - risk of bias graph. Few studies had low risk of bias. Only one study performed rationale for study size. Most studies (25) performed a complete initial evaluation by an ophthalmologist, but only 11 performed a follow-up of at least 1 month. Only 13 studies performed causality assessment for ADR and only 7 applied or presented WHO's definition of an ADR. Risk of bias summary, which contains detailed risk of bias assessment for each included study, is available if requested to contact author.

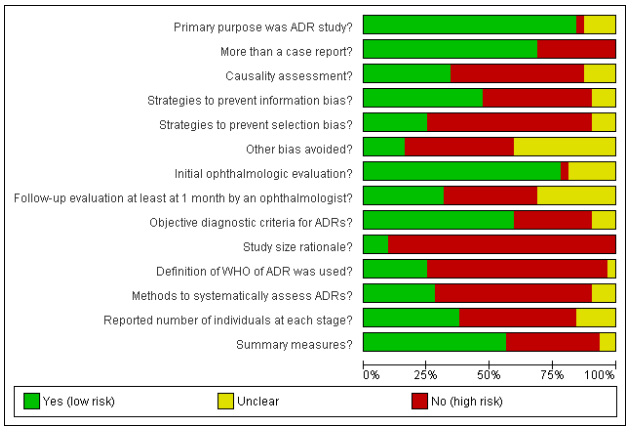

Figure 2. *Risk of bias graph.*

Discussion

What this study adds

There is an increasing number of studies of ophthalmic ADRs. In spite of the common belief that ADRs in Ophthalmology are rare, some ADRs might be extremely frequent (such as *cornea verticillata* caused by amiodarone[8]), but require specific ophthalmological examination for its detection. Every ocular structure might be affected by an ADR. There is a need for performing specific systematic reviews of ophthalmic ADRs, because the majority of included studies were narrative non-systematic reviews, most of which without the strict application of WHO's definition of ADR nor causality assessment of ADRs.

Several drugs that may provoke different ophthalmic ADRs were identified, namely amiodarone, sildenafil, psychotropic drugs, alpha-blockers, corticosteroids and topiramate. Although *cornea verticillata* is found very frequently in patients medicated with amiodarone (authors report a rate of 100%[46]), this finding rarely reduces visual function; on the other hand, amiodarone may provoke a rare optic neuropathy that may provoke marked visual loss[18]. Sildenafil and tadalafil have been recently studied, but while some authors report no difference between ERG patterns of placebo *versus* these drugs[53], others found several ADRs associated with sildenafil[58], namely: ischemic optic neuropathy, central retinal vein occlusion, cilio-retinal artery occlusion, acute angle closure glaucoma and optic atrophy.

Strengths of our systematic review lie in the comprehensive search performed, the general increase in systematization and characterization of ophthalmic ADRs, the summary of existing evidence according to WHO's causality criteria for ADR and WHO's definition of ADR, and finally the identification of specific ophthalmic ADRs that could benefit from future specific systematic reviews with possible meta-analysis.

Limitations of our systematic review include not only heterogeneity found in different types of ADRs but also the extreme variability in the methodologies of studies of ophthalmic ADRs (from isolated case reports to retrospective series of spontaneous reports, prospective observational studies and trials). These limitations were expected, because this was a systematic review with a very general scope; and because the detection of ophthalmic ADRs depends on the degree of suspicion and an adequately performed ophthalmologic examination. Many ophthalmic ADRs are only detected by case reports or spontaneous reports, representing a limitation but simultaneously an opportunity to improve. Consequently, there are many ophthalmic ADRs that are based on a low level of evidence. We believe this is an additional reason for applying systematically the WHO definition for ADR and a causality assessment (whether WHO's or Naranjo's), in order to decrease doubts. High risk drugs such as the ones identified in table 2 should be associated with protocols of evaluation (specially in susceptible individuals or in high doses) by an ophthalmologist, in order to detect sooner and with higher sensitivity and specificity the respective ophthalmic ADRs.

Conclusion

Ophthalmologists' education (to increase recognition of ophthalmic ADRs) and the dissemination of protocols of collaboration between Ophthalmology and other Medicine specialties whenever they prescribe high-risk drugs (such as sildenafil, biphosphonates, psychiatric medication, tamoxifen, hydroxichloroquine) are strong suggestions for the future.

Acknowledgments: the authors would like to thank MSD for obtaining the fulltext of 8 articles and Théa for obtaining the fulltext of 7 articles. None of the authors had conflict of interest.

Author disclosure statement: no competing financial interests exist.

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Year, author	Study type	Drug studied	Ophthalmic ADR(s) reported*	Summary of study
1986 Davidson[32]	Narrative review	Several	Many ocular ADRs caused by: corticosteroids, chloroquine, amiodarone, phenothiazines, tamoxifen...	Narrative review without definition of ADR nor causality assessment
1989 Curran[33]	Case series	Doxorrubicin	Iritis, conjunctivitis, periorbital edema, keratitis, optic neuropathy	Case series of 4 cases of ocular ADRs to doxorrubicin
1991 Hobley[34]	Case report	Digoxin	Scintillating visual field loss (central scotoma) + dischromatopsia	Case report: visual field defect due to digoxin (therapeutic level)
1992 Malek[35]	Narrative review	Oral contraceptives	• Retinal hemorrhage or emboli, macular or papillary edema, optic neuropathy	Narrative review of ocular ADRs by oral contraceptives.
1993 Goldman[36]	Narrative review	Anticonvulsivants	• **Carbamazepine**: diplopia, paresis of extraocular muscles, nistagmus, visual allucinations • **Phenytoin**: nistagmus without oscillopsia, mydriasis • Others: paresis of extraocular muscles	Narrative review of ocular ADRs of common anticonvulsivants
1994 Macarol[37]	Spontaneous reports	Pamidronate	Scleritis, conjunctivitis, anterior uveitis	Retrospective series of spontaneous case reports
1995 Oshika[38]	Narrative review	Neuropsychiatric drugs	• **Phenothiazine**: corneal et lens deposits • **Thioridazine**: retinopathy • **Tricyclic antidepressants:** glaucoma, decreased accommodation • **Lithium**: papilledema, exophthalmia • **Chlorpromazine**: keratopathy	A narrative review of ophthalmic ADRs of neuropsychiatric drugs
1995 Fraun-Felder[9]	Letter with spontaneous reports	Leuprolide	Blurred vision	A retrospective study of series of spontaneous reports of ocular ADRs of leuprolide
1995 *b* Fraun-Felder[39]	Retrospective case-control study	Niacin	Dryness, blurred vision, diplopia, cystoid maculopathy	ADRs of patients taking niacin were compared to other dyslipidemia drugs
1997 Sweeney[40]	Prospective study	Risperidone	Eye movements affected: prolonged latency after and alteration of saccadic movements	Prospective study of patients with risperidone (4 weeks)
1999 Dulley[41]	Narrative review	Tamoxifen	• Retinopathy with deposits • Keratopathy with deposits • Colour vision defects • Foveal disfunction and ERG change	Narrative review about ocular ADRs of tamoxifen
1999 Solomon[42]	Letter with case reports	Influenza vaccine	• Case 1: anterior uveitis • Case 2: reactivation of herpetic keratitis • Case 3: left keratoplasty rejection	Letter with case reports not previously published
1999 Doughty[43]	Narrative review	Migraine drugs	Cyproheptadine, pizotyline, amitriptiline, propranolol, timolol, clonidine, flunarizine: dry eye	A narrative review of medications of headaches and their ocular ADRs
2001 Ikaheimo[44]	Observational cross-sectional study	Flecainide	• Corneal deposits • Dry eye	Observational study in which 38 flecainide medicated patients were examined.
2001 Fraunfelder[45]	Case series of spontaneous reports	Isotretinoin	• Many ADRs: abnormal meibomian glands, blepharoconjunctivitis, corneal opacities, decreased vision, keratitis, ...	Analysis of 1741 spontaneous reports with possible ocular ADRs to isotretinoin
2002 Ikaheimo[46]	Observational cross-sectional study	Amiodarone	• Corneal deposits (in 100% of the patients) • Anterior subcapsular lens deposit (22.2%) • Dry eyes (9.1%)	Observational study in which 22 patients with long term amiodarone were studied
2003 Fraun-Felder[18]	Narrative review	Several	• **Amiodarone**: cornea verticillata, periocular staining, optic neuropathy • **Cetirizine**: mydriasis, oculogyric crisis... • **Hydroxychloroquine**: corneal deposits, epiphora, extraocular paresis, ptosis • **Isotretinoin**: conjunctitivis, corneal deposits, acute myopia, optic neuritis • **Biphosphonates**: episcleritis, conjunctivitis, nerve palsy,... • **Sildenafil**: dischromatopsia, blurred vision • **Topiramate**: acute glaucoma, acute myopia, ocular pain, uveitis,...	A narrative review was performed of ocular ADRs, without systematic study search but with systematic WHO causality assessment whenever possible. Offers good guidelines and clinical implications for each drug.
2004 Fraun-Felder[47]	Retrospective series of reports	Several	• **Biphosphonates**: conjunctivitis, uveitis, blurred vision, scleritis • **Cetirizine**: blurred vision, keratoconjunctivitis sicca, oculogyric crisis • **Isotretinoin**: blurred vision • **Topiramate**: acute glaucoma, acute	A large retrospective series of spontaneous reports of ocular ADRs to different systemic drugs. WHO's definition of ADR and WHO's causality assessment were performed.

			myopia, periorbital edema, scleritis	
2006 Fraun-Felder[48]	Letter with retrospective reports of spontaneous reports of ocular ADRs	Cyclooxygenase-2 Inhibitors	Blurry vision and conjunctivitis were the most reported ADRs	Letter with large series of spontaneous reports (1006) of ocular ADRs to cyclooxygenase-2 Inhibitors (238 reports of blurry vision and 71 of conjunctivitis from celecoxib).
2007 Santaella[49]	Narrative review	Several	Several drugs were assessed, such as: pamidronate, alendronate, risedronate, topiramate	Narrative review of several retrospective case series and reports of ocular ADRs to specific systemic drugs.
2007 Sowka[50]	Case report	Sildenafil	Optic atrophy after the use of sildenafil in a 68-year old man.	Case report with a follow-up of 4 months. No causality assessment of ADR nor WHO's definition of ADR was used.
2008 Mandal[51]	Two case reports	Topiramate, >6 months, 100-150mg/day	Defects in visual field (case 1-quadrantic defects, case 2-arcuate defects)	Two case reports of visual field alterations induced by topiramate, (Naranjo's CA was performed).
2009 Bell[52]	Retrospective study	Tamsulosin	Intra-operatory floppy iris (IFIS) and related surgical outcomes	Retrospective cohort study of 96128 patients: tamsulosine was associated with IFIS and intraoperatory complications
2009 Cordel[53]	Trial	Sildenafil and tadalafil	Electroretinography (ERG) responses were the same for placebo, sildenafil and tadalafil.	Subjects were randomized to use of a placebo (n=82), tadalafil (n=85) or sildenafil (n=77) daily for 6 months.
2009 El-Domyati[54]	Case report	Sildenafil	A 48-year-old nonsmoker patient suffered from nonarteritic ischemic optic neuropathy. "Several weeks later", the visual acuity gradually improved	Case report. Causality assessment of WHO was not performed. Follow-up of "several weeks later", not specified.
2010 Richa[55]	Narrative review	Psychotropics	• Phenothiazines, lithium: keratoconjunctivitis • Chlorpromazine: periocular pigmentation • Tricyclic antidepressants, topiramate: uveitis • TCAs, typical antipsychotics, selective serotonin reuptake inhibitors: mydriasis	A narrative review was performed with several psychotropic drugs
2010 Al-Hussaini[56]	Comprehensive narrative review	Alpha-Blockers	Intra-operative Floppy Iris Syndrome (IFIS). "There is no evidence to support alpha-blocker discontinuation prior to surgery."	Review about IFIS and drugs.
2011 Lebreton[57]	Narrative review with systematic search	Corticosteroids	• Ocular hypertension • Cataract (posterior subcapsular) • Central Serous Chorioretinopathy • Ptosis • Exophthalmia	A narrative review was performed of ophthalmic ADRs of corticosteroids
2011 Azzouni[58]	Systematic review	Sildenafil	Anterior and posterior nonarteritic ischemic optic neuropathy, central retinal vein occlusion, cilio-retinal artery occlusion, acute angle closure glaucoma and optic atrophy after sildenafil use.	Systematic review of ocular ADRs by sildenafil. WHO's causality assessment was performed and of National Registry of Drug-Induced Ocular Side Effects.
2012 Seitz[59]	Case-crossover study	Antidepressants	Acute angle-closure glaucoma (AACG) (odds ratio for any antidepressant exposure in the period immediately preceding AACG was 1.62, 95% confidence interval of 1.16-2.26).	Authors searched acute angle - closure glaucoma, and investigated whether they had an exposure to antidepressants previously, using administrative databases.
2012 Saint-Jean[60]	Case series	Inhibitor of epidermal growth factor receptor (EGFR)	Multiple epithelial defects, corneal melting, ectropion and corneal perforation (requiring a penetrating keratoplasty).	Retrospective case series of 10 patients with ocular ADRs. Definition of ADR was not used.
2012 Neudorfer[61]	Retrospective study of outcomes	Isotretinoin	An association was found between isotretinoin and conjunctivitis, hordeolum, chalazion, blepharitis, eye pain, and dry eye.	Retrospective study with medical databases to identify ADRs in patients using isotretinoin.

Table 1. Included studies in this systematic review. *Ophthalmic ADRs will be described with further detail in table 2.

Therapeutic group	Drug(s) responsible(s)	Description of ocular ADR - Patient (P), ocular segment/complaints (O) - Complementary examination (C) - Reversibility of ADR (R), follow-up time (F)	Classification of ADR - Rawlin's type A/B - Severity assessment (SA); causality assessment (CA)	- Reporting studies - Study's level of evidence (Oxford classification[62])
Acne treating agents	Isotretinoin	*Certain ADRs*: **pseudotumour cerebri, meibomian gland alterations, blepharoconjunctivitis, keratitis, myopia, corneal opacities, ocular discomfort, dry eye, photophobia, decreased vision, and teratogenic ocular abnormalities.** (Many other ADRs were reported). A recent study[61] identified a hazard ratio of 1.70 ($p<0.05$) for ocular ADRs after isotretinoin.	- Type A and B - With CA (WHO's)	Narrative review[18] and case series[45] (level 4) Retrospective study using medical databases[61] (level 2c)
Anti-allergic	Anti-histamines: cetirizine	**Pupillary changes, anisocoria, decreased accommodation** and **blurred vision. Dry eye**[47] **Oculogyric crisis**[18]: "eyes and lids are tonically elevated and the neck is hyperextended, usually without visual complaints". It is a *certain ADR*[18].	- Type B: all except oculogyric crisis (A). - WHO's causality assessment (CA) was performed[18].	Narrative reviews[18,47] (level 4)
Anti-arrhythmics	Flecainide	**Corneal deposits:** 14.5% **Dry eye:** 10.5% - 13 to 132 months of follow-up	- Type A - No CA nor SA	- Cross-sectional study[44] - Level 2c
	Amiodarone	**Corneal deposits**: 100% of the patients[32,46] Anterior subcapsular **lens deposits**[46]: 22% **Dry eye**[46]: 9% **Amiodarone-optic neuropathy**[18]: more insidious in onset and resolution, more bilateral, less involvement in visual acuity compared to non-arteritic ischaemic neuropathy. **Other**[47]**:** Photosensitivity, periocular skin pigmentation, blepharoconjunctivitis, thyroid eye disease, loss of eyelashes, pseudotumor cerebri. - 3 to 131 months of follow-up in a prospective study[46] *Certain ADRs*[18]: photosensitivity, corneal deposits, visual changes, skin pigmentation, blepharoconjunctivitis, thyroid eye disease.	- Type A: dry eye, corneal and lens deposits. Rest: type B. - WHO causality[18]	- Cross-sectional study[46] (level 2c) and narrative reviews[18,32,46] (level 4)
Anticonvulsivants	- Carbamazepine (CB) - Phenytoin(PH) - Phenobarbital(PB) and other barbiturates	**Diplopia:** caused by CB in 0.2-4% of patients[36] (if CB+ other anticonvulsivants, frequency can rise to 88%). Diplopia can be reversible with dose reduction[36]. **Nystagmus:** in 75% of patients with CB+PH[36]. Also reported after primidone and PH. **Decreased ocular movements:** by CB and PB[36] **Ophthalmoplegia:** by PB and PH **Oculogyric crisis:** by CB (in a 8-y., reversible[36]) **Blurred vision:** CB[36]; **Mydriasis**: PH[36] **Disorders of convergence, miosis:** barbiturates[36] **Papilledema:** CB[36] (C, F: not specified in any study)	- All Rawlin's type B (although diplopia may resolve with dose reduction[38]), except: Type A: decreased ocular movements, mydriasis, changes in convergence - No study with SA nor CA	- Narrative review based on case reports[36] - All studies Level 4
Antidepressants and antipsicotics	- Phenotiazine (PT) - Thioridazine - Tricyclic antidepressants (TA) - Lithium - Chlorpromazine (CP) - Monoamine oxidase inhibitors (MAOIs) - Risperidone	**Corneal and lens deposits:** by PT, CP[38], levopromazine; these deposits usually do not interfere with visual acuity **Keratopathy:** Corneal edema by PT (reversible if stopped), epitelial keratopathy by CP[38] (visual acuity remains good, may be reversible if CP is stopped) **Pigmentary retinopathy**[55]**:** by thioridazine (more frequent in high dose, may be irreversible); rarely also by CP and trifluoperazine[38] **Papilledema, exophthalmia:** lithium[38] **Alteration of saccadic eye movements:** risperidone[38,40] **Angle-closure glaucoma:** by TA, in susceptible patients with shallow anterior chamber[59,63] **Decreased accommodation:** TA, MAOIs (C, F, frequency: not specified)	- Usually type B (decreased accomodation is type A) - Na CA nor SA was performed	- Narrative reviews of case series of several psychiatric drugs[38,55] - Prospective study of risperidone[40] - Case crossover study[59] - Level 4 (low evidence) for the narrative reviews[38,55], level 2c for case crossover[59] and 2b for the prospective study[40]
Anti-erectile disfunction agents	Sildenafil	*Certain ADRs*[18,47]: **dyschromatopsia** (objects appear more blue/green), **blurred vision**, **changes in light perception**, **electrorretinogram changes, conjunctival hyperemia** and **photophobia**. Case report[50]: optic atrophy (without CA). Trial[53]: no changes in electroretinography responses for placebo, sildenafil and tadalafil (no ADR). Others[58]: Anterior and posterior nonarteritic ischemic optic neuropathy, central retinal vein occlusion, cilio-retinal artery occlusion, acute angle closure glaucoma.	- Type A and B - With CA: WHO's[18,47] and Naranjo's[58] - Without CA nor SA[50]	Narrative reviews[18,47], systematic review of case reports[58] and case report[50] (level 4) Trial[53] (level 1b)
Anti-inflammatory drugs	Cyclooxygenase-2 Inhibitors	**Blurry vision and conjunctivitis** by rofecoxib, celecoxib and valdecoxib (positive dechallenge and rechallenge tests)	- Type B - With CA	Retrospective series of spontaneous reports[48] (level 4)

	Corticosteroids	**Ocular hypertension**: Odds ratio 1.41 (CI95% 1.2-1.6)[64] Glaucoma reportedly in up to 30% of patients[32] **Cataract** (posterior subcapsular): 4.7%-15.3%[65,32] **Central serous chorioretinopathy**: OR 37(CI95% 6-222)[57] Others: **ptosis, exophthalmia** (6-8%[57])**, viral retinitis, delay in corneal cicatrization**	- Type A: cataract - Type B: other ADRs - Without CA nor SA	Narrative reviews[32,57] (level 4) Case-control studies[64,65] (level 3b)
Benign prostatic hyperplasia drugs	Alpha-blockers (e.g. tamsulosin)	More post-operatory complications (in 14 days) in patients with tamsulosine[52]: intra-operatory floppy iris Intra-operative Floppy Iris Syndrome (**IFIS**). IFIS severity is related with number of the following criteria: • iris billows with intraocular irrigation currents • iris prolapse tendency • intraoperatory pupilary constriction	- Without CA - With SA	Retrospective study[52] of 96128 patients(level 2b) Narrative review with systematic search[56]
Biphosphonates	Pamidronate Risedronate Alendronic acid Zolendronate Risedronate sodium Etidronate dissodium	**Anterior uveitis:** uni or bilateral, 24h to 17 days after medication[37], mild to severe (2 hospitalizations) **Scleritis, episcleritis:** unilateral, in 1-6 days. **Conjunctivitis:** mild, in 1-48h. **Nerve palsy, retrobulbar neuritis**, **yellow vision, blurred vision** C, F, frequency: not specified. Causality assessment[18,47]: *Certain ADR*: blurred vision, ocular irritation, conjunctivitis, pain, epiphora, photophobia, anterior uveitis, anterior scleritis, episcleritis, orbital edema. *Possible*: retrobulbar neuritis, yellow vision, diplopia, cranial nerve palsy, ptosis, visual hallucinations.	- Type B - No CA[37], but rechallenge was performed in 5 patients with uveitis (4 positive rechallenge tests) - With CA[18] performed in a narrative review	- Retrospective series of spontaneous case reports[37] and narrative reviews[18,47] - Level 4
Drugs used in heart failure	Digoxin	- 36 year-old female **Dischromatopsia + scintillating visual field** (VF) alterations, 3 months after administration of digoxin Colour test FM-100: defect on blue colour. - Reversibility, follow-up: not specified	- Rawlin's: B/idiosyncratic ADR - No SA - No CA	- Case report[34] - Level 4 (low evidence). Many other studies not included because toxic digoxin levels
Drugs used in neoplastic disorders	Imatinib	**Periorbital edema** (after CA, *certain ADR)*. **Epiphora**(*probable ADR)* Other possible ADRs: **extraocular muscle paresis, ptosis and blepharoconjunctivitis.**	- Type A: periorbital edema. Rest: type B. - With CA (WHO's)	Narrative review[18] (level 4)
	Inhibitor of epidermal growth factor receptor (EGFR)	**Multiple epithelial defects** (in 10 eyes of all cases), **corneal melting** (in 3 eyes of 2 patients), lower lid **ectropion** (2 eyes of 1 patient) and **corneal perforation** requiring a penetrating keratoplasty (in 2 eyes of 2 patients). Variable follow-ups (all > 1month).	- Type B - No CA nor SA	Retrospective series of spontaneous reports[60] (level 4)
Drugs used in Rheumatology	Chloroquine Hydroxychloroquine	**Corneal deposits, epiphora, ophthalmoplegia, ptosis** **Maculopathy:** dramatic retinopathy with macular atrophy in a bull's-eye pattern. No frequency is reported but: "approximately one million people have used hydroxychloroquine, with only 20 cases of retinal toxicity in the low dose range (< 6.5 mg/kg/day)"[18] Baseline and anual ophthalmic examinations are recommended with: visual acuity, amsler's grid, colour test, and ideally fundus photograph and visual field.	- Type A: maculopathy (related to cumulative dose), corneal deposits - Type B: ophthalmoplegia, ptosis - With CA (WHO)[18] and without[32]	Narrative reviews[18,32] (level 4)
Hormone-related therapy	Oral contraceptives	**Retinal hemorrhage or emboli, Macular edema, Papillary edema, Retrobulbar optic neuropathy** - Patient: not specified - Ocular segment: posterior (retinal alterations and papillary edema, vascular changes) - Complementary examination: angiography, CT scan - Follow-up: variable (case reports)	- Rawlin's type B - No SA - No CA	- Narrative review[35] based on few case reports (low evidence) - Level 4
	Leuprolide	**Blurred vision:** duration between 1h and 15 days, may be associated with headaches or dizziness. **Other:** papilledema, ocular pain, "ocular vascular accidents"	- Type B - No CA nor SA	- Series of spontaneous case reports[9] - Level 4
	Tamoxifen	**Crystallin retinopathy**: in the macula, may be associated with macular edema **Keratopathy** with whorl-like opacities **Colour vision** defects **Foveal disfunction** with ERG changes	- Usually type B - No CA nor SA[41] - CA(WHO causality)[47]	- Narrative review[41,47] - Level 4
	Doxorrubicin	Case 1: **iritis, conjunctivitis** Case 2: **periorbital edema** Case 3: **keratitis** Case 4: **optic neuropathy** (F, C, follow-up: not reported)	- Type B - No CA nor SA	- Case series of 4 cases[33] (level 4)
Lipid lowering agents	Niacin	**Dry eye** (Fisher exact test p=0.011), **Blurred vision**(p=0.0011) **Diplopia**(p=0.5, non statistically significant)	- Type B - No CA nor SA	- Case-control study[39] - Level 3b

		Cystoid maculopathy (2 cases)		
Migraine drugs	Cyproheptadine, pizotyline, amitriptiline, propranolol, timolol, clonidine, flunarizine	**Dry eye:** all **Diplopia:** cyproheptadine, pizotyline, amytriptiline **Mydriasis:** cyproheptadine, pizotyline, amytriptiline **Decrease in accommodation:** propranolol, timolol **Changes in intraocular pressure:** all	- Type A - No SA nor CA	- Narrative reviews[43,18] - Level 4
	Topiramate	*Certain ADRs by topiramate*: **acute angle closure glaucoma** (usually bilateral, in 1-14 days, suprachoroidal effusion), **decreased vision, headaches, hyperemia, mydriasis, uveitis, visual field defects, myopia.** *Probable ADRs by topiramate*: **blepharospasm** and **oculogyric crisis**. Case reports of others ADRs, as visual field defects[51]	- CA performed by Fraunfelder[18]	- Narrative reviews[18,51] - Level 4
Vaccines	Influenza vaccine	Case1: 41y, man, reversible **anterior uveitis** Case 2: 72 y, woman, reactivation of **herpetic keratitis** Case 3: 74 y, man, **left keratoplasty rejection**	- Type B - No CA nor SA were performed	- Letter with case reports[42] - Level 4

Table 2. Summary of ophthalmic adverse drug reactions.

APPENDIX 6

Ophthalmic adverse drug reactions provoked by statins

Protocol information

Authors

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Citation example: Miguel AIM, Henriques F, Azevedo LF, Pereira AC. Ophthalmic adverse drug reactions provoked by statins [Protocol]. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Contact person

Ana IM Miguel

Dates

Assessed as Up-to-date:	
Date of Search:	
Next Stage Expected:	31 January 2013
Protocol First Published:	Not specified
Review First Published:	Not specified
Last Citation Issue:	Not specified

What's new

Date / Event	Description

History

Date / Event	Description

Background

Description of the condition

Adverse drug reactions (ADRs) are frequent, important, expensive and can be fatal (a study estimated that they are between the fourth and the sixth causes of death in the United States (Lazarou 1998). More recent estimates report that ADRs may occur in a mean of 16.88% of patients during hospitalization (CI95%:13.56-20.21) (Miguel 2012) and that they are associated with an overall median of 5.3% of hospital admissions (interquartile range 2.7-9.0%) (Kongkaew 2008).

However, Ophthalmology represents a challenge in Pharmacovigilance (Fraunfelder 2007). Several ophthalmic ADRs provoked by systemic drugs are known by spontaneous reporting, without systematic assessment nor definitive evidence. An ophthalmic ADR can affect every structure in the eye (Fraunfelder 2007), but some systemic drugs tend to provoke specific ophthalmic ADRs, namely amiodarone which frequently provokes cornea verticillatta (Hollander 2004) and rarely provokes (but with potential for irreversible

blindness) optic neuropathy (Carelli 2002).

Statins are widely used for the treatment of dyslipidemia and cardiovascular pathologies (Taylor 2011). They provoke general ADRs that are well documented, such as myopathy, liver transaminases elevation and renal failure (Andrejak 2003). On the other hand, ophthalmic ADRs provoked by statins have been reported by some authors (Hermans 2011), but lack a systematic review. Specific types of ADRs that were reported to occur after statin use include cataract formation (which is controversial, with some studies reporting an increase in the incidence of cataract (Hippisley-Cox 2010) and others reporting a decrease (Klein 2006)). Other ADRs that have been reported are: dry eye (Smidt 2011), diplopia (Fraunfelder 2008), ptosis (Fraunfelder 2008, Ertas 2006) and ophthalmoplegia (Fraunfelder 2008).

On the other hand, statins may have a protective role also in the delay of vitreous haemorrhage in diabetic patients (Banerjee 2004) and in the development of age-related maculopathy (McGwin 2003).

Description of the intervention

We will consider the following definitions:

***Adverse drug reaction (ADR)**:* “any noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy”, according to WHO’s definition (WHO 2005).

Statins (or **HMG-CoA reductase inhibitors**) are a class of drugs used to lower cholesterol levels. They inhibit the enzyme HMG-CoA reductase, which plays a central role in the production of cholesterol in the liver. They are widely used as lipid-lowering agents (Taylor 2011).

We will search ophthalmic adverse drug reactions provoked by statins systemically administered, in the correct dose, administration and indication.

How the intervention might work

The specific ocular anatomy of the eye may facilitate the occurrence of ADRs. After a drug (namely a statin) is administered systemically, it can reach ocular tissues through uveal or retinal circulations, and the fenestrated endothelium may allow the drug to pass through ocular barriers and to accumulate in ocular structures such as the lens, cornea, and trabecular meshwork (Wren 2000). This may cause a pathological alteration of ocular structure or function, provoking an ophthalmic ADR. Nevertheless, there is controversy regarding statins: some state that its antioxidative and antiinflammatory power may decrease the risk of cataract formation (Klein 2006), while others report an increase in the incidence of cataracts (Collins 2012, Hippisley-Cox 2010) and others report no association (Hermans 2011). Statins have been found inside the lens (Grosse 2004), and therefore may alter the lens fiber functioning, disrupting the delicate lens metabolism and accelerating cataract formation. Also, the lens membrane contains cholesterol, therefore, statins can induce cataract formation because they may reduce lens cholesterol synthesis (Cenedella 1996).

Why it is important to do this review

The detection and prevention of ADRs is of increasing importance in Medicine. In Ophthalmology, there are several isolate reports of ophthalmic ADRs provoked by systemic drugs, but few specific systematic reviews, reducing evidence and increasing doubt. Statins are widely used and may provoke ophthalmic ADRs, such as the reported increase in cataratacts. It is important to systematically review these reports and to identify other ophthalmic ADRs provoked by this drug. On the other hand, if there is a protective effect in cataract formation, it is crucial to confirm it, since many studies have tried but failed to identify a drug that can offer protection against cataract formation, such as was tried with vitamin E (McNeil 2004) and with other micronutrients (Sackett 2002). It is also important to investigate whether statins have a protective role in ocular pathologies, such as vitreous haemorrhage in diabetic patients and in age-related maculopathy.

Objectives

To determine whether statins provoke an increased incidence of cataratacts, myositis of ocular muscles, and to identify other ophthalmic ADRs provoked by statins. To classify the probability and the causality of each of these ophthalmic ADRs, according to the specific causality classification of WHO (WHO 2005). To investigate the clinical impact in each of the ADRs found, namely: visual acuity, symptoms, quality of life, need of any therapy or procedure, and improvement (whether spontaneous improvement, improvement after suspension of the drug or improvement after therapies/procedures). To perform a risk of bias assessment for each of the included studies.

Methods

Criteria for considering studies for this review

Types of studies

- We will include randomized controlled trials (RCTs) for this review preferably. However, since ophthalmic adverse drug reactions is a particular theme probably with few trials, we will consider also different types of studies, which will be analyzed separately according to study type and added only if they add new evidence. Clarifying, we will search:

First - randomized controlled trials (in which ophthalmic ADRs to statins are searched)

Second - prospective observational studies (searching for ophthalmic ADRs to statins)

Third (IF no evidence is found in first and second) - observational case-control studies and cross-sectional studies that searched ophthalmic ADRs to statins

Fourth (IF no evidence is found in the above search) - case series, case reports and letters (if they include new evidence of new ophthalmic ADRs not detected in the above search).

This phased search is proposed by us as an adapted search methodology to this particular theme, in order to increase sensibility and detection of ophthalmic ADRs.

- Additionally to including different types of studies, we will include studies with different languages (English, Portuguese, Spanish, French, German), any country, any ward. We will only include studies after WHO’s definition of ADR of 1972. We will do so to have a more thorough and complete literature search and to have the opportunity to analyze them as subgroups and identify sources of heterogeneity.

Types of participants

Patients taking statins, that have ophthalmic symptoms or pathologies, presumably due to these drugs.

Indications for statins' use will include: dyslipidemia and other cardiovascular pathologies.

We will exclude errors in prescribing and administration of statins. We will also exclude patients which already have risk factors for the presumable ophthalmic ADR (for example, if the presumable ADR is cataract formation, we will exclude studies concerning patients already with cataratacts)

We will not exclude age, gender, ethnicity nor country.

Types of interventions

Systemic administration of statins. We will include all types of statins, namely: Atorvastatin; Cerivastatin; Fluvastatin; Lovastatin; Mevastatin; Pitavastatin; Pravastatin; Rosuvastatin; Simvastatin.

We will also study associations in which there is a statin, such as: Simvastatin+Ezetimibe; Lovastatin+Niacin extended-release; Atorvastatin+Amlodipine Besylate; Simvastatin+Niacin extended-release.

Types of outcome measures

Primary outcomes

Primary outcomes will be the types of ophthalmic ADRs presumably provoked by statins.

We will apply assessments and classifications for each ADR found in each study, namely:

- Study types in which the ophthalmic ADR was reported

- WHO causality assessment of ADRs (appendix 1) (WHO 2005)

- Classification of type of ADR according to Rawlin's (Rawlin 1977)

- Schumok's preventability assessment of ADR (Schumok 1992)

- Classification of severity of ADR (Hartwig 1992)

Secondary outcomes

Secondary outcomes will include, for each ophthalmic ADR found:

-visual acuity at presentation

-ophthalmic symptoms,

-quality of life,

-need of any therapy or procedure, and

-improvement at 6 months and at 12 months or at available/reported follow-up (we will register whether this improvement is spontaneous, or after suspension of the drug or even after therapies/procedures).

-Risk of bias assessment for each study will also be a secondary outcome.

Search methods for identification of studies

Electronic searches

We intend to search several databases:

- Cochrane Central Register of Controlled Trials and The Cochrane Library)

- MEDLINE (search strategy in appendix 2)

- SCOPUS

- EBSCO

- ISI web of knowledge, ISI Conference Proceedings

- International Pharmaceutical Abstracts

- EMBASE

- LILACS

- www.controlled-trials.com and www.clinicaltrial.gov

- Google scholar

Searching other resources

- Emails and letters sent to experts (namely Fraunfelder)

- Grey literature and unpublished studies as suggested or reported by experts

- Manual search of journals of Ophthalmology

- Search of references of included studies

- Search of references of general systematic or narrative reviews about ophthalmic ADRs, if they include information about ADRs provoked by statins

Data collection and analysis

Selection of studies

Two independent reviewers, AM and FH, will first examine each title and abstract to exclude obviously irrelevant reports. Disagreements will be solved by consensus, recorded, and analyzed using kappa statistics. If doubt remains after consensus, full-text of the articles will be obtained for further analysis.

Data extraction and management

Two independent reviewers, AM and FH, will examine full-text of articles to determine eligibility according to inclusion criteria.

If a study is excluded, the reviewers will fill a form with reasons for exclusion.

If a study is included, the reviewers will fill a form (previously build for this review: appendix 2) with: study type, summary of study, demographic data, number of patients assessed per study, dose and duration of statin therapeutics, name of the statin used, indication for statin, type and frequency of each ophthalmic ADR, baseline distance visual acuity (converted to LogMAR scale), patient symptoms, biomicroscopy findings, complementary examination performed, all diagnoses, all drugs administered, causality assessment (if performed by authors; if not, it will be performed by reviewers whenever possible), treatments performed (if any), distance visual acuity (logMAR) at 6 and 12 months after presentation (and all findings reported during follow-up, which will be registered for each study).

If a study lacks information for assessment, authors of the study will be contacted for further clarification. Disagreements will be solved by consensus and recorded for analysis using kappa statistics at this point; if doubt remains after consensus, a third author (LA) will decide. A pilot test will be performed to evaluate the selection procedure and criteria on a sample of 5 random reports, to refine criteria and train reviewers.

Assessment of risk of bias in included studies

Two independent reviewers will assess risk of bias in included studies, using a standardized form to evaluate the methodological quality of included studies, which will include: complete description of study design, verification if all parts of study were prospective, number of hospitals in which study occurred, number of patients, adequate selection criteria, presentation of a definition of ADR, rationale for study size, causality assessment of ADR, avoidability assessment of ADR, description of all statistical methods, characterization of study participants and of number of participants at each stage, visual acuity assessment at presentation, at 6 months and at 12 months, description of methods to prevent information and selection bias, intensive monitoring for the detection of ophthalmic ADR, description of methods to avoid other bias, presentation of complete summary measures.

Disagreements will be solved by consensus. Studies will be divided in low risk of bias (five or less parameters

with medium, unclear, or high risk of bias), medium risk (six to nine) and high risk (ten or more parameters evaluated as medium, unclear, or high risk of bias). This evaluation will follow Cochrane's guidelines and allow us to build a Risk of Bias Summary and Risk of Bias Graph.

Measures of treatment effect

Chi-square test will be performed for categorical variables, Student’s t-test for normally distributed continuous variables, and Mann–Whitney or Kruskal–Wallis when dealing with variables without normal distribution, using SPSS v20. Excel will be used for simple calculations, such as incidence and standard error calculations. Quality evaluation graphs, heterogeneity analysis, subgroup analysis, and random effects meta-analysis will be performed using Review Manager - version 5.0. The a priori level of significance for all hypothesis tests will be $p<0.05$.

Unit of analysis issues

We will assess whether original studies use patients, eyes or other unit of randomization in each case.

Dealing with missing data

Intention to treat analysis, contacting authors for further information.

Assessment of heterogeneity

Heterogeneity is expected, considering the theme and the scarce and heterogeneous original studies. Our objective is to obtain and summarize evidence about ophthalmic ADRs provoked by statins, raising Ophthalmologists' attention about this issue (and therefore, improving quality of future publications). Consequently, we believe that this systematic review will be useful even if significant heterogeneity is found. We will use the I2 statistic, the Q test and the forest plots to identify statistical heterogeneity. We will review original studies thoroughly to identify sources of methodological heterogeneity. Subgroup analysis will be performed, based on: study type, ophthalmic ADR type, location, type of statins and indications for statins treatment.

Assessment of reporting biases

Risk of bias evaluation will be extremely important in the assessment of reporting biases, as well as type of study and description of the study methodology.

For trials, we will assess sequence generation, allocation concealment, masking of participants and outcome assessors, incomplete outcome data, selective outcome reporting and other potential sources of bias. For other studies (and for trials), we will register: complete description of study design, verification if all parts of study were prospective, number of hospitals in which study occurred, number of patients, adequate selection criteria, presentation of a definition of ADR, rationale for study size, causality assessment of ADR, avoidability assessment of ADR, description of all statistical methods, characterization of study participants and of number of participants at each stage, visual acuity assessment at presentation, at 6 months and at 12 months, description of methods to prevent information and selection bias, description of methods to avoid other bias, presentation of complete summary measures.

We will build a funnel plot for the detection of publication bias (which we will try to avoid by manually searching studies, by searching grey literature and by emailing experts requesting unpublished studies with information on ophthalmic ADRs provoked by statins).

Data synthesis

If we have enough data to perform quantitative review, we will perform meta-analysis with a random-effects model. If not, we will perform a narrative analysis and summary of the available evidence.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis will be performed, based on: study type, ophthalmic ADR type, location, type of statins and indications for treatment with statins.

Sensitivity analysis

If possible, a sensitivity analysis will be performed with the exclusion of observational studies, of high risk of bias studies and of studies with less than 5 patients (such as case reports or case series). We will also try to identify the individual studies that contribute the most to statistical heterogeneity.

Acknowledgements

Contributions of authors

Planning the review: AM, LA, AP
Designing the review: AM, LA, AP
Co-ordinating the review: AM, AP
Data collection for the review: AM, FH
Designing search strategies: AM, LA
Undertaking searches: AM
Screening search results: AM, FH
Organising retrieval of papers: AM, FH
Screening retrieved papers against inclusion criteria: AM, FH
Appraising quality of papers: AM, FH
Extracting data from papers: AM, FH
Writing to authors of papers for additional information: AM, LA, FH
Providing additional data about papers: AM, LA, FH
Obtaining and screening data on unpublished studies: AM, LA, FH
Data management for the review: AM, FH
Entering data into RevMan: AM, FH
Analysis of data: AM, FH, LA, AP
Interpretation of data: AM, FH, LA, AP
Providing a methodological perspective: AM, LA
Providing a clinical perspective: AM, FH, AP
Providing a policy perspective: AM, AP
Writing the review: AM, LA
Draft of the final review: AM, LA, FH, AP

Declarations of interest

No confict of interest

Published notes

Additional tables

Other references

Additional references

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Figures

Sources of support

Internal sources

- No sources of support provided

External sources

- No sources of support provided

Feedback

Appendices

1 WHO causality assessment

WHO's causality assessment	
1. Certain ADR	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
2. Probable ADR	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition. A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
3. Possible ADR	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear

4. Unlikely ADR	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
5. Conditional / unclassified ADR	A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.
6. Inaccessible / unclassifiable	A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

2 Data extraction form

Nº; I ncluir/ **E** xcluir (se E, justificar)	**Ano; apelido 1ºautor**	**Tipo estudo** (assinalar a opção +correcta)	**Caracterísitcas estudo**	**Sumário do estudo** (se caso, descrever; escrever métodos, exames, resultados, conclusão)	Dose e duraçã o estatin a (em média) Nome e indica ção	**T**ipo (descrever) e **F**requência(em % ou nº) de ***cada*** RAM ocular a tamoxifeno. **S**=sim; **N**=não; **?**=não especifica)	**Caracterísitcas doentes após diagnóstico de RAM ECD:** especificar quais se fizeram e quais alterações (N=normal)	Avalia ção da qualid ade -Ensaio **=> conso rt** -Prosp ect **=>stro be** -Casos **=>pre ench er só esta tabela**	**Notas, dúvidas, frases importa ntes a citar, etc.**
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			Hospital: U£ C£ D£ O£ Serviço de _____		_____	autores? S£ N£ Causalidade WHO revisores: _____		RAM? £ Descreve resultados (sinais &ECD)? £Claro? £Follow-up≥ 6m	
2 I		£Ensaio rand. £Coorte(prospectivo) £Caso-controlo £Transversal £Série de casos £Caso clínico	Duraçã o__ _meses Nºparticipantes _____ Idade média___ País__ ____ Hospital: U£ C£ D£ O£ Serviço de _____		___ meses ___mg (___mg/Kg) Via: oral£ ev£ Dose cumul. _____ Nome _____ _____ _____ _____ _____ Indic_ _____ _____	**1.** Tipo_____ _____ F___. Severo?___ Parou estatin?___ Reversível?____Totalmente rev?____ Causalidade autores? S£ N£ Causalidade WHO revisores: _____ **2.** . Tipo_____ _____ F___. Severo?___ Parou estatin?___ Reversível?____Totalmente rev?____ Causalidade autores? S£ N£ Causalidade WHO revisores: _____	AV OD=____; OE=____ Sx:_____ _____ _____ __ Sinais:____ _____ _____ __ ECD ... Follow-up_ _____ _____ __	£Descrição desenho? £Prospectivo? £Critérios selecção? £Descreve doente(s) £Causalidade RAM? £Caracteriza RAM? £ Descreve resultados (sinais &ECD)? £Claro? £Follow-up≥ 6m	

APPENDIX 7

World Journal of Meta-Analysis

Online Submissions: http://www.wjgnet.com/esps/
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doi:10.13105/wjma.v1.i2.1

World J Meta-Anal 2013 August 26; 1(2): 1-00
ISSN 2308-3840 (online)

META-ANALYSIS

Ophthalmic adverse drug reactions: A nationwide detection using hospital databases

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Received: February 4, 2013 Revised: June 10, 2013
Accepted: July 18, 2013
Published online: August 26, 2013

Abstract

AIM: To detect ophthalmic adverse drug reactions (ADRs), that occurred in Portugal from 2000 to 2009, through the utilization of administrative hospital databases. We also intended to compare the results of this methodology with spontaneous reporting.

METHODS: We conducted a retrospective nationwide study using hospital administrative databases, which included all inpatients and outpatients in all public hospitals in Portugal, from 2000 to 2009. We used International Classification of Diseases - 9th Revision - Clinical Modification (ICD-9-CM) coding data that allowed the detection of ADRs. We used WHO's definition for ADR. We searched all of ICD-9-CM terms in Ophthalmology for codes that included "drug-induced", "iatrogenic", "toxic" and all other that could signal an ADR, such as "362.55 - toxic maculopathy" or "365.03 - steroid responders", and also "E" codes (codes from E930 to E949.9, that exclude intoxications and errors).

RESULTS: From 11944725 hospitalizations or ambulatory episodes within that period of time, we identified 1524 probable ophthalmic ADRs (corresponding to a frequency of 1.28 per 10000 episodes) and an additional 100 possible ophthalmic ADRs. We used only 4 person-hours in the application of this methodology. A total of 113 spontaneous reports arose from ophthalmic ADRs from 2000 to 2009 in Portugal (frequency of 0.095 per 10000 episodes).To our knowledge, this was the first estimate of the frequency of ophthalmic ADRs through the use of databases, and the first nationwide estimate of ophthalmic ADRs, in Portugal. We identified 1524 probable ADRs and 100 possible ADRs.

CONCLUSION: This database methodology adapted for Ophthalmology may represent a new approach for the detection of ophthalmic ADRs, since these codes exist in the ICD-9-CM classification. Its performance was clearly superior to spontaneous reporting.

Key words: Adverse drug reactions; Ophthalmology; Ocular; Databases; Pharmacovigilance

Core tip: We used International Classification of Diseases - 9th Revision - Clinical Modification coding data for the detection of adverse drug reactions (ADRs). From 11944725 episodes, we identified 1524 probable ophthalmic ADRs. 113 spontaneous reports arose from that population. This was the first nationwide study of ophthalmic ADRs and may represent a new Pharmacovigilance approach, with a higher detection than spontaneous reporting.

Miguel A, Henriques F, Marques B, Marques J, Freitas A, Lopes F, Azevedo L, Pereira AC. Ophthalmic adverse drug reactions: A nationwide detection using hospital databases. *World J Meta-Anal* 2013; 1(2): 1-00 Available from: URL: http://www.

wjgnet.com/2308-3840/full/v1/i2/2.htm DOI: http://dx.doi.org/10.13105/wjma.v1.i2.2

INTRODUCTION

Adverse drug reactions (ADRs) are responsible for significant morbidity, mortality and costs in Health Care systems[1]. They may occur in 16.9% of patients during hospitalization (95%CI: 13.5-20.2)[2] and provoke 5.3% of hospital admissions (interquartile range 2.7%-9.0%)[3]. ADRs are a frequent cause of death in developed countries[4]. However, in Ophthalmology the evidence is scarce and lacks systematization[5]. A review about challenges in ADRs in Ophthalmology[5] concluded that there are several areas that can be improved, namely by applying always the definition of ADR of the World Health Organization (WHO)[6], by performing a causality assessment in each ADR (which determines the probability of representing a true ADR; the most utilized causality assessments of ADRs are from WHO[7] and from Naranjo[8]).

The development and validation of new methodologies for an improved detection of ADRs would be another area of improvement[5,9]. There are Pharmacovigilance methodologies[9] used for the detection of ADRs and that can be adapted for detecting ADRs in Ophthalmology, but they may have methodological issues: Spontaneous reporting is the most used (it needs low resources) and is the only Pharmacovigilance method continuously used in the majority of countries, being the main support of WHO International Drug Program. However, it has several limitations, namely, the smallest detection rate of several Pharmacovigilance methods[10], under-reporting[11], heterogeneous report quality[12] and increased risk of bias[12]. Intensive and prospective monitoring are methodologies with good detection rates but too resource-consuming for continuous application[13].

Administrative hospital databases have large clinical information and thus may represent an interesting Pharmacovigilance approach with readily available and cheap information[10]. Some authors have utilized databases[10,14] for the detection of ADRs, taking advantage of the large quantity of clinical information readily available, containing coding data that can be used as an alert for the detection of an ADR, with low relatively low resources required.

Our purpose was to identify and characterize ophthalmic ADRs in a Nationwide study in Portugal, using hospital databases with clinical information.

MATERIALS AND METHODS

Study design

A retrospective study was performed for ADR identification using hospital administrative databases with information from all public hospitals in Portugal, from 2000 to 2009, obtained from our National Health Department (data from the second semester of 2009 was not available). These databases contain anonymized data for patient identification, episode and process number, and also information on age, sex, admission date, discharge date, ward(s), hospital attended (tertiary, university), area of Healthcare, district, outcome (death, discharge, transfer), payment data and International Classification of Diseases - 9th Revision - Clinical Modification (ICD-9-CM)[15] codes for: diagnoses (principal diagnosis, other diagnosis up to 19), procedures (up to 20) and external causes (up to 20). Patient population included all patients hospitalized or admitted for ambulatory care, in all public hospitals in Portugal, from 2000 to 2009 (inpatients and outpatients). All investigations were performed according to the guidelines of the Declaration of Helsinki and Institutional Review Board approval from was obtained.

Definition of ADR

There is some misuse of terms in this matter; therefore we present definitions.

An ADR[6] is: "any noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy". Therefore, to increase specificity, we wanted to assess only ADRs. Adverse drug event is not a synonym of ADR. There are other definitions of ADR, namely from Karch *et al*[16] and from Edwards *et al*[17], but we used the definition of WHO. An adverse event[18] is: "an injury related to medical management (all aspects of care, including diagnosis and treatment, failure to diagnose or treat, and the systems and equipment used to deliver care), in contrast to complications of disease". An adverse drug event[19] is: "An injury related to the use of a drug, although the causality of this relationship may not be proven". These include medication errors (namely the prescription of a wrong dose) and ADRs.We aimed to assess strictly ADRs.

Detection of ADRs

Hospital administrative databases include information of diagnosis. Codes searched for ADR identification were adapted to the specificities of Ophthalmology and resulted from a thorough search of: all terms of ICD-9-CM in Ophthalmology that included "drug-induced", "iatrogenic", "toxic" and all codes that could signal an ADR, such as "362.55 - toxic maculopathy" or "365.03 - steroid responsers", as detailed in the Results Section.

We also performed a search of general ADRs through the use of 'E' codes (ICD-9-CM codes from E930 to E949.9, designed to represent ADRs and already excluding wrong doses, errors and intoxications) to assess if these general ADRs could detect ophthalmic ADRs.

In this study, we performed a query of Ophthalmology in a nationwide study using administrative databases, including inpatients and ambulatory patients. Our main outcome was ADR detection. Secondary outcomes included: type of ADR, age, sex, admission diagnosis, other diagnoses, hospital length-of-stay and year of discharge. We performed WHO's causality assessments of ADRs,

with two independent reviewers. Differences were resolved by consensus. A third review was consulted to help resolved differences. We also registered how many person-hours were spent in the application of this methodology, to estimate cost (resources spent). The number of person-hours refers to the number of hours and number of people used in the application of this methodology; commonly used in the comparison of different Pharmacovigilance methodologies[19]. The number of spontaneous reporting of ADRs in hospitalized patients from 2000 to 2009 was obtained from Portuguese National Authority of Medicines (INFARMED), for comparison[20].

Statistical analysis

Statistical analyses were done using the χ^2 test for categorical variables (or exact Fisher's test whenever possible), Student's *t*-test for normally distributed continuous variables and Mann-Whitney or Kruskal-Wallis for variables without normal distribution, using SPSS v20. The *a priori* level of significance was $P < 0.05$.

RESULTS

Study population

There were 11944725 patients hospitalized or with ambulatory episodes in public hospitals of Portugal, from 2000 to the first semester of 2009.The baseline characteristics of the study population (n = 11944725) are shown in Table 1. The mean age of hospitalized patients was 48 ± 27 years and in 55.2% of episodes the patient was female. We spent only 4 person-hours in the application of this methodology.

From 2000, there was a slight increase in the number of hospitalizations in Portugal. Specific ophthalmic ADRs (n = 1524) were detected through the search of codes that could represent particular ophthalmic ADRs, as shown in Table 2. This corresponds to a frequency of 1.28 ophthalmic ADR per 10000 episodes. Additionally, 100 episodes that could possibly correspond to an ophthalmic ADR were also detected (Table 2). Therefore, a total of 1624 possible ophthalmic ADRs were detected. These possible ADRs included: conjunctival concretions, pigmentations and deposits (which can be caused by drugs such as topical adrenaline[21], but also by other factors, therefore may correspond to an ADR in some cases) and acquired color vision deficiencies (which may be caused by drugs such as sildenafil[22], but have other non related causes).

The search of general ADRs through the use of "E" codes allowed us to identify 116720 ADRs, but only 62 of them corresponded to the ophthalmic ADRs that were identified.

The total number of spontaneous notifications of ADRs in Portugal from 2000 to 2009 was 13562, from which 113 were spontaneous reports specific of ophthalmic ADRs. There were 553 additional spontaneous reports of systemic ADRs that included some ophthalmic manifestations.

Table 1 Socio-demographic characteristics of study population

Characteristic	Value
Number of episodes (inpatient, ambulatory)	11944725
Mean age (yr, mean ± SD)	48 ± 27
Female gender n (%)	6598266 (55.2)
District with higher number of hospitalizations	1st: Lisbon 21.2% 2nd: Oporto 17.2% 3rd: Setubal 7.66%
Mean hospital length-of-stay for inpatients (d, mean ± SD)	7.1 ± 3.21
Number of probable ophthalmic ADRs	1524

ADRs: Adverse drug reactions.

Table 2 Clinical codes searched and respective results in the portuguese database

ICD-9-CM code	Diagnosis	No. of episodes
Specific ophthalmic ADR codes		
362.55	Toxic maculopathy	1388
365.03	Steroid responders	4
365.31, 365.32	Corticosteroid-induced glaucoma	0
364.55	Miotic pupillary cyst (provoked by pilocarpine)	2
364.81	Floppy iris syndrome	2
366.45	Toxic cataract	83
367.89	Other drug-induced disorders of refraction and accommodation, Toxic disorders of refraction and accommodation	25
377.34	Toxic optic neuropathy, Toxic amblyopia	20
Possible signs of ophthalmic ADRs		
366.46	Cataract associated with radiation and other physical influences	10
372.54	Conjunctival concretions	67
372.55	Conjunctival pigmentations, including conjunctival argyrosis	
372.56	Conjunctival deposits	
368.55	Acquired color vision deficiencies	23
368.59	Other color vision deficiencies	
	Sub-Total specific	1524
	Total	1624

ICD-9-CM: Classification of Diseases - 9th Revision - Clinical Modification; ADRs: Adverse drug reactions.

DISCUSSION

To our knowledge, this is the first estimate of the frequency of ophthalmic ADRs through the use of administrative databases, and the first to apply a nationwide estimate of ophthalmic ADRs, in Portugal. We identified 1524 probable ADRs and 100 possible ADRs. This may represent a new approach for the detection of ophthalmic ADRs, since these codes exist in the ICD-9-CM classification.

The strengths of our study include: our comprehensive database, which contains data from all hospitalizations and ambulatory episodes in every public hospital in Portugal within almost a decade, the fact that this is a new methodology to aid ADR detection (until now only case reports and spontaneous reports were available for

ADR detection), and the fact that these codes are widely available and universal, making possible to easily build estimates of ophthalmic ADRs in other countries and other years. In fact, it would be very interesting to see if ophthalmic ADRs in Portugal have the same distribution, frequency and characteristics in comparison with other countries, therefore further studies are necessary.

Limitations of our work are inherent to the use of administrative databases, which may contain incomplete or wrong data and coding bias[23] (in which coders select a different code to increase reimbursement to their hospital). The small number of ADRs found may be considered a limitation, but on the other hand this is a methodology resource-sparing (only 4 person-hours spent in its application), having potential for widespread application in other countries. Also, this method identified 1524 probable ADRs, a much higher number than the number of ophthalmic ADRs found by spontaneous reporting: 113.

We suggest complementing spontaneous reporting with this database methodology to increase detection of ophthalmic ADRs. In fact, the complementary use of several methodologies is defended by several authors[24], in order to enhance ADR detection and increase patient safety. Finally, we believe that after this study, these codes should be applied prospectively in a future study in a nation-wide basis, enabling an expert to confirm each ADR and causing drug, to further complete and validate the data suggested here, and to integrate this method as a Pharmacovigilance methodology.

In conclusion, Ophthalmology represents simultaneously a challenge and an opportunity to identify ADRs. This is the first nationwide estimate of ophthalmic ADRs. Administrative databases are a useful methodology for the detection of ocular ADRs, but require adapted diagnoses codes. They may underestimate the real number of ADRs, but nevertheless they have the potential to complement spontaneous reporting as a methodology for ophthalmic ADR detection, with a higher detection rate.

ACKNOWLEDGMENTS

The authors would like to thank ACSS for providing access to the data, and express gratitude to the statistical support given by the research project HR-QoD - Quality of data (outliers, inconsistencies and errors) in hospital inpatient databases: methods and implications for data modeling, cleansing and analysis (project PTDC/SAU-ESA/75660/2006). The authors would also like to thank the INFARMED, Portuguese National Authority of Medicines and Health Products, for the data kindly provided about spontaneous reporting in Portugal.

COMMENTS

Background

Adverse drug reactions (ADRs) are a frequent cause of death in developed countries. However, in Ophthalmology the evidence is scarce and lacks systematization.

Research frontiers

There are Pharmacovigilance methodologiesused for the detection of ADRs and that can be adapted for detecting ADRs in Ophthalmology, but they may have methodological issues.

Innovations and breakthroughs

This is the first estimate of the frequency of ophthalmic ADRs through the use of administrative databases, and the first to apply a nationwide estimate of ophthalmic ADRs, in Portugal.

Applications

The authors suggest complementing spontaneous reporting with this database methodology to increase detection of ophthalmic ADRs.

Peer review

This is a well written article reporting the adverse effects of ophthalmic drugs. The methods are well described, and the results are easy to understand.

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P- Reviewers Onakpoya I, Saokaew S **S- Editor** Zhai HH
L- Editor A **E- Editor** Zheng XM

APPENDIX 8

Adverse Drug Reactions in Ophthalmology - are they a Myth?

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Abstract: Sometimes ocular (and systemic) therapeutics may cause ocular (and systemic) diseases, namely adverse drug reactions (ADRs). The Journal of Ocular Diseases and Therapeutics is therefore doubly adequate for discussion of the theme of ADRs in Ophthalmology.

Many terms are utilized as synonyms but the correct definition of ADR (according to the World Health Organization, WHO) is: "any noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy".

Ophthalmology is one of the medical specialties in which there is a high difficulty in continuous diagnosis, assessment and treatment. Additionally, the specific and delicate anatomy and physiology of the eye may easily be disrupted by an ADR, with possible irreversible consequences. Ocular ADRs may be frequent (such as *cornea verticillata* caused by amiodarone) or specific. On the other hand, systemic ADRs may occur after ocular treatments (such as hypotension after instillation of a beta-blocker drop).

The timely detection and recognition of ADRs is therefore critical. Several methods exist for the detection of ADRs, but few are specific or apply to ADRs in Ophthalmology. Spontaneous reporting is a low-resource method for detection of ADRs but has flaws, namely under-detection and risk of bias. The literature can be confusing or incomplete, with several case reports and case series about ocular ADRs lacking a causality assessment (such as Naranjo's or WHO's).

In conclusion, ADRs in Ophthalmology are a heterogeneous group of ADRs that lack detection, assessment and systematization. Studies about ADRs should increase their quality for further clarification. Each ophthalmologist should know the specific ocular ADRs to systemic medication, the specific systemic ADRs to ocular medication, and to detect and treat them adequately for good clinical practice.

Keywords: Adverse drug reactions, Pharmacovigilance, Ophthalmology, Clinical practice, Therapeutics, Toxicology, Causality assessment, World Health Organization, Systemic drugs, Ocular Therapy.

INTRODUCTION

The Journal of Ocular Diseases and Therapeutics has an ambitious purpose of equipping professionals with skills to increase the detection of eye diseases and to improve the management of ocular therapeutics into good clinical practice.

These skills are invaluable in the world of adverse drug reactions (ADRs), where many confusions and myths persist.

This manuscript addresses ADRs in Ophthalmology, discusses some of the myths related to ADRs and attempts to clarify them, and provides recommendations to increase the quality in studies about ADRs and to improve recognition and management of ADRs in the clinical context.

ADRS IN OPHTHALMOLOGY

There are three basic types of ADRs in Ophthalmology:

1. Topical ADRs to a Topical Ocular Drug

These ADRs are usually easy to recognize, since the prescribing ophthalmologist is the one who detects these ADRs in the follow-up of the patient. They can be caused either by the drug administered or by its topical conservatives. One example is ocular hyperemia frequently caused by topical prostaglandins for the treatment of glaucoma [1].

2. Systemic ADRs to a Topical Ocular Drug

Topical ocular medications can be absorbed by the ophthalmic mucosa and nasal mucosa [2, 3] and reach levels in the blood enough to cause ADRs. The most common topically administered ocular drugs causing systemic side effects are the epinephrine-like compounds, which can rapidly lead to increased blood pressure and tachycardia [3]. Periocular injection of anesthetics combined with epinephrine can cause the same effects quite rapidly, leading to respiratory collapse and even death [3].

3. Topical/Ocular ADRs to a Systemic Drug

These ADRs may be difficult to diagnose, considering that in this case a general physician

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prescribes a drug, but a different physician usually is required for the diagnosis (an ophthalmologist). Other difficulty is the need of obtaining a complete medical history and registering the countless systemic medications prescribed for each patient.

The correlation of the symptoms and ocular signs of the patient with the suspect of an ADR caused by a particular drug is another difficulty, and confirming the causality of an ADR is by far even more difficult. With all these difficulties, it is not surprising that myths and confusion persist around ADRs, particularly in Ophthalmology.

MYTHS, ADRs AND OPHTHALMOLOGY

1. First Myth: Many Terms are Erroneously Applied as Synonyms of ADRs

To clarify this myth, we present definitions of different drug-related problems.

- An adverse event is [4]: "an injury related to medical management, in contrast to complications of disease". Medical management includes "all aspects of care, including diagnosis and treatment, failure to diagnose or treat, and the systems and equipment used to deliver care" [4].

- Drug-related problems are [5]: “a circumstance that involves a patient’s drug treatment that actually, or potentially, interferes with the achievement of an optimal outcome". They include ADRs.

- An adverse drug event is [6]: “An injury related to the use of a drug, although the causality of this relationship may not be proven”. These events include medication errors (namely the prescription of a wrong dose) and ADRs.

- A medication error is [7]: “Any error in the process of prescribing, dispensing or administering a drug, whether there are adverse consequences or not”.

- An adverse drug reaction (ADR) is: “any noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy”, according to WHO’s definition [8] of 1972. This definition is the most widely used. Karch and Lasagna’s [9] have a definition for ADR which excludes therapeutic failures. An ADR according to Edwards and Aronson [10] is: “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”.

2. Second Myth: ADRs are not Important Nor Frequent

Some years ago, Lazarou and colleagues [11] estimated ADRs to be between the fourth and sixth more frequent causes of death. Although this study was criticized due to heterogeneity [12], it brought attention to the scientific community about the importance of ADRs. The mean frequency of ADRs that occur during hospitalization is estimated to be of 16.88% (95%CI: 13.56–20.21) [13] and the overall median of ADRs associated with hospital admissions is 5.3% (interquartile range 2.7–9.0%) [14].

ADRs are costly, representing US$1.56 billion in direct hospital costs per year (in the US) [15] and US$136.8 billion in indirect costs [16]. In fact, the cost of drug-related problems (including ADRs) is estimated to be higher than the total cost of cardiovascular or diabetes disease [5].

Consequently, ADRs are frequent, expensive and can be fatal, deserving to be studied in order to be detected and prevented.

3. Third Myth: ADRs in Ophthalmology are Not Specific

The theme of ADRs in Ophthalmology presents a challenge in assessment and systematization [17]. ADRs in Ophthalmology can be frequent and specific (and even irreversible), therefore healthcare team members (namely the ophthalmologist, physician, nurse, pharmacist, pharmacologist or other) should have skills for detection of an ADR to a drug in each patient.

The eye benefits of many barriers that limit access of drugs to intraocular structures, namely: tight junctions of the corneal epithelium and endothelium (which limit anterior access to the interior of the eye and belong to the blood-aqueous barrier), the vascular endothelium of the retina (non fenestrated and with tight junctions: inner blood-retinal barrier), tight junctions between the retinal pigment epithelium (with the Bruch's membrane: outer blood-retinal barrier) [2, 18].

Nevertheless, there is a plethora of possible ocular ADRs to ocular and systemic drugs. Fortunately, some systemic drugs tend to provoke specific ocular ADRs, enabling recognition of clinical patterns in specific drugs, namely: amiodarone which frequently provokes cornea verticillatta [19] and rarely provokes the potentially irreversible optic neuropathy [20], floppy iris syndrome caused by tamsulosine [21] and uveitis caused by rifabutin [22], among many others.

4. Fourth Myth: ADRs can Only be Identified by Spontaneous Reports

Many methods exist to aid Pharmacovigilance in the detection and verification of ADRs, but all have their methodological issues [23].

Spontaneous reporting (a health team member reports a presumable ADR) is the most utilized Pharmacovigilance method in Europe [24], however subnotification [25] is a problem. ***Administrative databases*** (which contain large amounts of information with clinical data that can be searched for the identification of an ADR) have been explored for ADR detection [26, 27] and present good detection rates with low resources, enabling nationwide perspectives [27].

Computerized methods are used for automatic alerts of ADRs with good results [28, 29].

Chart review (the revision of charts by an expert) is a reasonable methodology for ADR detection [30], however it is resource and time consuming, such as ***prospective monitoring*** and ***intensive monitoring*** [31] (both are monitoring methodologies performed by experts in a group of patients to detect ADRs) which are too costly to be performed regularly. Other methods exist, namely trials and pharmacogenetics studies.

ADRs that occur in the context of Ophthalmology can be detected through each of the methods above, however spontaneous reporting (and studies such as case reports and case series) are frequently utilized due to practical reasons [17]. It is important to increase the quality of these studies about ADRs to enable the scientific community to decide which conclusions can be drawn about each specific reported or presumable ADR.

INCREASING QUALITY IN STUDIES ABOUT ADRs

A few simple steps can be useful to increase quality in every study about ADRs.

First, I suggest the utilization of a definition of ADR (either WHO's definition of ADR [8], or other definition of ADR) which should have a reference in the study.

Second, a causality assessment (the assessment of the probability of a suspected ADR being a true ADR) is crucial and lacks in many ADR manuscripts. The most important and widely used causality assessments are Naranjo's [32] and WHO's [33], which apply to all ADRs, and are presented in this manuscript.

Third, if possible add further characterization of the ADR: present a classification of ADR according to Rawlins and Thomson's [34], evaluate the predictability of ADRs (using Hartwig's predictability scale, for example [35]), use Schumok and Thornton's preventability criteria [36], among others. Many technological breakthroughs in Ophthalmology allow us to provide an increased depth in the characterization of ocular ADRs with complementary testing and should be used [37].

Finally, many bibliographic or general reviews exist about ocular ADRs, but few attempt to be systematic. I

Table 1: Naranjo's Causality Assessment for ADRs [32]

Naranjo's causality assessment	Yes	No	Don't know
1. Are there previous conclusive reports of this reaction?	+1	0	0
2. Did the adverse event appear after the suspect drug was administered?	+2	-1	0
3. Did the adverse reaction improve when the drug was discontinued?	+1	0	0
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0
5. Are there alternate causes that on their own could have caused the reaction?	-1	+2	0
6. Did the reaction appear when a placebo was given?	-1	+1	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0
8. Was the reaction more severe when the dose was increased or less severe when decreased?	+1	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0
Total score*			

*****Interpretation of the Total Score: a) ≥9: *Highly probable* ADR; b) 5-8: *Probable* ADR; c) 1-4: *Possible* ADR: d) ≤ 0: *Doubtful* ADR.

Table 2: WHO's Causality Assessment for ADRs [33]

WHO's causality assessment	
1. Certain ADR	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
2. Probable ADR	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition. A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
3. Possible ADR	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear
4. Unlikely ADR	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
5. Conditional / unclassified ADR	A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.
6. Inaccessible / unclassifiable	A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

and my co-authors have identified ocular ADRs to systemic drugs that have recent original studies but are currently lacking a specific systematic review, including ocular ADRs from the following drugs: statins (we are performing a systematic review in collaboration with the Cochrane -Eyes and Vision Group), antituberculous agents, angiotensin-converting enzyme inhibitors and cidofovir. These may represent opportunities for a specific systematic review.

CONCLUSION

Confusion and myths about ADRs persist. Future studies about ADRs should: present a definition of ADR, describe a methodology for ADR detection, present standard assessments (causality assessment of Naranjo or WHO, severity assessment, classification of ADR, among others) and should increase their methodological quality.

Although spontaneous reporting is the most widely used method for detecting ADRs, other methods exist for that purpose. All methods have their methodological issues and probably should be used in conjunction to increase ADR detection.

In Ophthalmology, the theme of ADRs deserves clarification and assessment. Ocular ADRs may be frequent, specific, serious or even cause irreversible blindness. Therefore, the detection of ADRs is very important.

Methods of ADR detection should be explored and adapted to the specificity of ocular ADRs.

Additionally, each health care member (ophthalmologist, physician, nurse, pharmacist, pharmacologist or other) should know the specific ocular ADRs to systemic medication, the specific systemic ADRs to ocular medication, and should detect and treat ADRs in Ophthalmology adequately for good clinical practice.

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Received on 21-06-2013 Accepted on 26-06-2013 Published on 16-08-2013

APPENDIX 9

Reações adversas medicamentosas em Oftalmologia

"The remedy often times proves worse than the disease" - William Penn

Introdução

Uma **reação adversa medicamentosa** (RAM) é, segundo a Organização Mundial de Saúde (OMS)[1]:

- Uma resposta *prejudicial e indesejada* a um medicamento, que
- Ocorre com a *dose* habitualmente usada no homem para profilaxia, diagnóstico ou modificação de uma função fisiológica, e em que
- Existe um nexo de *causalidade* entre a ocorrência de RAM/medicamento.

As RAM não devem ser confundidas com outros tipos de eventos adversos, cujas definições apresentamos seguidamente:

- Evento adverso: "qualquer lesão relacionada com o tratamento médico, incluindo todos os aspetos relacionados com os cuidados de saúde"[2]. Esta definição inclui as complicações cirúgicas, erros de medicação e RAMs.
- Evento adverso medicamentoso: "uma lesão relacionada com a utilização de um medicamento, apesar da causalidade desta relação poder não estar provada"[3]. Estes eventos incluem erros de medicação e RAMs.
- Erro de medicação: "qualquer erro no processo de prescrição, dispensa ou administração de um medicamento"[4].

O diagnóstico de uma RAM nem sempre é fácil, e resulta de interacção complexa entre vários factores, como esquematizado na figura 1.

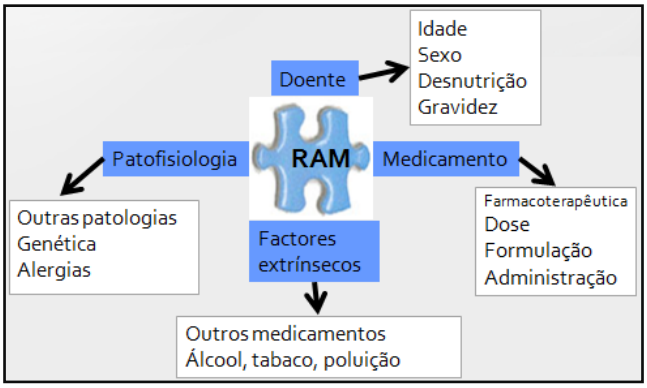

Figura 1: Factores de risco e modificadores de uma reação adversa medicamentosa (RAM).

As reacções adversas medicamentosas (RAMs) são frequentes e importantes. As RAM **gerais** podem ser fatais, estando entre a 4ª e a 6ª causa de morte nos países desenvolvidos[5], e são responsáveis por 15-20% dos gastos hospitalares[6]. Estima-se que cada RAM seja responsável por um custo adicional de 2500 dólares (aproximadamente 1890 euros)[6] e que ocorram em média em 16.88% dos doentes hospitalizados (intervalo de confiança a 95%: 13,56-20,21)[7].

Quanto às RAM **oftalmológicas**, há algumas revisões sistematizadas ou bibliográficas[8-11] mas poucas revisões sistemáticas ou outros estudos que nos levem à frequência e gravidade reais. O conhecimento das RAM oftalmológicas advém frequentemente de notificações espontâneas[10], o que nem sempre permite sistematização ou verificação de causalidade. Todavia, são indubitavelmente importantes e podem ser específicas, pelo que devem ser matéria de estudo e devem pertencer ao conhecimento de todos e de cada oftalmologista.

Pode haver três situações distintas de **RAM em Oftalmologia**:

1. *RAM oculares a medicação sistémica*

- Por exemplo, maculopatia provocada por utilização de tamoxifeno[12].

2. *RAM sistémicas a medicação ocular tópica*

- Por exemplo, 1 gota de atropina numa criança susceptível pode causar rubor, agitação, taquicardia e até convulsões[13]. De fato, a atropina pode ser fatal, na dose de 100mg numa criança (1 simples frasco) - note-se que no caso de 100mg falar-se-ia de uma intoxicação e não de uma RAM (cujo conceito implica dose e administração correta).

3. *RAM oculares a medicação ocular tópica*

- Por exemplo, hiperemia ocular provocada por latanoproste[14], colírio utilizado no tratamento de glaucoma.

As RAM ocorrem frequentemente na *1ª semana*, mas podem ocorrer em meses a anos após a exposição da medicação causadora, nomeadamente:

- Cloroquina e retinopatia[15]
- Ouro e queratopatia
- Tamoxifeno e maculopatia[12]

A maioria felizmente é reversível (algumas RAM são reversíveis mesmo sem a suspensão do fármaco causador), mas há excepções (vide infra).

Este texto não pretende ser exaustivo, mas pretende exemplificar algumas RAM oftalmológicas frequentes ou graves que devemos conhecer.

Exemplos de RAM de acordo com estrutura ocular afectada

Seguem-se alguns exemplos de RAM seguidas de fármacos que frequente ou tipicamente podem causar essas reacções.

Córnea

Apesar de alguns fármacos provocarem depósitos corneanos frequentemente (como a amiodarona, em que um estudo[17] estimou que a percentagem de doentes com depósitos corneanos era de 100% após 2 anos), raramente há diminuição da acuidade visual por esta RAM.

- **Queratite**
  - Fenilbutazona
  - Vacinas
- **Depósitos corneanos** (frequentemente em espiral: *córnea verticillata)*
  - Amiodarona[17]
  - Ciprofloxacina
  - Cloroquina
  - Clorpropamida
  - Clorpromazina (provoca depósitos no estroma e endotélio corneanos, assim como na cápsula anterior do cristalino e até na retina)
  - Clofazimina
  - Indometacina (anti-inflamatório não esteróide)
  - Fenotiazinas (antipsicótico)
  - Vitamina D
  - Sais de ouro[16]: frequentemente pode acumular-se na córnea (denominando-se crisíase) particularmente se a dose cumulativa de 1g for ultrapassada
  - Prata: argirose (ocorrem depósitos na córnea, na membrana de Descemet e na conjuntiva)

Conjuntiva

- **Inflamação e proliferação folicular**
  - Antibióticos
- **Conjuntivite**
  - Barbitúricos
  - Guanetidina e metildopa
  - Metisergida, Fenilbutazona
  - Inibidores da enzima de conversão de angiotensina (também podem provocar angioedema, entre outras RAM)
- **Síndrome de Stevens-Johnson**
  - É uma reação rara (1 por milhão/ano) e frequentemente fatal. Consiste numa reacção de hipersensibilidade tipo III tipo *graft versus host disease*, com deposição imunocomplexos na mucosa superficial, inflamação e degeneração fibrinóide do colagéneo. Causas incluem:
    - Barbitúricos
    - Clorpropamida (antidiabético oral)
    - Sulfonamidas

Sistema lacrimal

São inúmeros os fármacos que podem alterar a produção lacrimal ou as características da lágrima, com sintomas inconvenientes para os doentes. Destacam-se os mais importantes.

- **Aumento do lacrimejo**
  - Agonistas adrenérgicos
  - Agonistas colinérgicos
  - Anti-hipertensores
- **Diminuição da produção lacrimal**
  - Anticolinérgicos
  - Ansiolíticos e antidepressivos (tricíclicos e outros)
  - Anti-histamínicos
  - Análogos da vitamina A
  - Bloqueadores beta

Músculos extraoculares

- **Nistagmo**
  - Sais de ouro
  - Diazepam
  - Cetamina
  - Anticonceptionais orais (ACO)
  - Fenitoína
  - Salicilatos
- **Paralisia de um ou vários músculos**
  - Penicilamina (agente quelante, usado também na doença de Wilson)
  - Fenitoína (antiepiléptico)
  - Clorpropamida (antidiabético oral)
  - Anestésicos e derivados *curare*
- **Ptose**
  - Barbitúricos
  - Penicilamina
  - Guanetidina (antiHTA adrenérgico)

Câmara anterior

- **Aumento da pressão intraocular**
  - Corticosteróides
  - AINEs
  - Anfetaminas
  - Antidepressivos tricíclicos
  - Etambutol (causa um síndrome típico apesar de raro, com *myopic shift* e glaucoma agudo bilateral, devido a efusão uveal)
- **Intraoperative floppy iris syndrome** (figura 2)
  - Tansulosina e outros fármacos utilizados na hiperplasia benigna da próstata

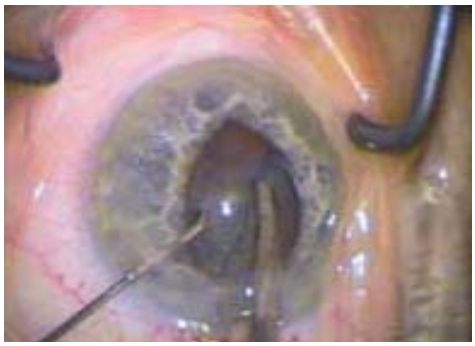

Figura 2: Síndrome de íris flácida (*floppy iris syndrome*).
Trata-se de uma RAM que torna a facoemulsificação mais difícil.

Cristalino

De um modo geral, os fármacos que associados a depósitos corneanos também estão associados a depósitos no cristalino.

- **Catarata ou depósitos de fármaco no cristalino**
  - Corticóides
    - Quer sistémicos, quer tópicos (mais frequentemente nos últimos)
    - Tipicamente deposição a nível subcapsular posterior
    - Apesar de estudos sugerirem que está relacionado com dose e duração, não há dose considerada segura.
  - Lovastatina (particularmente se associada a eritromicina)
    - Está atualmente a decorrer uma revisão sistemática, em associação com a Cochrane Collaboration, que visa determinar se as estatinas aumentam ou diminuem a incidência de cataratas. Os estudos originais atuais estão em conflito, porque uns indicam aumento de risco de cataratas[18], outros indicam diminuição de risco[19] (as estatinas funcionariam assim como fator protetor) e outros não identificaram associação.

– Alopurinol (maior risco se a dose cumulativa for >400g ou se houver mais do que 3anos de exposição)
– Bussulfano (quimioterápico utilizado no tratamento da LMC)
– Haloperidol (antipsicótico)
– Clorpromazina (antipsicótico)
– Sais de ouro (particularmente se exposição > 3 anos)
– Fenotiazinas (depósitos subcapsulares anteriores)

Úvea

- **Uveíte**
  - Antibióticos (rifabutina, sulfonamidas)
    - A rifabutina é utilizada no tratamento de infecções provocadas por Mycobacterium avium em doentes HIV+
    - Pode provocar uveíte anterior aguda grave, tipicamente unilateral e frequentemente com hipópion, que pode ser confundida com endoftalmite.
  - Bifosfonatos (utilizados no tratamento da osteoporose)
  - Dietilcarbamazina (utilizada no tratamento da filariose)
  - Antihipertensores
  - Anticoncepcionais orais
  - Cidofovir
    - Pode ser utilizado no tratamento de retinite por citomegalovírus
    - Pode ocasionar uveíte anterior aguda, frequentemente com vitrite e hipópion. Caracteristicamente tem poucas células na câmara anterior e muita fibrina.
    - Geralmente não é necessário suspender cidofovir, podendo bastar corticoterapia associada a midríase farmacológica para que haja resolução desta RAM.

Nervo ótico

O atingimento do nervo ótico, apesar de ser raro, é de relevância particular porque pode estar associado a perda visual irreversível. Consequentemente, o conhecimento dos fármacos que podem dar RAM relacionadas com o nervo ótico é imperativo para diagnóstico atempado.

- **Atrofia ótica**
  - Etambutol[20]
    - Se administrado numa dose 25mg/Kg, associa-se a atrofia óptica em 6% dos doentes
    - Se a dose for ≥15mg/Kg/dia, aconselha-se avaliação oftalmológica mensal
    - Em doses <15mg/Kg/dia: aconselha-se avaliação oftalmológica semetral ou bianual
  - Barbitúricos
  - Cloranfenicol
  - Iodoquinol (antiprotozoário)
  - Inibidores monoamina-oxídase (iMAO)
  - A atrofia ótica também pode decorrer, por exemplo de glaucoma induzido por corticóides

- **Nevrite óptica**
  - Amiodarona
  - Antibióticos (nomeadamente cloranfenicol)
  - Antituberculosos (rifampicina, isoniazida, etambutol, estreptomicina)
  - Penicilamina
  - Dissulfiram
  - Morfina
  - Vigabatrina

- **Edema do disco óptico**
  - Clorambucil
  - Antibióticos (tetraciclina, ácido nalidíxico)
  - Anticoncepcionais orais (pseudotumor cerebral)
  - Vitamina A

Retina

- **Retinopatia**
  - Digitálicos
  - Cloroquina
    - Pode provocar uma retinopatia (RP) em **olho de boi** (típica, mas não patognomónica), com diferentes estádios[20]:
      1. **Pré-RP** (Acuidade visual (AV) normal, fundoscopia normal, campo visual com escotoma central ou com alterações da grelha de Amsler)
      2. **Precoce** (AV ≈ 6/10, fundoscopia com ilha foveal pigmentada com um anel despigmentado circundante por atrofia do epitélio pigmentar da retina, angiografia permitindo identificar um defeito de janela)
      3. **Moderada**: maculopatia em olho de boi, AV 3/10
      4. **Grave**: atrofia coriorretiniana marcada além da maculopatia em olho de boi
      5. **Terminal**: atrofia coriorretiniana extensa, com visualização dos grandes vasos da coróide.
    - Esta RAM está relacionada com a dose, tendo maior risco a partir das **300g** (dose cumulativa) ou com duração do tratamento superior a 6 anos. Contudo, *não existe dose segura*.
    - Recomenda-se triagem anual a partir de 6 anos de tratamento, com exame oftalmológico, ERG e grelha de Amsler

- Hidroxicloroquina
    - Considerada mais segura do que a cloroquina. Todavia, também não tem dose segura (considera-se risco aumentado se dose **>400mg/dia**)
- Fenotiazinas (antipsicóticos)
    - Pode provocar um tipo de RP em sal e pimenta, especialmente se doses altas (com **800mg por dia**, pode surgir em semanas).
    - Sintomas: diminuição da acuidade visual e nictalópia (dificuldade em ver à noite).
    - Sinais: RP em **sal e pimenta** (resulta de pigmentação em placas por perda do epitélio pigmentar da retina).
- Tamoxifeno (utilizado no tratamento de cancro da mama)
    - Pode provocar dois tipos de RAM no pólo posterior:
        - Depósitos maculares cristalinos amarelo-brancos (inócuos e frequentes)
        - Cistos maculares ou edema macular (relativamente raro, contudo causa diminuição da AV)
    - Nem sempre é necessário suspender a medicação
- Cantaxantina (autobronzeador, pode originar depósitos na retina)
- Metoxiflurano (origina depósito de cristais de cálcio)
- Nitrofurantoína
- Interferão alfa (associado a exsudados e hemorragias retinianas)
- Deferoxamina (quelante): pode provocar degeneração pigmentar macular diagnosticada por electroculograma (revela < *light peak&dark through*)
- Ácido nicotínico
    - Está associada a edema macular cístico, particularmente se ultrapassar 1,5g de dose cumulativa. Esta RAM é geralmente reversível com a suspensão da medicação.

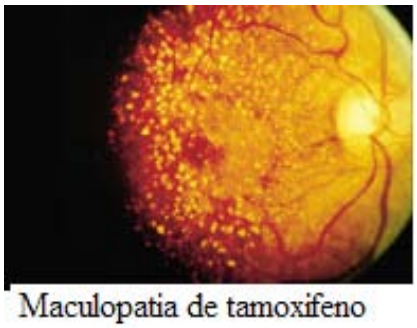

Figura 3: Depósitos maculares provocados por tamoxifeno (esta imagem aguarda permissão de copyright)

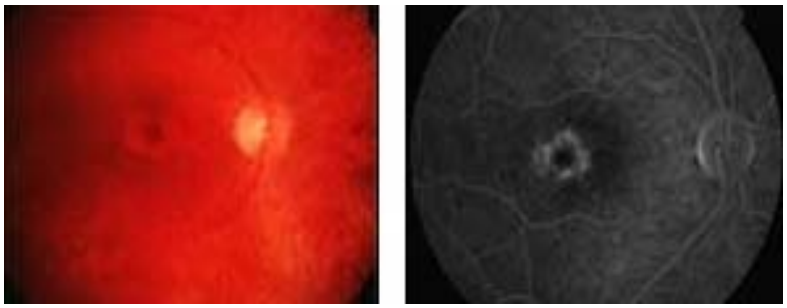

Figura 4: Maculopatia em olho de boi causada pela cloroquina (esta imagem aguarda permissão de copyright)

- **Edema da retina**
  - Anticoncepcionais orais
- **Hemorragias retinianas**
  - Anticoagulantes
  - Salicilatos e fenilbutazona
  - Antibióticos (sulfonamida)
- **Alteração do padrão vascular**
  - Anticoncepcionais orais
  - Quinina
  - Hexametónio
- **Discromatopsia azul-verde**
  - Sildenafil e família

Gostaríamos ainda de destacar dois tipos de RAM que nem sempre correspondem a estrutura ocular isolada, mas devem ser do conhecimento dos oftalmologistas.

Alteração do estado refrativo/acomodativo/"visão turva"

São inúmeros os fármacos que podem provocar visão turva[21-22]:

- Antihistamínicos
- Antidepressivos
- Anticonvulsivantes
- Antineoplásicos
- Bifosfonatos
- Bloqueadores dos canais de cálcio
- Corticóides
- Diuréticos
- iECAs
- Sildenafil e família
- Topiramato

"Fotossensibilidade"[10,21,22]

- AINEs
- Antagonistas do ácido fólico
- Antiarrítmicos e digitálicos
- Antibióticos (ciprofloxacina, tetraciclinas)
- Anticolinérgicos
- Anticoncepcionais orais
- Antidepressivos, antipsicóticos, tranquilizantes, fenotiazinas e estimuladores do sistema nervoso central
- Antihistamínicos
- Bloqueadores dos canais de cálcio, diuréticos tiazídicos, iECAs
- Retinóides
- Alguns produtos naturais (como *Hyperium perforatum*)

RAM sistémicas a medicação ocular

Primeiramente, para reduzir a probabilidade de ocorrerem RAM, o doente deve ser ensinado a administrar correctamente a sua medicação ocular, como demonstram as figuras seguintes.

Figura 5: Exemplo de colocação correta de colírio ocular. Não existe contacto do frasco com a superfície ocular, administra-se apenas uma gota de colírio.

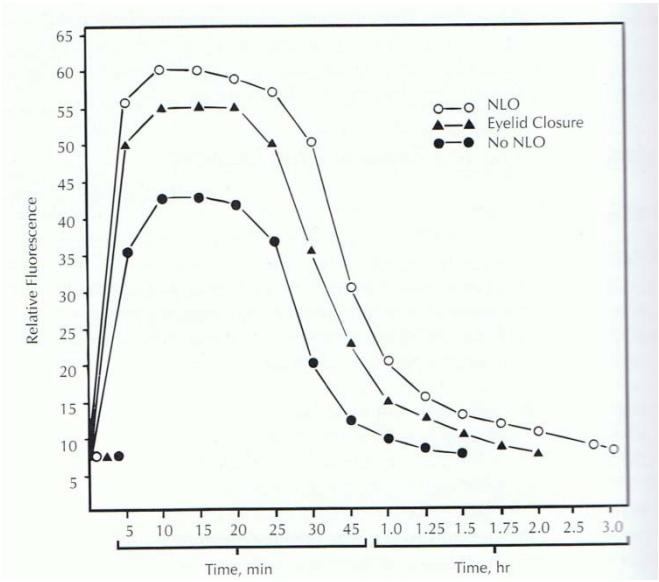

Figura 6: Concentração de fluoresceína no olho após colocar uma gota de acordo com diferentes técnicas. (Imagem da Academia Americana de Oftalmologia[13], aguarda permissão de copyright). Legendas "**NLO**": oclusão ponto lacrimal, "**Eyelid closure**": com encerramento palpebral, "**No NLO**": simples colocação de colírio sem medidas adicionais. Podemos verificar que a concentração do princípio activo é bastante inferior caso o doente não faça encerramento palpebral nem oclusão dos pontos lacrimais.

Passos aconselhados na técnica correta de colocação de colírios

1) Lavar bem as mãos

2) Inclinar a cabeça para trás e olhar para cima

3) Expôr bem a conjuntiva palpebral e depois instilar uma gota no fórnix conjuntival inferior (idealmente sem aplicar o colírio directamente na córnea; e nunca tocar com o frasco na superfície ocular)

4) Fechar os olhos e pressionar o canal nasolacrimal

- Este aspecto é extremamente importante. Além de aumentar a concentração da substância activa (como demonstrado na figura 6), reduz a frequência de RAM sistémicas. Ao ocluir o canal nasolacrimal e os pontos lacrimais, estamos a reduzir a quantidade de colírio que vai para as mucosas nasal e oral. Estas mucosas, por serem densamente vascularizadas (particularmente a mucosa nasal), causam absorção sistémica rápida e eficaz, com consequente aumento do risco de RAM sistémicas.

5) Limpar o excesso de medicação que tenha caído para a face

Fármacos tópicos associados a RAM sistémicas

Os medicamentos oftalmológicos que mais frequentemente podem causar RAM sistémicas encontram-se enumerados abaixo.

- **Adrenalina/epinefrina**
  - É a RAM sistémica de medicação ocular mais *frequente*[20]
  - A absorção através das mucosas pode levar a *taquicardia e hipertensão*
  - A injecção periocular de anestésicos associados a adrenalina pode ser fatal
- **Outros midriáticos como a atropina e ciclopentolato**
  - **Atropina**
    - Rubor, agitação, taquicardia, convulsões (particularmente nas crianças)
    - Pode ser fatal
  - **Ciclopentolato**
    - Nas crianças pode ser fatal (o antídoto é a fisostigmina)

- **Parassimpaticomiméticos**
  - Exemplos: **pilocarpina, carbacol**
  - Podem provocar várias RAM
    - Diarreia
    - Hipersudorese
    - Miose
    - Náuseas/vómitos
    - Urgência urinária
    - Hipotensão
    - Dispneia

- **Antibióticos**
  - Alergia
  - Síndrome Stevens-Johnson
  - Dispneia

- **Antivíricos**
  - Alergia e dermatite contacto

- **Bloqueadores beta**
  - Arritmias, bradicardia
  - Dificuldade respiratória
  - Hipotensão
  - Recorde-se que apesar de ser apenas um colírio, tem contraindicações absolutas: asma e doença pulmonar crónica obstrutiva, bloqueio auriculoventricular, bradicardia.

Outros produtos … inofensivos?

Não devemos esquecer que mesmo os produtos tipicamente "inofensivos" podem causar reações adversas oftalmológicas graves. Nestes exemplos, apenas os anticonceptionais orais estão associados a RAM. O tabaco e o etanol não são evidentemente medicamentos, pelo que se aplica o termo genérico *evento adverso*. Os produtos naturais, apesar de serem estudados e regulamentados pelo INFARMED, não têm neste momento o estatudo de medicamento, pelo que o termo correto é também *evento adverso*.

- **Anticoncepcionais orais**
  - Hipovisão, miopia, diplopia, oclusão venosa/arterial retina, nevrite óptica, entre outros.
- "Produtos naturais" (Camomila, Ginkgo biloba, niacina, vitamina A[5])
  - Maculopatia tóxica e neuropatia foram demonstradas.

- Tabaco
  - Ambliopia tóxica e cegueira nocturna.
- Etanol
  - Hipovisão, diplopia, cegueira nocturna, nistagmo, paralisia acomodação, oftalmoplegia e ambliopia tóxica.

Conclusão

Em conclusão, as RAM são mais frequentes e mais graves do que se imagina. Todos os oftalmologistas devem saber reconhecer as principais RAM oftalmológicas à medicação sistémica, quais as contraindicações de cada fármaco que administrem, e quais as RAM sistémicas à medicação oftalmológica - antes de a prescrever ou aplicar.

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APPENDIX 10

0917

Adverse Drug Reactions

Ana Miguel[1,2], Luis Azevedo[1], Altamiro Costa-Pereira[1]

ABSTRACT

Biotechnology continuously improves living, however it also presents challenges. Biotechnology has several applications in the pharmacy industry, with an increasing numbers of new drugs being developed. Nevertheless, each and every drug poses a risk of undesired affects, namely adverse drug reactions (ADRs). ADRs are frequent, important, expensive and can be fatal: they are estimated to be between the 4th and 6th more frequent causes of death. Pharmacovigilance, which includes the detection and prevention of ADRs, represents one of the few ways in which it is possible to increase Healthcare quality while decreasing related costs. We present an overview about the importance of ADRs and their methodological issues.

***Key words*:** Pharmacovigilance, Adverse drug reactions, Biotechnology, Methodologies, Databases, Intensive monitoring

1. INTRODUCTION

Background: Biotechnology, Pharmacology and Adverse Drug Reactions

Biotechnology has been extremely useful for Humanity in many aspects, from agriculture (Cantley, 2012) to medicine. The recent advances in

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biotechnology, including genomics, recombinant gene technologies, applied immunology and biological engineering, have allowed an improvement in the quality and number of pharmaceutical therapies (Mesko B *et al.,* 2012).

However, with an increase in the number of new drugs available, comes an increase in the risk of adverse drug reactions (ADRs), which can be serious and fatal (Davies *et al.*, 2007). Consequently, Pharmacovigilance, whose functions include the monitoring, detection and prevention of ADRs, has a fundamental role in healthcare. The detection of ADRs can be difficult and require experts. There are several methods aimed at the detection of ADRs, but all have their methodological issues.

ADRs: Some Concepts

To avoid confusion between many different terms, we present the definition of ADR.

An adverse drug reaction is: "any noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy", according to WHO's definition of 1972 (WHO, 1972). This definition is the most widely used, but there are others, like Karch and Lasagna's (1975) and Edwards and Aronson (2000).

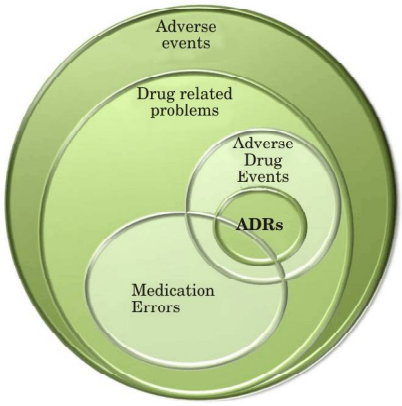

Fig. 1: Schematic conceptualization of adverse events

An adverse drug event includes medication errors (namely the prescription of a wrong dose) and adverse drug reactions. An adverse event includes any injury related to medical management (WHO, 2005). These and other concepts are represented in the figure below. Unfortunately, not enough studies that aim to detect ADRs present or

respect the correct definitions of ADR; we suggest the use of WHO's definition of ADR.

Adverse events are injuries related to medical care. Drug related problems are caused by drugs and include medication errors, adverse drug events (ADE) and adverse drug reactions (ADR). Adapted from WHO, 2005.

B. PHARMACOVIGILANCE

Identification, Causality Assessment and Characterization of ADRs

From hundreds of newly released drugs, administered to thousands of people, several ADRs can arise, with different manifestations, signs and symptoms. These are usually detected by healthcare team members (such as a physician, pharmacist or nurse), when a patient seeks help as an outpatient or when he is hospitalized, or by an expert during a study aimed to identify ADRs.

Previous studies have reported many risk factors for developing an ADR, namely: other comorbidities (Seiber, 2007), diabetes (Zhang *et al.*, 2009), renal failure (Corsonello *et al.*, 2005), female sex (WHO, 2012), increased age (Davies *et al.*, 2007) and also genetic factors (Pirmohamed *et al.*, 2001). These genetic factors might be used in Biotechnology aiming to increase the detection of ADRs (as discussed below).

ADRs may be classified in type A (*augmented*, predictable ADRs which are dose-dependent, such as bleeding after the use of acetylsalicylic acid) or type B (*bizarre*, unpredictable, idiosyncratic reactions, such as Stevens-Johnson syndrome) (Rawlins and Thompson, 1977).

In studies about ADRs, a causality assessment must be performed in order to assess the probability of a suspected ADR being a true ADR. Tables 1 and 2 detail the most used causality assessments.

Naranjo's causality assessment	***Yes***	***No***	***Don't know***
1. Are there previous conclusive reports of this reaction?	+1	0	0
2. Did the adverse event appear after the suspect drug was administered?	+2	–1	0
3. Did the adverse reaction improve when the drug was discontinued?	+1	0	0

Contd...

Contd...

Naranjo's causality assessment	***Yes***	***No***	***Don't know***
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0
5. Are there alternate causes that on their own could have caused the reaction?	-1	+2	0
6. Did the reaction appear when a placebo was given?	-1	+1	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0
8. Was the reaction more severe when the dose was increased or less severe when decreased?	+1	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0
Total score*			

Table 1: Naranjo's causality assessment for ADRs (Naranjo *et al.*, 1981). *Interpretation of the Total Score: **a)** ≥ 9: *Highly probable* ADR; **b)** 5-8: *Probable* ADR; c) 1-4: *Possible* ADR: d) ≤ 0: *Doubtful* ADR.

WHO's causality assessment	
1. Certain ADR	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
2. Probable ADR	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition. A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
3. Possible ADR	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear
4. Unlikely ADR	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Table 1: Contd...

Table 1: Contd...

WHO's causality assessment	
5. Conditional / unclassified ADR	A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.
6. Inaccessible / unclassifiable	A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

Table 2: WHO's causality assessment for ADRs (WHO, 2005).

The American Food and Drug Administration uses the following criteria for characterizing an ADR as serious, if associated with either of:

- Death
- Life-threatening
- Hospitalization (an ADR that causes or prolongs hospitalization)
- Disability
- Congenital anomaly
- Requires intervention to prevent permanent impairment or damage

A severe ADR is an intense or painful ADR (not to be confused with a serious ADR).

ADRs can also be characterized according to predictability (Hartwig *et al.,* 1992), preventability (Schumock and Thornton, 1992) and other factors.

Frequency of ADRs

Although ADRs may be difficult to detect, they are frequent: they are estimated to cause 5.3% of hospital admissions (Kongkaew *et al.*, 2008) and to occur in a mean of 16.88% of patients during hospitalization (CI95%:13.56-20.21) (Miguel *et al.,* 2012).

Fatal ADRs may be between the fourth and sixth leading causes of death in the US (Lazarou *et al.*, 1998). They may lead to US$1.56 billion in direct hospital costs per year in the US (Classen *et al.,* 1997), and drug related morbidity may lead to US$136.8 billion in indirect costs (Johnson and Bootman, 1995). Each ADR may represent a cost of US$2500 per patient (Bates *et al.*, 1995).

Drug development and detection of ADRs

At the time a drug is licensed, information about its ADRs is limited. Some ADRs are difficult to detect during the clinical research phases prior to commercialization, namely ADRs of low incidence or ADRs that occur several years after administration. This may also be due to the fact that pre-marketing trials are often underpowered, have limited follow-up or that drug information sent from companies to health authorities might sometimes be incomplete (Psaty *et al.*, 2004).

In Fig. 2, we depict the four stages of clinical trials, in which ADRs of a drug can be detected, before and after a drug commercialization. In Phase 1 trials, researchers test an experimental drug or treatment in a small group of volunteers (20-80) for the first time, to evaluate its general safety. In Phase 2 trials, the experimental study drug is administered to a larger group of people (100-300) to see if it is effective and to further evaluate its safety. In Phase 3 trials, the experimental study drug is administered to large groups of people (1000-3000) under strict inclusion criteria to confirm its effectiveness, to identify further ADRs, to compare it to commonly used treatments, and to collect information that will allow the experimental drug or treatment to be used safely. In Phase 4 trials, post marketing trials identify additional information such as rare or late-effect ADRs. There is an increasing number of patients throughout the different trial phases. After the drug approval, not only post marketing trials but also postmarketing observational studies can be performed to identify ADRs.

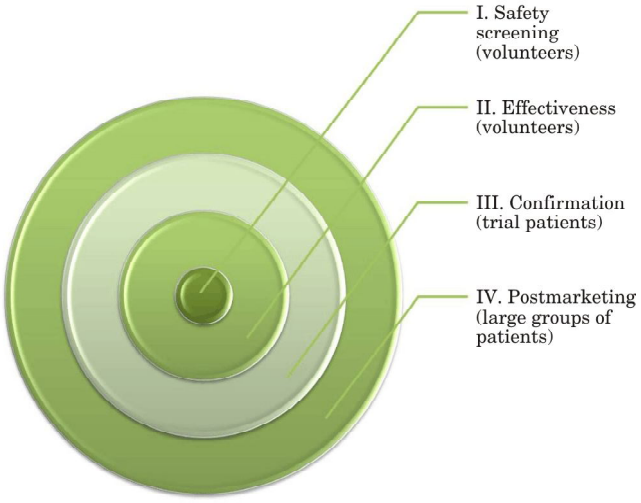

Fig. 2: Trial phases and possibilities for ADR detection.

Several drugs have been withdrawn from the market in the last decade after being approved by competent health authorities, such as rofecoxib, that has caused 100000 cardiovascular events in the US before the market withdrawal (Gudbjornsson, 2010). This demonstrates the importance of postmarketing surveillance.

C. POSTMARKETING METHODOLOGIES FOR THE DETECTION OF ADRS

Several methods can be used for the detection of ADRs:

1. **Spontaneous reporting** (in which a health team member reports a presumable ADR) is the main Pharmacovigilance method used in Europe, since it is cheap; however subnotification (Figueiras *et al.,* 2006; Herdeiro *et al.,* 2008) is a problem.
2. **Administrative databases**. Recurring to national hospital administrative databases is not a widely used method, but it may have some advantages, like low cost and the possibility of a National perspective (Salmerón-García *et al*., 2010).
3. **Chart review** (prospective or retrospective) is a reasonable methodology for ADR (Mullins *et al.*, 2011), however it is also resource and time consuming.
4. **Computerized systems** include all methods in which a computerized hospital system generates ADR alerts in several groups of patients, later validated by an expert team (Tinoco *et al.,* 2011). This is an evolving and interesting method of Pharmacovigilance, but attention is needed to build rules and algorithms with high specificity (too many ADR alerts with little specificity consume time in ADR validation and make it unpractical).
5. **Intensive monitoring** is the gold standard, in which an expert team prospectively examines a cohort of patients (recurring to chart review, patient examination and medical team interview) and applies strict criteria to identify and classify ADRs. However, this method is extremely resource and time consuming (Pourseyed *et al.,* 2009), making it unpractical to perform regularly.
6. **Prospective monitoring** is a monitoring similar to intensive monitoring but less rigorously (Fattinger *et al.*, 2000).
7. **Trials** are not used solely for the identification of ADRs of a particular drug, but are growingly assessing ADRs as an essential component of a drug evaluation (de Vries and van Roon, 2010).
8. **Other** methods are promising for the detection of ADRs.

These methodologies are different, although not always mutually exclusive (for example, intensive monitoring can and should include chart review and prospective monitoring), and each of which presents with its advantages and disadvantages.

1. Spontaneous reporting - International Drug Monitoring Program

The World Health Organization (WHO) has built an International Drug Monitoring Program, that incorporated adverse events' (and ADRs) information derived from State Members later in 1971. The Program for International Drug Monitoring relies on spontaneous reports from more than 100 countries, and builds a global database to identify possible relationships between the use of a drug and adverse effects and ADRs. Whenever a report of a suspect ADR arises, its data is shared through every State Member. Also, the majority of countries have a *National Health Drug Regulatory Agency*. However, these agencies rely mainly on spontaneous reporting (WHO, 2005), largely underestimating the real number of ADRs (as will be described below).

In summary, National and International Drug Regulatory Agencies currently use spontaneous reporting as a continuous Pharmacovigilance method.

Methodological issues of spontaneous reporting

In spite of being the most commonly used method for Pharmacovigilance due to its reduced costs, there are several limitations to spontaneous reporting: under-reporting, heterogeneous report quality and risk of bias.

Under-reporting is the main limitation: several studies have estimated that spontaneous reporting only detects 5-10% of ADRs (McGettigan *et al.*, 1997; Smith *et al.*, 1996), due to intrinsic factors (knowledge, attitudes) and extrinsic factors (relationship between patient-doctor, the national health system and pharmaceutical companies) (Herdeiro *et al.,* 2004). Some studies have demonstrated that spontaneous reporting rate can be increased (Biagi *et al.,* 2012; Figueiras *et al.*, 2006), however this effect was temporary. Health Professionals that can report ADRs should be subject to continuous education on Pharmacovigilance, to maintain an acceptable reporting rate, which has costs.

Other limitation is the *report quality*. Different quality in reporting will result as different skilled health professionals assess and write that information about ADRs. Also, in different countries there are different forms, which might result in discrepancy (Bandekar *et al.*, 2010).

The third limitation is *methodological bias*. This occurs because a simple report with uncontrolled information and variables, in comparison with namely a trial, is more prone to suffer from bias, as suggested by some authors (Pariente *et al.,* 2007).

2. DATABASES

The utilization of hospital episodes statistics has been performed only by a few authors to identify ADRs. Although not widely used, it may have advantages if developed and validated as a methodology, such as: information of several hospitals, years and countries already available, clinical coding data from which signals of ADRs might be extracted, low resources needed and a detection rate higher than spontaneous reporting.

Hospital administrative databases are built in many countries for reimbursement and/or administrative purposes, and contain useful clinical information that can be utilized for detecting ADRs. This information may include: anonymized patient identification, episode and process number, age, sex, admission date, discharge date, ward(s), hospital attended (tertiary, university), district, outcome (death, discharge, transfer), payment data (Diagnosis Related Groups) and ICD-9-CM codes for: diagnoses (principal diagnosis, and secondary diagnoses usually up to 19), procedures (up to 20) and external causes (up to 20).

Therefore, these large sources of information can be very useful to identify ADRs even in nation-wide studies, namely allowing to detect ADR frequencies of: 0.89% in Spain (Salmerón-García A *et al.,* 2010), 0.9% in England (Wu *et al,* 2010), 1.83% in the Netherlands (van der Hooft *et al.*, 2006), 0.8% in Australia (Whitstock *et al.*, 2011) and 1.26% in Portugal (throughout the same study period and population, spontaneous reporting only detected a prevalence of 0.001% ADRs) (Miguel *et al.,* 2013b).

Methodological issues of databases

There are limitations in the database methodology, such as: probable incomplete and wrong information might occur in every large database,

and coding creep (this is a possible bias of all billing databases, in which more expensive codes are preferred and registered to increase the case-mix, diagnosis-related group and consequently to increase reimbursement of that hospital) (Seiber, 2007).

Multi-centered validation studies of databases in different countries should be performed to select specific diagnostic codes associated with ADRs within each country, and to build an estimate of error associated with each methodology.

Although the database methodology allows us to detect a higher frequency of ADRs than spontaneous reporting, it is low in comparison with prospective monitoring and intensive monitoring.

3. MANUAL CHART REVIEW

Manual chart review for ADR detection consists of retrospectively or prospectively reviewing patient charts to identify ADRs, generally performed by one or two experts in ADRs, that latter assess concordance for verification of ADRs (Mullins *et al.,* 2011; Tinoco *et al.,* 2011). Specific, strict and objective guidelines are recommended for this assessment (Cornelius *et al.,* 2009), namely the use of a definition of ADR (usually WHO definition) and causality assessment of ADRs.

Methodological issues of chart review

Manual chart review has good detection rates (Tinoco *et al.,* 2011), but it is time and personnel costly: some studies estimated a cost of 55 person-hours per week (Jha *et al.*, 1998). We performed two studies of ADRs using chart review, the first detecting a prevalence of 9% ADRs with a cost of 35 person-hours for 100 patients, in comparison with 2 person-hours for 100 patients in the database methodology (Miguel *et al.,* 2013). Our second chart review, more detailed to further characterize ADRs, unfortunately obtained a similar prevalence of ADRs, 10.2%, at a much higher cost: 69 person-hours (Miguel *et al.,* 2013b).

Other limitations of chart review include the methodological heterogeneity between the different studies (Davies *et al.*, 2007), namely because of the use of different definitions of ADR, the use of different causality assessment for ADRs, prospective or retrospective design of study (and different time of data collection), and the use of different number of sources for detection of ADRs: some just search through patient charts (Bates *et al.,*1993), while others also interview health team whenever doubts arise (Somers *et al.*, 2003).

Additionally, the quality of records in different hospitals can vary, generating differences in the detection of ADRs through chart review (Davies *et al.,* 2007; Cassidy *et al.,* 2002), further adding heterogeneity.

4. COMPUTERIZED METHODOLOGIES

Computerized methodologies for the detection of ADRs are appealing. Many different strategies of computerized Pharmacovigilance were assessed in a recent systematic review (Forster *et al.,* 2012), with different levels of complexity in implementation and integration, and consequently with a variety of costs in acquisition and maintenance.

Computerized methods are frequently used in US hospitals, in which almost all clinical data is already computerized and structured.

Methodological issues of computerized methods

In the one hand, low level of automation methods may be resource-sparing and interesting for the use of simple ADR detection in hospitals without computerized clinical information. On the other hand, integrated and high complexity computerized methods are more complete and allow prospective detection (and prevention of ADRs, alerting the physician and even suggesting dose changes in certain patients) (Hassan *et al.,* 2010). Additionally, computerized methods require algorithms and continuous adjustment (and resources) to avoid too many alerts without specificity for a true ADR.

5. OTHER METHODS: INTENSIVE MONITORING, PROSPECTIVE MONITORING AND TRIALS

Intensive monitoring is the gold standard because it implies direct and prospective observation by an expert team, having the highest detection rate - and the highest cost (Pourseyed *et al.,* 2009; Davies *et al.,* 2007). For that reason, it is impossible to use as a continuous Pharmacovigilance method in all patients.

Although prospective monitoring is cheaper and has high detection rates, it is also too resource-consuming to use continuously.

Trials are performed in extremely selected populations within a relatively short period of time, therefore other methods must be used to detect ADRs in the general population.

6. BIOTECHNOLOGY AND PHARMACOGENOMICS FOR THE DETECTION OF ADRS

Biotechnology not only has offered new methods of designing drugs, but also aids in the detection of ADRs, namely through the development of pharmacogenomics. Pharmacogenomics is the study of how genes and gene variation can produce different phenotypic drug responses (Altman and Klein, 2012). Consequently, for each patient these phenotypic drug responses may be predicted, either to increase effectiveness according to the drug response rates (Wilkinson, 2005) and to prevent ADRs, namely by changing the drug type or dose according to each specific genotype) (Davies *et al.,* 2007; Pirmohamed and Park, 2001).

Pharmacogenomics and personalized medicine are connected and are promising in Pharmacology, Pharmacovigilance and Medicine (Desiere and Spica, 2012). However, many issues of regulation, ethics and cost-effectiveness must be addressed with the use of pharmacogenetics testing (Howland, 2009) and a rational global drug use policy must be applied (Roederer *et al., 2011).*

Mesko B and colleagues (Mesko *et al*, 2012) propose the utilization of a triad in the control of personalized medicine: biotechnology, pharmacogenomics (including gene expression profiling) and regulatory issues.

C. CONCLUSIONS

Many developments in biotechnology have allowed an improvement in medicine and pharmacology, with an increase in the discovery of new drugs. However, this leads to an increase in the risk of ADRs. Consequently, Pharmacovigilance must evolve to increase the detection rate of ADRs. Several methods can be used for that detection, all with methodological issues.

Spontaneous reporting is widely used due to its low cost, being a part of the International Drug Monitoring Program; however, there is an extremely low detection rate. Nevertheless, this method is very good for identifying new ADRs to new drugs.

Database and computerized methodologies are promising and might be integrated as effective Pharmacovigilance methodologies. The database methodology is resource-sparing for continuous application but with a detection rate much higher than spontaneous reporting,

allowing nation-wide estimates. Computerized chart review may allow regular surveillance with a good ADR detection.

Chart review, prospective monitoring and trials have a very good detection rate, however their costs are too high for continuous surveillance.

Biotechnology application in Pharmacogenomics is promising for the individualized prevention of ADRs.

Different methods tend to identify different ADRs, therefore, multiple methods for ADR detection should be used complementarily for patient safety enhancement.

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