Tipos de Estudos Científicos e Níveis de Evidência

Francisco Batel Marques, PhD
Professor, School of Pharmacy, University of Coimbra

Director,
CHAD – Centro de Avaliação de Tecnologias em Saúde e Investigação do Medicamento
AIBILI – Associação para Investigação Biomédica e Inovação em Luz e Imagem

Tipos de estudos e níveis de evidência

- Em saúde somos chamados a fazer julgamentos sobre:

  – Se uma exposição causa uma doença

  – Se uma intervenção é eficaz/segura numa determinada indicação terapêutica

Tipos de estudos e níveis de evidência

- *Sir* Austin Bradford Hill* publica, em 1965, um conjunto de critérios que poderiam ser usados para avaliar se uma associação poderia ser considerada como causal.

Hill AB, The environment and disease: association or causation ?

Proc Royal Soc Med 1965 May; 58: 295-300

Tipos de estudos e níveis de evidência

Os nove critérios de Bradford-Hill
- Força (RR, OR)
- Consistência (observação em diferentes ocasiões)
- Especificidade
- Temporalidade (causa precede a consequência)
- Gradiente biológico (relação dose-resposta)
- Plausabilidade (consistente com evidência biológica)
- Coerência
- Evidência experimental
- Analogia (considerar explicação alternativa)

Tipos de estudos e níveis de evidência

- Na realidade, o que normalmente queremos significar por "causalidade" é um "aumento de probabilidade".

- O problema mais importante deste aumento de probabilidade reside na sua inferência:

  – Da população para o individuo, e

  – Do indivíduo para a população

Modelos de estudo, validade interna e hierarquização da prova

Modelos de estudo, validade interna e hierarquização da prova

- O modo de questionar associações e relações causais pode ser colocado de várias maneiras. Por exemplo:

    – Conhecer as determinantes da doença

    – Antecipar o prognóstico da doença

    – Questionar a mais-valia terapêutica de um procedimento

    – Avaliar a eficácia de um medicamento

   – Associar prognóstico à acção terapêutica

Modelos de estudo, validade interna e hierarquização da prova

- A avaliação da existência ou não de associação e de relação causal, deve compreender dois aspectos fundamentais:

  – Identificação do efeito

  – Quantificação do efeito

Modelos de estudo

- Estudos sem grupo controlo
  - Estudos de casos individuais ou de conjuntos de casos individuais

- Estudos com grupo controlo

Modelos de estudo
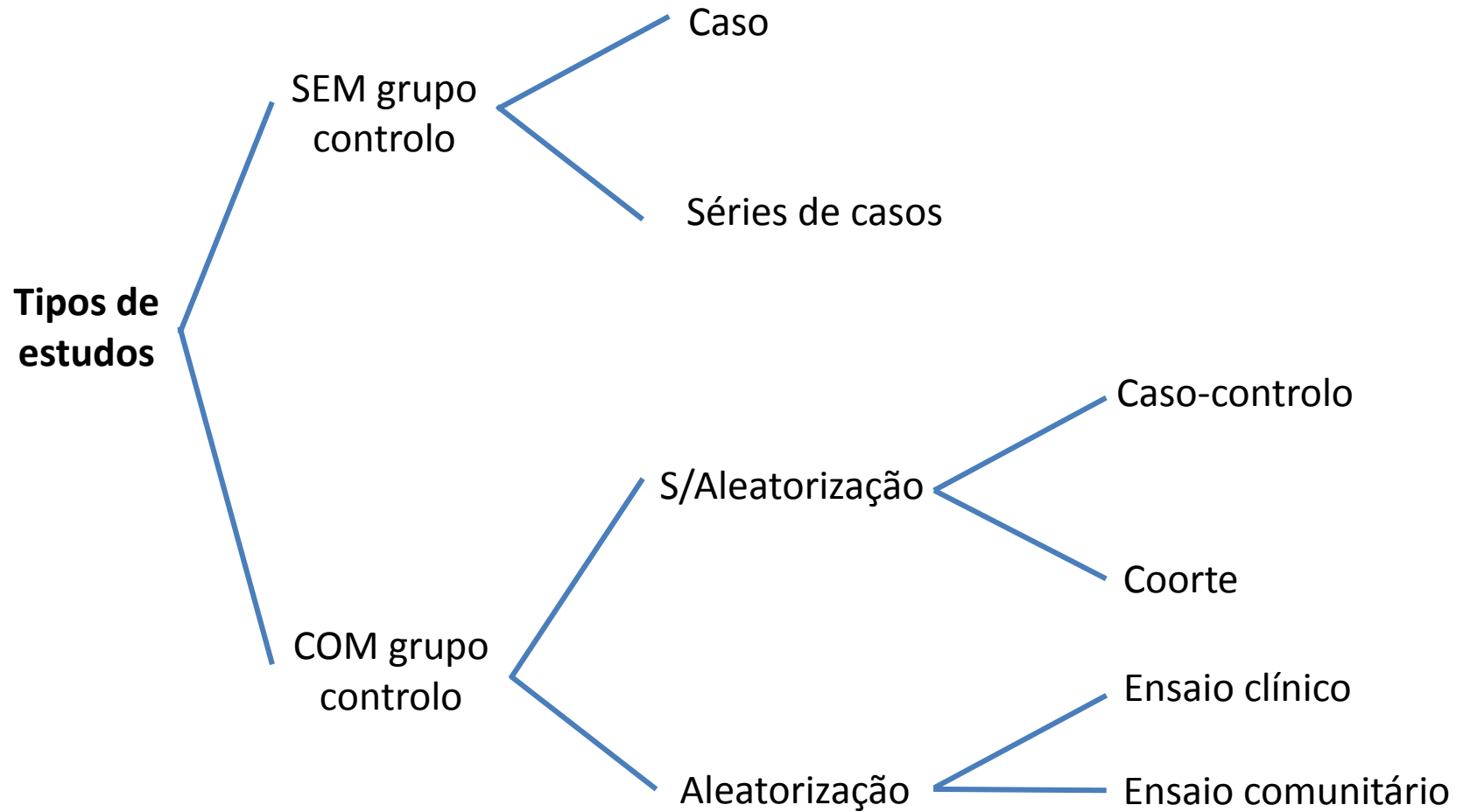
Estudo de casos individuais ou de conjuntos de casos individuais

- Estudo de casos individuais ou de conjuntos de casos individuais

    – Forma mais simples de responsabilizar uma exposição como factor de risco

    – Podem ser passíveis de validação com recurso aos critérios de Bradford-Hill, *mas*:

        - Podem não representar a maioria dos indivíduos em circunstâncias análogas
        - Podem modificar comportamentos devido à atenção do investigador (efeito de Hawthorne)

Estudos com grupo controlo

- Estudos com grupo controlo

  - Permitem uma comparação directa e objectiva entre o grupo em estudo e um outro grupo que não possuirá as mesmas características em apreciação (ex: exposto/não exposto ao medicamento em estudo).

  - Esta distinção é fundamental para a detecção e quantificação das variáveis em estudo.

  - A validade é tanto maior quanto mais "potente" for o controlo dos viéses.

Estudos com grupo controlo

- Dois tipos fundamentais

  – A variável em estudo é introduzida (idealmente de forma aleatorizada) pelo investigador: São estudos experimentais: ensaio clínico.

  – O investigador limita-se a observar a evolução da variável em estudo. São estudos observacionais: coorte e casos e controlos.

Estudos com grupo controlo

- ## **Estudos experimentais (ensaios clínicos)**

  - Características fundamentais
    - Selecção da amostra a partir de uma população
    - Critérios de inclusão e de exclusão rígidos
    - Definição estrita das diferenças que se pretendem detectar
    - Definição da aceitação do erro
      - tipo I – probabilidade de rejeitar a hipótese nula quando ela é verdadeira
      - tipo II – probabilidade de confirmar a hipótese nula quando ela é falsa)
    - Cálculo da dimensão amostral
    - Distribuição aleatória dos participantes por grupos
    - Possibilidade de ocultação da exposição

Aleatorização: peça nuclear dos RCTs

- Alocação causal e probabilística com vista à homogeneização dos grupos

  - Cada participante tem a mesma probabilidade de integrar cada um dos grupos formados

  - Comparabilidade entre grupos

  - Vantagem dos estudos experimentais sobre os estudos observacionais: igualando os grupos, as diferenças observadas ficar-se-ão a dever à intervenção (fármaco em estudo)

  - Permite um adequado tratamento estatístico

Estudos com grupo controlo

- ## Estudos observacionais
  - Estudos de metodologia de coorte
  - Prospectivos e retrospectivos
  - A causa precede o efeito
  - Partem da identificação da presença ou da ausência de exposição ao factor de risco em causa

- ## Estudos de metodologia de casos e controlos
  - Retrospectivos
  - O efeito precede a causa

Estudos observacionais

- **Coorte**
  - Permitem avaliar incidência
  - Acompanhamento com supervisão
  - Muito caros
  - Necessidade de grandes efectivos populacionais
  - Obrigam a grandes horizontes temporais, particularmente para investigar causalidade com grandes tempos de latência

- **Casos e controlos**
  - Permitem estudar acontecimentos raros
  - Mais baratos
  - Mais rápidos
  - Efectivos populacionais mais reduzidos

Estudos observacionais – vieses

- **Metodologia de coorte**
  - Selecção
    - Erro sistemático que resulta em coortes não comparáveis
  - Migração
    - Taxa de erosão
  - Observação
    - Inclusão de aspectos de valorização pessoal
  - Factores de confusão
    - Variável que não está incluída na cascata de causalidade, mas que se encontra relacionada com a associação entre a exposição e o efeito

- **Metodologia de casos e controlos**
  - Selecção
  - Informação (memória)
    - Informação a pesquisar, normalmente mais presente e correcta nos casos do que nos controlos
  - Factores de confusão

Indicadores gerais de resultado

- O facto de os estudos pesquisarem uma associação entre duas variáveis dicotómicas – exposição e efeito – permite que possam ser colocadas numa tabela binária 2 x 2.

Indicadores gerais de resultado

**Tabela binária para cálculo da associação entre exposição e efeito**

	Efeito +	Efeito -	Total
Exposição +	a	b	a +b
Exposição -	c	d	c + d
Total	a + c	b + d	

- Num ensaio clínico ou num estudo de coorte, a incidência entre os indivíduos expostos é de **a/(a+b)**; a incidência entre os indivíduos não expostos é de **c/(c+d)**. O risco relativo (RR) é **a/(a+b) / c/(c+d)**.

- Num estudo de casos e controlos, uma vez que não temos taxas de incidência (partimos da doença e não da exposição) recorre-se a uma estimativa do RR: a razão de Odds (odds ratio) OR que se calcula **a*c/b*d.**

Hierarquização da robustez do nível de evidência científica

- Da menor para a maior robustez:

  – Sem controlo

  – Com controlo não experimental

  – Com controlo experimental

Hierarquização da robustez do nível de evidência científica
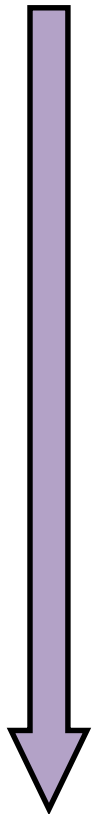
- Caso
- Séries de casos
- Estudo caso-controlo
- Estudo de coorte
- Estudo de intervenção comunitária
- Ensaio clínico
- Meta-análise de ensaios clínicos

Níveis de evidência científica

Classificação de Oxford Centre for Evidence-Based Medicine

Nível de evidência	Tipo e qualidade do estudo
1A	RS/Meta-análise de RCTs
1B	RCT individual com IC-95% estreito
2A	RS de estudos de Coorte
2B	Estudo de coorte
	RCT de baixa qualidade
2C	Outcomes research
	Estudos ecológicos
3A	RS de estudos de caso-controlo
3B	Estudo individual de caso-controlo
4	Série de casos
	Estudos de Coorte e de caso-controlo de baixa qualidade
5	Opinião de peritos

Sources of information used by regulatory agencies on the generation of drug safety alerts

**Carlos Alves · Ana Filipa Macedo ·
Francisco Batel Marques**

Abstract

Purpose The study of the grounds on which data regulatory authorities base their decisions on drug safety evaluations is an important clinical and public health issue. The aim of this study was to review the type and publication status of data sources supporting benefit/risk ratio re-evaluations conducted by the major regulatory authorities on safety issues.

Methods A website search was carried out to identify all safety alerts published by the U.S Food and Drugs Administration, Health Canada, European Medicines Agency and the Australian Therapeutics Goods Administration. Safety alerts were included if the causal relation between a suspected drug exposure and the occurrence of an adverse event was evaluated for the first time between 2010 and 2012. Type of data sources evaluated by these regulatory authorities, publication status of the data sources and status of the drug label section with respect to updating were evaluated.

Results A total of 59 safety alerts were included in this study. Of these, 33 (56%) were supported by post-marketing spontaneous reports, 24 (41%) evaluated randomized clinical trials, 16 evaluated cohort studies (27%), 13 were case–control studies (22%) and 11 evaluated case report/case series (17%). Twenty-three safety alerts (39%) were issued based. on unpublished evidence, corresponding mainly to post-marketing spontaneous reports. The "Warnings and precautions section" was the drug label section most frequently updated ($n=40$; 68%).

Conclusion Despite the different lengths of time taken by the different regulatory authorities to come to similar decisions on the same issues—an issue which would seem to deserve further harmonization—post-marketing spontaneous reports have supported most of the benefit/risk ratio re-evaluations, thereby confirming the value of such re-evaluations in detecting unknown adverse events.

Electronic supplementary material The online version of this article (doi:10.1007/s00228-013-1564-y) contains supplementary material, which is available to authorized users.

C. Alves (✉) · F. B. Marques
Centre for Health Technology Assessment and Drug Research

Introduction

ORIGINAL ARTICLE

Safety of biologics approved for treating rheumatoid arthritis: analysis of spontaneous reports of adverse events

Diogo Mendes · Carlos Alves · Francisco Batel Marques

Abstract Despite the effectiveness of biologics approved for the treatment of rheumatoid arthritis, they have been associated with serious adverse events (AEs). Biologics are used under close supervision of health care professionals. In Portugal, they are legally required to report AEs occurring during the treatment. This study aims at investigating post-marketing safety monitoring data of biologics in Portugal by comparing the frequency of spontaneously reported adverse events between 2009 and 2011 with the frequency of such events in the summary of the product characteristics of each biologic. Sales data for biologics were obtained from IMS Health and converted into defined daily doses/1,000 inhabitants/day in order to estimate a proportion of the population treated. The frequency of AEs was estimated as the percentage of patients in which an AE may have occurred. The use of each biologic was estimated for adalimumab at 1,439 patients/year, etanercept 1,944 patients/year, and infliximab 3,211 patients/year. A total of 992 AEs were reported: 207 for adalimumab, 199 for etanercept, and 586 for infliximab. Of the 515 different spontaneously reported AEs, 194 were included for comparisons with the SPCs. Of those, 31 (16 %) were similarly frequent, and 163 (84.0 %) occurred less frequently compared with SPCs' data. These results suggest an insufficient post-marketing safety monitoring of biologics in Portugal.

Keywords Adverse events · Biologics · Pharmacovigilance · Rheumatoid arthritis · Spontaneous reporting

Introduction

Many biologics have been introduced to treat rheumatoid arthritis (RA) in recent years. Those drugs target specific components of the immune system that are involved in the pathologic inflammation cascade [1], such as tumor necrosis factor (TNF) alpha, T cells, B cells, and interleukins [2].
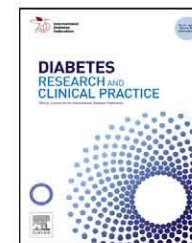
Despite the effectiveness of biologics in treating RA, there is uncertainty regarding their safety profile [3].

A meta-analysis of serious adverse events reported with exenatide and liraglutide: Acute pancreatitis and cancer

Carlos Alves [a,b,c,*], *Francisco Batel-Marques* [a,b], *Ana F. Macedo* [c]

[a] Health Technology Assessment (HTA) Centre, AIBILI, Coimbra, Portugal
[b] School of Pharmacy, University of Coimbra, Coimbra, Portugal
[c] CICS-UBI – Health Sciences Research Centre, University of Beira Interior, Covilhã, Portugal

ARTICLE INFO

ABSTRACT

Aims: The association between GLP-1 agonists, acute pancreatitis (AP), any cancer and thyroid cancer is discussed. This meta-analysis was aimed at evaluating the risk of those serious adverse events associated with GLP-1 agonists in patients with type 2 diabetes.

Methods: Medline, EMBASE, Cochrane Library and clinicaltrials.gov were searched in order to identify longitudinal studies evaluating exenatide or liraglutide use and reporting data on AP or cancer. Odds ratios (ORs) were pooled using a random-effects model. I^2 statistics assessed heterogeneity.

Results: Twenty-five studies were included. Neither exenatide (OR 0.84 [95% CI 0.58–1.22], $I^2 = 30\%$) nor liraglutide (OR 0.97 [95% CI 0.21–4.39], $I^2 = 0\%$) were associated with an increased risk of AP, independent of baseline comparator. The pooled OR for cancer associated with exenatide was 0.86 (95% CI 0.29, 2.60, $I^2 = 0\%$) and for liraglutide was 1.35 (95% CI 0.70, 2.59, $I^2 = 0\%$). Liraglutide was not associated with an increased risk for thyroid cancer (OR 1.54 [95% CI 0.40–6.02], $I^2 = 0\%$). For exenatide, no thyroid malignancies were reported.

Conclusions: Current available published evidence is insufficient to support an increased risk of AP or cancer associated with GLP-1 agonists. These rare and long-term adverse events deserve properly monitoring in future studies evaluating GLP-1 agonists.

Glucagon-like peptide-1 (GLP-1) agonists are a new class of

ociação para
estigação biomédica e
vação em luz e imagem

Nurses' spontaneous reporting of adverse drug reactions: expert review of routine reports

DIOGO MENDES PharmD [1], CARLOS ALVES PharmD [2,3] and FRANCISCO BATEL MARQUES PharmD, PhD [4]

[1]Research Assistant, *Central Portugal Regional Pharmacovigilance Unit, Health Technology Assessment Centre, AIBILI, Coimbra,* [2]PhD Student, *School of Pharmacy, University of Coimbra and at CICS-UBI – Health Science Research Centre, University of Beira Interior,* [3]Collaborator, *Health Technology Assessment Centre, AIBILI, Coimbra and* [4]Associate Professor, *School of Pharmacy, University of Coimbra, Central Portugal Regional Pharmacovigilance Unit, Health Technology Assessment Centre, AIBILI, Coimbra, Portugal*

Correspondence
Diogo Mendes
Unidade de Farmacovigilância do Centro
AIBILI
Azinhaga de Santa Comba - Celas
3000-548 Coimbra
Portugal
E-mail: diogomendes26@gmail.com

MENDES D., ALVES C. & BATEL MARQUES F. (2012) *Journal of Nursing Management*
Nurses' spontaneous reporting of adverse drug reactions: expert review of routine reports

Aim The aims of this study were to analyse spontaneously reported adverse drug reactions according to their previous description, seriousness, causality and the reporting professional.

Background Previous findings showed that fewer nurses than physicians and pharmacists report adverse drug reactions. This is not attributed to any lack of ability in identifying adverse drug reactions.

Method Adverse drug reactions received by the Central Portugal Regional Pharmacovigilance Unit, between 2001 and 2011, were studied. Certain and probable adverse drug reactions were included to test differences between professional groups for serious and non-serious adverse drug reactions.

Results The Central Portugal Regional Pharmacovigilance Unit received 1014 adverse drug reactions. Fifty-four nurses reported 66 adverse drug reactions, whereas 232 physicians and 145 pharmacists reported 589 and 357 adverse drug reactions, respectively. Considering the number of practising professionals, it was estimated that 0.55% of nurses, 3.96% of physicians and 7.08% of pharmacists have reported an adverse drug reaction. Of the 633 adverse drug reactions assessed as certain or probable, 46 (21 serious), 387 (192 serious) and 198 (77 serious) were reported from nurses, physicians and pharmacists, respectively. There were no differences in the reporting of serious adverse drug reactions among nurses, physicians or pharmacists.

Conclusions Nurses are able to identify serious adverse drug reactions although they report less than other professionals.

Implications for Nursing Management Nurses need to increase their involvement in spontaneous reporting schemes by undertaking responsibility in routinely reporting suspected adverse drug reactions.

Keywords: adverse drug reaction, nurses, pharmacovigilance, seriousness

Apixaban and Rivaroxaban Safety After Hip and Knee Arthroplasty: A Meta-Analysis

Carlos Alves, PharmD[1,2,3], Francisco Batel-Marques, PharmD, PhD[1,2], and
Ana Filipa Macedo, PharmD, PhD[1,3]

Abstract

Direct experimental safety comparisons of Xa coagulation factor direct inhibitors, apixaban and rivaroxaban, on their approved therapeutic indications have not been identified. Due to recently raised safety concerns, a meta-analysis was carried out pooling data from studies identified on a Medline and Cochrane Library search in order to better evaluate the safety profile of both drugs. Abstracts from scientific meetings were also searched from 2003 to 2011. Primary and secondary outcome measures were major bleeding and total bleeding, respectively. Relative risks (RRs) were estimated using random effects models and statistical heterogeneity was estimated with I^2 statistics. Of the 160 screened publications, 12 clinical trials were included in which enoxaparin was the active control. For knee arthroplasty, apixaban was associated with significantly fewer major bleeding events (6496 patients, RR 0.56, 95% confidence interval [CI] 0.32-0.96) and fewer total bleeding events (6496 patients, RR 0.81, 95% CI 0.67-0.97). There were no significant differences in the incidence of major bleeding events (5699 patients, RR 1.40, 95% CI 0.56-3.52) or in the incidence of total bleeding events for rivaroxaban (5699 patients, RR 1.09, 95% CI 0.91-1.30). No differences were found when thromboprophylaxis after hip replacement was the case. Apixaban seems to be associated with a lower risk of the incidence of hemorrhagic events after total knee arthroplasty. For hip arthroplasty, no differences were found between the studied drugs.

Keywords

meta-analysis, safety, thromboprophylaxis, rivaroxaban, apixaban

Introduction

Patients submitted to major orthopedic surgery, such as elective total knee or hip arthroplasty, represent a group at high risk of venous thromboembolism (VTE).[1] Almost half of the patients who underwent arthroplasty are affected by asymptomatic deep venous thrombosis (DVT), although most of these thrombi resolve without long-term complications.[2-4] For some patients, propagation of the existing thrombus can cause symptoms as a result of venous occlusion.[5] Symptomatic VTE is

of injection site hematomas.[12,13] Furthermore, subcutaneous administration of anticoagulants is difficult to provide after hospital discharge. Vitamin K antagonists are being abandoned in Europe due to concerns about their delayed onset of action, unpredictable pharmacokinetic and pharmacodynamic effects, and need for frequent monitoring.[14,15] Mechanical VTE prophylaxis is known to be cumbersome, and its efficacy is found to be lower when compared with anticoagulant therapy, especially after hip arthroplasty.[2]

ORIGINAL REPORT

Data sources on drug safety evaluation: a review of recent published meta-analyses

Carlos Alves[1,2,3]*, Francisco Batel-Marques[1,2] and Ana Filipa Macedo[1,3]

[1] *Central Portugal Regional Pharmacovigilance Centre, AIBILI, Coimbra, Portugal*
[2] *School of Pharmacy, University of Coimbra, Coimbra, Portugal*
[3] *Health Sciences Research Centre, University of Beira Interior, Covilhã, Portugal*

ABSTRACT

Purpose   Meta-analysis is a quantitative approach to summarize the findings from several studies and has been applied with increasing frequency to clinical trials. Because of their sample size and duration limitations, experimental studies (ESs) could not be able to detect late or rare adverse events (AEs), which may be identified in well-designed observational studies (OSs). This study aims to identify and analyze meta-analyses from both ES and OS where safety was found to be an outcome measure.

Methods   The meta-analyses inclusion criteria was established as at least one AE as primary outcome. Safety outcomes were considered as the increase in the risk for an AE after a pharmacological intervention. A MEDLINE search for meta-analyses published in the *New England Journal of Medicine*, *The Lancet*, *Journal of American Medical Association*, *British Medical Journal*, *Annals of Internal Medicine*, *PLoS Medicine*, *Annual Review of Medicine*, and *Archives of Internal Medicine*, between October 2005 and September 2010, was carried out.

Results   Sixty meta-analyses met the inclusion criteria. Of these, 53 included only ES, 4 included both ES and OS, and 2 included only OS. Of the 6 meta-analyses that included OS, 4 included cohort and case–control studies, and 2 included cohort, case–control, and cross-sectional studies. One meta-analysis did not report the type of studies included.

Conclusions   Experimental studies were found to be the main source of meta-analyses on drug safety. The role of meta-analyses in pharmacovigilance is a matter of ongoing debate, and efforts are being made to develop guidelines on the use of meta-analysis in drug safety assessments, to better combine evidence about harms. Copyright © 2011 John Wiley & Sons, Ltd.

KEY WORDS—meta-analysis; pharmacovigilance; adverse events; experimental studies; observational studies

BACKGROUND

Medicine use is a fundamental component of health care, and the optimization of drug prescribing has become an important public health problem worldwide.[1,2] It is now becoming clear that, to assess the overall effect of medical interventions, adverse effects should be reviewed with similar rigour as therapeutic benefits.[3–5]

increasing frequency to randomized controlled trials (RCTs), which are considered to provide the strongest evidence of efficacy regarding an intervention.[8,9] This is due to the fact that randomized controlled designs have better control and protection against bias than other study designs.

However, evidence on adverse events reported by clinical trials can be considered insufficient at some

"a randomised controlled trial (RCT) is one of the simplest, most powerful and revolutionary tools of research"

Alejandro Jadad

Director, McMaster Evidence Based Practice
Co-Director, Canadian Cochrane Network
McMaster University, Hamilton, Canada

One view of the value of epidemiology