REVIEW ARTICLE

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Case Series in Drug Safety
A Review to Determine Characteristics and Quality

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Contents

Abstract

Case series and case reports are a cornerstone of drug safety research; however, the characteristics of case series published in the literature remain poorly examined. A narrative review of case series addressing drug safety, published in the literature between 1 January 2003 and 15 July 2009, and identified through a PubMed search, was conducted in order to determine their characteristics and quality according to the criteria found in the US FDA Pharmacovigilance Guidance 2005.

Of 130 publications that met the search criteria, 11.5% included an analytical component and 88.5% were descriptive. The median number of cases included in a given case series was 7 (range 2–2195) and the median time period for recruitment of the cases was 23 months (range 0.5–96). Overall, 43.1% of case series consisted of individual case reports, while 24.6% originated from cohorts and 21% from pharmacovigilance databases. Of the case series, 65.1% concerned adults (age ≥18 years), 11.6% elderly (age ≥65 years) and 8.5% youth (<18 years). Adverse effects involved mainly the skin (18.5%) and the circulatory system (13.8%). The main suspected drug classes (Anatomical Therapeutic Chemical classification) were nervous system drugs (23.1%) and antineoplastic and immunomodulating agents (20.0%). On average, six out of the possible nine US FDA Pharmacovigilance Guidance Criteria were fulfilled, with 27% of publications fulfilling at least seven criteria. Only 10% reported data on co-morbidity.

In conclusion, this review highlights the reporting gaps and heterogeneity in published case series with respect to size, recruitment period and quality.

Case series have often been one of the tools used to monitor drug efficacy and safety ever since the report by McBride[1] on the risks associated with thalidomide. Case series have been a cornerstone of drug safety surveillance and the basis of the majority of drug market withdrawals in history.[2-4] The reporting of individual cases is often the first step in the acquisition of new scientific knowledge.

However, for the evaluation of drug effectiveness, since the emergence of methods that generate higher levels of evidence, such as randomized clinical trials, individual cases and information from case reports or case series no longer constitute an important source of data. An exception perhaps is orphan drugs for which the very small number of patients available does not always allow the use of quantitative research methods.

In drug safety surveillance, case reports and case series are still the leading sources of scientific data inducing changes in the regulatory status of drugs.[4] This paradox might originate from differences in perspectives between drug effectiveness and drug safety, mainly due to the precautionary principle as well as differences in the expected rates of events. Usually, the expected rates of drug benefits are amenable to the methods used in clinical research. Conversely, since some safety events are rare, clinical trials may not be adequate to evaluate risks.

In 1994, the French drug regulatory agency developed the Good Pharmacovigilance Practice guidelines[5] and, in 2005, the US FDA recommended good reporting practices and a summary descriptive analysis of case series.[6] More recently, guidelines for the reporting of drug adverse events were also published by an international group of experts.[7-9] It is unknown, however, whether the publication of these guidance documents led to changes in the nature and characteristics of case series published in the literature.

We conducted a literature review that aims to describe the characteristics of drug-related case series, and to explore whether the characteristics and quality of published case series have changed over time.

All publications (in English or French) listed in PubMed from 1 January 2003 to 15 July 2009 were identified using the following search terms: 'case series' AND 'adverse drug reaction', 'case series' AND 'pharmacovigilance', 'case series' AND 'drug safety', 'case series' AND 'drug toxicity'. We used keywords directly in PubMed, which allowed us to make a wide scan of the literature. Medical Subject Heading (MeSH) terms were also tested but no items were found under 'case series'. 'Pharmacovigilance' was not found as a MeSH term, and only two publications were found using the term 'drug safety'. Under 'drug toxicity', the entry terms found were mainly drug toxicities, drug safety, adverse drug reaction and adverse drug event. These terms were used as keywords in PubMed.

Other references were identified through 'snowballing', i.e. by examining the bibliography of articles found in the electronic searches.

To be included in the review, publications needed to address a minimum of two distinct patients experiencing a given adverse effect in order to be considered as a case series. Reviews and methods articles, editorials and guidelines, single case reports, clinical trials and epidemiological studies with control groups and not based on cases only, as well as studies with missing abstracts were excluded (figure 1). All abstracts of potentially relevant studies were screened and the full-text articles were sought when the study appeared to meet the eligibility criteria.

The characteristics of each case series were recorded into a standardized information matrix, and consisted of the following elements: study design, time period for patient recruitment and/or duration of follow-up for observational cohort studies, number of patients included in the case series, source population, main suspected drug(s) according to Anatomical Therapeutic Chemical classification, type of adverse effect (*International Classification of Diseases, 10th edition* [ICD-10] codes),[10] type of data source and country.

ICD-10 coding was retained to classify adverse effects for this research since it is used by clinicians and health practitioners. Classifications, such as the Medical Dictionary for Regulatory Activities (MedDRA®), are mainly used by health authorities and the biopharmaceutical industry as part of their pharmacovigilance activities.

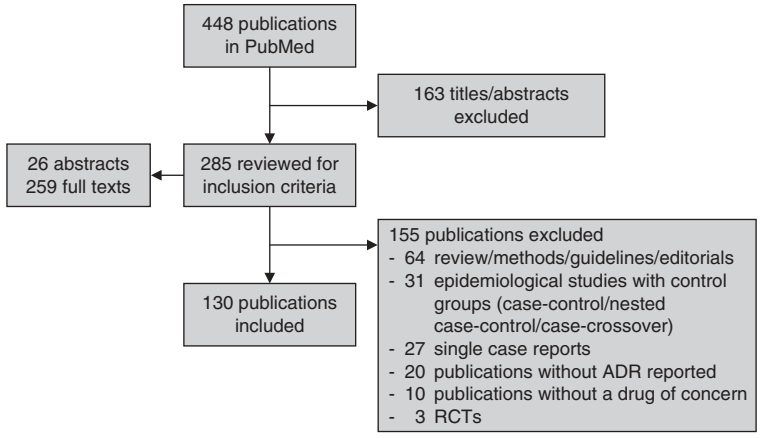

Fig. 1. Outcome of the literature search. **ADR** = adverse drug reaction; **RCT** = randomized controlled trial.

Since some of the case series originated from cohort studies or registries, this classification could not be applied.

The most frequent source of data and adverse events were obtained – case reports, cohorts and pharmacovigilance databases. Because of the small number of studies, we did not tabulate adverse effects that were not original cases in the review [e.g. meta-analysis (n = 4), health databases (n = 4), teleoanalysis (n = 4), nor those from clinical settings (n = 3)].

Case series were also evaluated against the reporting criteria described in the *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment Guidance* (chapter IV, section D).[6] The number of fulfilled criteria was considered as a relative assessment of the quality of the published case series. Although the batch (lot) number is a quality item included in the guidance, it was not retained in the present review since it was not felt to be relevant for a journal publication. This criterion was not taken into consideration in the final score of fulfilling the quality criteria.

1. Findings

1.1 Characteristics of Included Studies

A total of 448 publications were identified in PubMed. Among those, 130 (29.0%) met the eligibility criteria and were reviewed (figure 1) [see Supplemental Digital Content 1, http://links.adisonline.com/DSZ/A35]. The number of eligible case series per publication year (table I) was similar for 2003–5 and has almost doubled since then.

A total of 129 publications reported patient age. The majority concerned adults (age ≥18 years; n = 85 [65.1%]), followed by elderly (age ≥65 years; n = 15 [11.6%]) and youth (age <18 years; n = 11 [8.5%]). Nineteen (14.7%) of the case series included patients of all ages.

Reports of multiple cases that originated from a clinical practice accounted for 43.1% of eligible case series (n = 56) and cohorts accounted for 24.8% (n = 32). In the other published series, cases had originated from spontaneous reporting databases (21%; n = 27), health databases or several sources combined (both 3.1%; n = 4).

Table I. Description of published case series included in the review (by year)

Description	2003	2004	2005	2006	2007	2008	2009[a]
No. of eligible publications	13	14	14	25	22	27	15
No. of full-text publications	9	11	10	17	18	27	13
Average no. of fulfilled publication criteria[6]	6.1	5.7	6.4	6.1	6.3	5.6	5.8

a Up to 15 July 2009.

The median number of patients included in a given case series was 7.5 (range 2–2195). The time period over which the cases were identified was defined in 52 of the 130 publications, with a median of 23 months (range 2 weeks–96 months). Only 11.5% of publications included an analytical component or statistical tests, while 88.5% were descriptive only.

The majority of case series originated from North America {USA (n = 49) or Canada (n = 6) [42.3%]}, European countries (n = 45 [34.6%]) and Asia {China, India, Japan, Singapore, Thailand and Vietnam (n = 12) [9.23%]}.

1.2 Distribution of Adverse Effects and Suspected Drugs

The distribution of the types of adverse effects by system organ class and main suspected drugs by Anatomical Therapeutic Chemical classification are presented in tables II and III, respectively. The most frequently reported adverse effects involved the skin and subcutaneous tissues (18.5%), the circulatory system (13.8%), and the eye and adnexa (13.1%). The main drug classes suspected as causal factors for the reported cases consisted of nervous system drugs (23.1%), antineoplastic and immunomodulating agents (20.0%), and anti-infectives for systemic use (18.5%), among which vaccines accounted for 8.5% overall.

Table II. Distribution of case series by system organ class (SOC) of the adverse effect of interest (*International Classification of Diseases, 10th edition*)[10]

SOC	Publications on a case series [n (%)]
Skin and subcutaneous tissue	24 (18.5)
Circulatory system	18 (13.8)
Eye and adnexa	17 (13.1)
Other	18 (13.8)
Injury, poisoning and consequences of external causes	14 (10.8)
Nervous system	13 (10.0)
Digestive system	12 (9.2)
Symptoms, signs and abnormal clinical findings	5 (3.8)
Musculo-skeletal system	4 (3.1)
Blood and blood-forming organs	4 (3.1)
Total	**130 (100)**

Table III. Distribution of case series according to the suspected drug(s) [Anatomical Therapeutic Chemical (ATC) classification]

ATC class	Publications on a case series [n (%)]
Nervous system	30 (23.1)
Antineoplastic and immunomodulating agents	26 (20.0)
Anti-infectives for systemic use	24 (18.5)[a]
Other	12 (9.2)
Cardiovascular system	8 (6.2)
Musculo-skeletal system	8 (6.2)
Alimentary tract and metabolism	8 (6.2)
Sytemic hormonal preparations	5 (3.8)
Blood and blood forming organs	5 (3.8)
Dermatologicals	4 (3.1)
Total	**130 (100)**

a Among which, 11 (8.5% overall) were associated with vaccines.

The main specific drugs were infliximab (n = 8),[11-18] HMG-CoA reductase inhibitors (n = 4),[19-22] NSAIDs (n = 4),[23-26] leflunomide (n = 3)[27-29] and bisphosphonates (n = 3).[30-32]

When the case series were examined according to the data source (table IV), data obtained from clinical practice focused mostly on adverse effects involving the skin (30.4%) and the eye (16.1%). Series arising from observational cohorts mostly involved injuries and poisoning (21.8%) or the circulatory system (18.7%), while series from pharmacovigilance databases and spontaneous reporting involved the circulatory system (29.6%), the eye and the digestive system (both 14.8%). The median number of cases was 3.5 (range 2–34) in series originating from clinical practice, 15 (range 3–431) in observational cohorts and 36 (range 3–497) in series from pharmacovigilance databases.

Adverse effects and main suspected drugs appeared to change over time (figures 2 and 3, respectively). The number of case series with adverse effects involving the nervous system, the circulatory and digestive systems and the skin has been increasing since 2006. In parallel, the number of case series involving anti-infectives, immunomodulating agents and the nervous system has also been increasing since 2005.

Table IV. Adverse effects (%) in case series by system organ class (SOC) according to the source of data

Source of data	Skin and subcutaneous tissue	Eye and adnexa	Circulatory system	Nervous system	Digestive system	Injury and poisoning
Clinical practice (n = 56)	30.4	16.1	3.7	8.9	12.5	12.5
Observational cohorts (n = 32)	12.5	15.6	18.7	6.3	3.1	21.8
Pharmacovigilance databases (n = 27)	11.1	14.8	29.6	3.7	14.8	0

1.3 Quality of Published Case Series

Using the criteria listed in the Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment document,[6] 77.4% of case series included information on dosage, 76% reported the time since the initiation of the drug, 70% described the use of concomitant medications and only 14% reported the presence or absence of co-morbid conditions (table V).

As shown in figure 4, the average number of criteria fulfilled was six out of the possible nine (range 1–9). Co-morbidity was the criterion that was most often missing. The average number of fulfilled criteria was relatively constant over time (table I), but differed according to the country of origin; the average was 7 for publications originating from France (n = 7) and Turkey (n = 4), 6.7 for those from Australia (n = 3) and 5.7–5.9 for studies from New Zealand (n = 6), Canada (n = 6) and the US (n = 45).

2. Discussion

This review was aimed at describing the characteristics and quality of published case series and trends over time. An important heterogeneity in the nature and characteristics of studies has been observed over a period of 5.5 years. Case series are heterogeneous with respect to sample size and recruitment period, the longest case series not always being the largest in terms of number of patients.

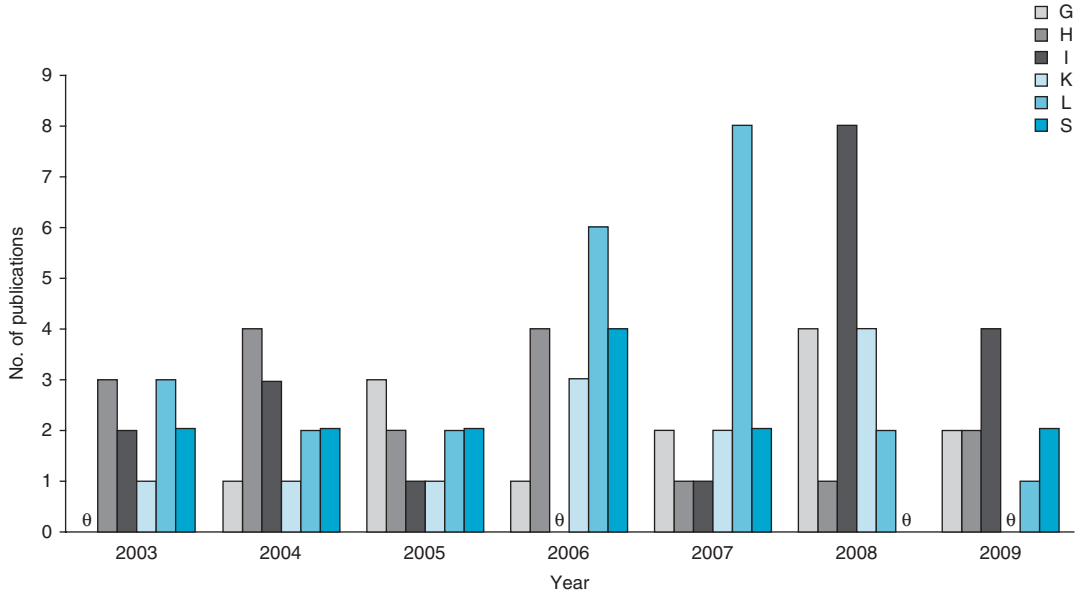

Fig. 2. Distribution of adverse effects (*International Classification of Diseases, 10th edition* codes[10]) reported in case series over time. **G** = Nervous system; **H** = Eye and adnexa; **I** = Circulatory system; **K** = Digestive system; **L** = Skin and subcutaneous tissues; **S** = Injury, poisoning and certain other consequences of external causes.

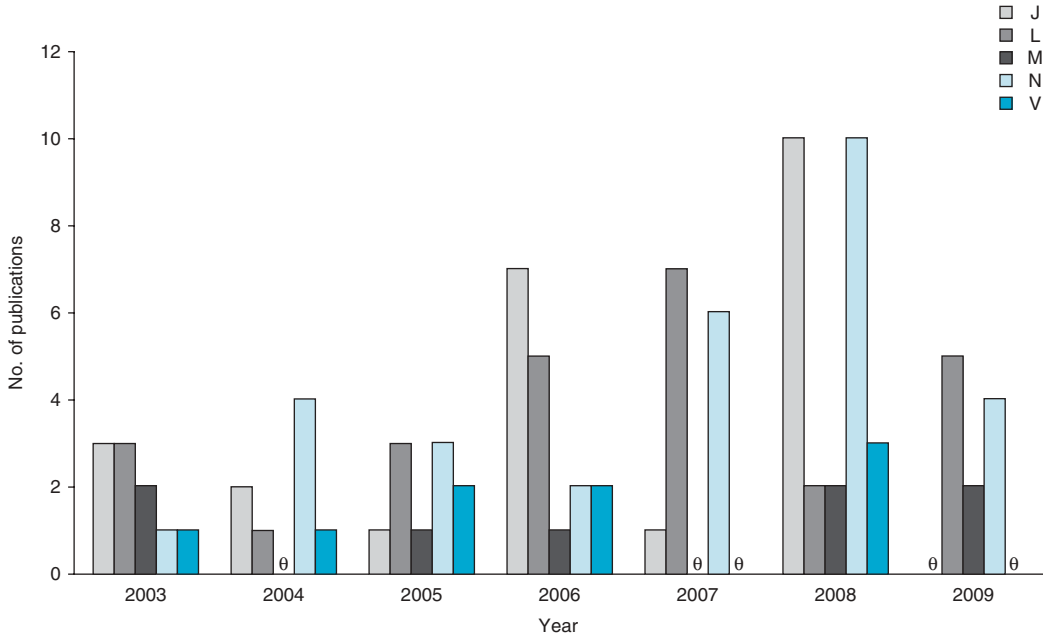

Fig. 3. Distribution of suspected drugs (Anatomical Therapeutic Chemical classification) reported in case series over time. **J** = Anti-infectives for systemic use; **L** = Antineoplastic and immunomodulating agents; **M** = Musculo-skeletal system; **N** = Nervous system; **V** = various.

Even in case series involving high-risk populations such as the elderly, only 14.2% of publications reported on the presence of co-morbid conditions, which are highly prevalent in this population.

Of the case series, 88.5% were strictly descriptive and 11.5% included an analytical component. Although a thorough description of individual clinical history is very important for causality assessment, quantitative measures of risk or rate ratios obtained from such case series may introduce an etiological component. Other advanced methodologies, such as self-controlled designs, may allow one to make inferences about drug-event associations using cases only. The recommendations for published datasets in individual case reports might also be applied to the individual cases in case series.[33] Insufficient reporting criteria may, however, compromise their contribution in drug safety research. As published case series are highly heterogeneous, meta-analysis does not appear to be a valid option.

As PubMed was the only electronic database used in the review, publication bias and the grey literature may have influenced the results. In our review, the possible effect of editorial requests and constraints regarding publications could not be assessed since case series were published in numerous journals. The application of criteria may increase the value of the evidence generated by case series, but is offset by the possible non-publication of case series that could add valuable

Table V. Fulfilment of US FDA guidance criteria[6]

Criteria	Publications fulfilling the criterion [n (%)]
Demographic characteristics	95 (89.6)
Exposure duration	93 (87.7)
Doses used in cases	82 (77.4)
Time from initiation of product exposure to the adverse effect	80 (75.5)
Use of concomitant medications	74 (69.8)
Route of administration	53 (50.0)
Clinical and laboratory manifestations	66 (62.3)
Presence of co-morbid conditions	15 (14.2)
Changes in event reporting rates	9 (8.5)
Lot number	0 (0)

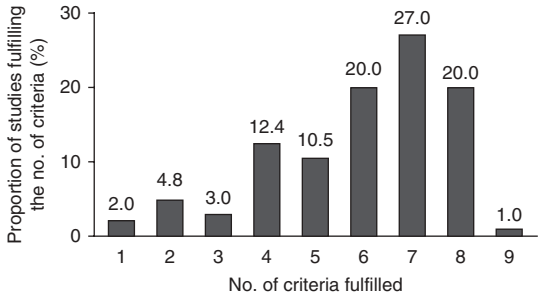

Fig. 4. Distribution of studies according to the number of quality criteria that have been fulfilled. Quality criteria correspond to items published in the Good Pharmacovigilance Practices and Pharmacoepidemiologic Guidance (chapter IV, section D[6]).

information. Missing abstracts or full texts decreased the number of potential studies for the review; however, it is likely that most unpublished or grey literature studies would be of lower quality, which would reinforce our conclusions.

3. Conclusions

An increase in the number of published case series has been observed following the introduction of risk management planning. Whether this increase is due to changes in the drug regulation, publication of guidance documents or greater awareness with drug safety cannot be inferred from this study. Nevertheless, the quality of the published case series does not appear to have changed over time. The heterogeneity in case series found in the literature highlights methodological gaps. Further awareness of guidance documents by reporters and editors could be a useful approach to ensure that all relevant data are reported in published case series.

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References

1. McBride W. Thalidomide and congenital abnormalities [letter]. The Lancet 1961; 278 (7216): 1358
2. Arnaiz JA, Carne X, Riba N, et al. The use of evidence in pharmacovigilance: case reports as the reference source for drug withdrawals. Eur J Clin Pharmacol 2001; 57: 89-91
3. Olivier P, Montastruc JL. The nature of the scientific evidence leading to drug withdrawals for pharmacovigilance reasons in France. Pharmacoepidemiol Drug Saf 2006; 15: 808-12
4. Lexchin J. Drug withdrawals from the Canadian market for safety reasons, 1963-2004. CMAJ 2005; 172: 765-7
5. Auriche M, Bertrand P, Blay N, et al. Good practices of publication of clinical cases of pharmacovigilance: comments, Groupe de Travail sur les Bonnes Pratiques de Publication de Cliniques en Pharmacovigilance: commentary. Therapie 1997 Mar-Apr; 52 (2): 123-7
6. FDA. Guidance for industry: good pharmacovigilance practices and pharmacoepidemiologic assessment [online]. Available from URL: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126834.pdf [Accessed 2010 Jul 30]
7. Kelly W, Arellano F, Barnes J, et al. Guidelines for submitting adverse event reports for publication. Therapie 2009 Jul-Aug; 64 (4): 289-94
8. Kelly WN, Arellano FM, Barnes J, et al. Guidelines for submitting adverse event reports for publication. Pharmacoepidemiol Drug Saf 2007 May; 16 (5): 581-7
9. Kelly WN, Arellano FM, Barnes J, et al. Guidelines for submitting adverse event reports for publication. Drug Saf 2007; 30 (5): 367-73
10. World Health Organization. International classification of diseases (ICD), 10th ed. [online]. Available from URL: http://www.who.int/classifications/icd/en/ [Accessed 2010 Sep 9]
11. Kwon HJ, Cote TR, Cuffe MS, et al. Case reports of heart failure after therapy with a tumor necrosis factor antagonist. Ann Intern Med 2003; 138: 807-11
12. Botsios C, Ostuni P, Todesco S. Frequenza e trattamento delle reazioni all'infusione di infliximab in 186 pazienti con artrite reumatoide: esperienza di Padova. Reumatismo 2005; 57: 44-51
13. Rajaraman RT, Kimura Y, Li S, et al. Retrospective case review of pediatric patients with uveitis treated with infliximab. Ophthalmology 2006; 113: 308-14
14. Merino G, Varas G, Diaz G, et al. Eficacia del infliximab en pacientes con sindrome de Behcet portadores de uveoretinitis grave. Rev Med Chil 2006; 134: 875-82
15. Scollard DM, Joyce MP, Gillis TP. Development of leprosy and type 1 leprosy reactions after treatment with infliximab: a report of 2 cases. Clin Infect Dis 2006; 43: e19-22
16. Fardet L, Dupuy A, Kerob D, et al. Infliximab for severe hidradenitis suppurativa: transient clinical efficacy in 7 consecutive patients. J Am Acad Dermatol 2007; 56: 624-8
17. Severs GA, Lawlor TH, Purcell SM, et al. Cutaneous adverse reaction to infliximab: report of psoriasis developing in 3 patients. Cutis 2007; 80: 231-7
18. Wegscheider BJ, El-Shabrawi L, Weger M, et al. Adverse skin reactions to infliximab in the treatment of intraocular inflammation. Eye 2007; 21: 547-9
19. Fraunfelder FW. Ocular hemorrhage possibly the result of HMG-CoA reductase inhibitors. J Ocul Pharmacol Ther 2004; 20: 179-82

20. Carvajal A, Macias D, Sainz M, et al. HMG CoA reductase inhibitors and impotence: two case series from the Spanish and French drug monitoring systems. Drug Saf 2006; 29: 143-9
21. Fraunfelder FW, Richards AB. Diplopia, blepharoptosis, and ophthalmoplegia and 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitor use. Ophthalmology 2008; 115: 2282-5
22. Tuccori M, Lapi F, Testi A, et al. Statin-associated psychiatric adverse events: a case/non-case evaluation of an Italian database of spontaneous adverse drug reaction reporting. Drug Saf 2008; 31: 1115-23
23. Marques S, Milpied B, Foulc P, et al. Toxidermies graves au celecoxib (Celebrex). Ann Dermatol Venereol 2003; 130: 1051-5
24. Brinker A, Goldkind L, Bonnel R, et al. Spontaneous reports of hypertension leading to hospitalisation in association with rofecoxib, celecoxib, nabumetone and oxaprozin. Drugs Aging 2004; 21: 479-84
25. Kidon MI, Kang LW, Chin CW, et al. Early presentation with angioedema and urticaria in cross-reactive hypersensitivity to nonsteroidal antiinflammatory drugs among young, Asian, atopic children. Pediatrics 2005; 116: e675-80
26. Layton D, Marshall V, Boshier A, et al. Serious skin reactions and selective COX-2 inhibitors: a case series from prescription-event monitoring in England. Drug Saf 2006; 29: 687-96
27. Savage RL, Highton J, Boyd IW, et al. Pneumonitis associated with leflunomide: a profile of New Zealand and Australian reports. Intern Med J 2006; 36: 162-9
28. Shastri V, Betkerur J, Kushalappa PA, et al. Severe cutaneous adverse drug reaction to leflunomide: a report of five cases. Indian J Dermatol Venereol Leprol 2006; 72: 286-9
29. Jian X, Guo G, Ruan Y, et al. Severe cutaneous adverse drug reaction to leflunomide: a report of two cases. Cutan Ocul Toxicol 2008; 27: 5-9
30. Marunick M, Miller R, Gordon S. Adverse oral sequelae to bisphosphonate administration. J Mich Dent Assoc 2005; 87: 44-9
31. Gwynne Jones DP, Savage RL, Highton J. Alendronate-induced synovitis. J Rheumatol 2008; 35: 537-8
32. Grosso A, Douglas I, Hingorani A, et al. Post-marketing assessment of the safety of strontium ranelate; a novel case-only approach to the early detection of adverse drug reactions. Br J Clin Pharmacol 2008; 66: 689-94
33. Kelly WN, Arellano FM, Barnes J, et al. Guidelines for submitting adverse event reports for publication. Drug Saf 2007; 30: 367-73

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