LEADING ARTICLE

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An ABC of Drug-Related Problems

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Abstract

The problems relating to the use of medicines are manifold. They may differ in pharmacological, pathological, epidemiological and legal respects, and may have different consequences, for example, as regards scientific study, regulation or rational use. Pharmacovigilance is concerned with all such problems: adverse effects and interactions as well as problems relating to ineffectiveness, inappropriate use, counterfeiting, dependence or poisoning.

Practically all medicine-related problems can be classified in one basic system, taking into account their characteristics and distinctions. This system distinguishes between appropriate and inappropriate drug use, dose-related and dose-unrelated problems, and types A ('drug actions'), B ('patient reactions') and C ('statistical') adverse effects. This classification may serve as an educational tool and may be useful in when choosing a study method and for the design of effective strategies in pharmacovigilance.

1. Background

By tradition pharmacovigilance, is primarily concerned with the adverse effects of medicines. Adverse effects are usually grouped together, in data sheets, formularies or handbooks, as if they were a more or less uniform group of related diseases, such as viral infections or rheumatic diseases. On the contrary, medicine-induced disorders constitute an extremely wide and heterogeneous group of complaints, symptoms, disorders and syndromes, their only commonality the fact that at some point in their development a medicine has, directly or indirectly, played a role. Thirty years ago the World Health Organization (WHO) defined an *adverse drug reaction* as 'one that is noxious and unintended and occurs at doses normally used in man'.[1,2] In this definition the 'normal dose' clause distinguishes adverse reactions from poisoning, whereas the mechanism underlying the reaction is disregarded. Colitis during the use of an antibacterial may well be an adverse reaction to the drug, even if it is caused by an identified bacterial toxin. A *side effect* is 'a pharmacological effect other than the intended one', and an *adverse drug event* is an 'unintended noxious event occurring during drug therapy' which may or may not be drug-related.[2] The precise wordings of the internationally agreed definitions are given in table I.[2] In many patients the relationship between an adverse reaction and the drug is uncertain, however, and in pharmacovigilance case reports usually and characteristically concern *suspected* adverse drug reactions.

Table I. Definitions[2]

Side effect Any unintended effect of a pharmaceutical product occurring at doses normally used in humans, which is related to the pharmacological properties of the drug
Adverse event Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment
Adverse reaction A response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function
Unexpected adverse reaction An adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorisation, or expected from characteristics of the drug

In this paper adverse reaction and adverse effect are used as synonyms.

In line with the WHO definition and regulatory legislative tradition, adverse effects and poisoning have, for many years, been treated separately. However, a 'dose normally used in man' is a less explicit notion that it may seem. In many patients who have experienced an adverse effect, the amount taken, although below the maximal recommended dose, was too high, because of impaired excretion or some other reason. Untoward responses may occur when a medicine is not taken according to the instructions for use or with wrong expectations (for instance because of unrealistic advertising). Adverse effects, inappropriate use and poisoning are all examples of medicine-related problems, where the interaction between a patient and a medicinal product has for one or another reason lead to a disadvantageous result, for the patient or for the community.

In addition to adverse effects, medicines may give rise to an array of problems, ranging from ineffectiveness to poisoning, from counterfeit to administration error. Recent research has confirmed that such problems are a significant cause of morbidity, hospitalisation and even death.[3-5] Study findings may be difficult to compare or to extrapolate, however, for instance because of differences in definitions or design. On the basis of pharmacological, pathological and epidemiological criteria a number of major categories of medicine-related problems can be recognised.[6-9] These categories can be placed in one integral classification scheme, as shown in figure 1. In this figure dose-related problems are placed above and dose-unrelated problems below, whereas adverse effects occurring during appropriate medicine use are on the right side and those resulting from inappropriate use are on the left. The distinction between these categories is not always sharp, however, and in practice medicine-related problems may have aspects of more than one of these categories.

2. Adverse Effects

A variety of pharmacological, immunological, metabolic or genetic mechanisms can underlie the

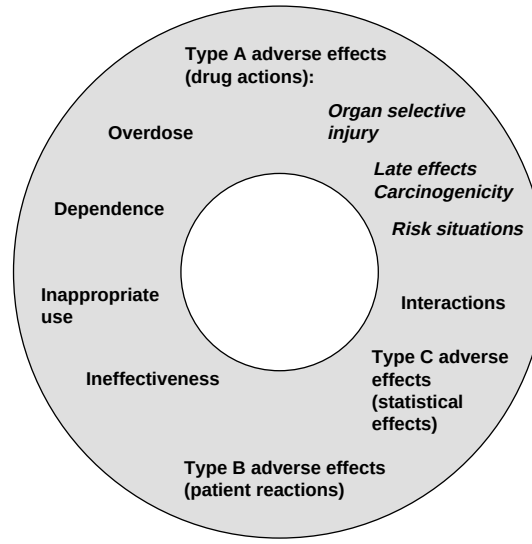

Fig. 1. The zodiac of medicine-related problems. In this figure dose-related problems are placed above and dose-unrelated problems below, whereas adverse effects occurring during appropriate medicine use are on the right side and those resulting from inappropriate use are on the left. The distinction between these categories is not always sharp, however, and in practice medicine-related problems may have aspects of more than one of these categories.

Table II. Type A adverse effects ('drug actions'): pharmacological adverse effects

Common (>1%)
Dose relationship
Suggestive time relationship
Reproducible

development of adverse effects of medicines and, likewise, their clinical manifestations are extremely diverse and variable. In spite of their pluriformity, 3 major groups of adverse effects can be recognised, which are often referred to as types A, B and C.[6-9]

2.1 Type A Adverse Effects: Drug Actions

Type A effects are adverse effects in the true sense of the word. They are pharmacological actions as much as therapeutic effects are; the essential difference being that they are unintended. Examples are constipation during the use of morphine for analgesia, or sedation caused by a hypnotic. Undoubtedly, type A effects are by far the most prevalent. As a rule there is a dose-response relationship: type A effects are more frequent and more severe when higher doses are taken (table II). There is often also a suggestive time relationship between exposure and effect, in accordance with the pharmacokinetic or pharmacodynamic properties of the drug. Because of their pharmacological nature, type A effects are comparatively easy to study (table III). Clinical trials give information on efficacy and tolerability; the latter is largely determined by type A adverse effects. In addition, type A effects can often be reproduced and clarified in a variety of experimental tests (e.g. animal experiments or *in vitro* studies).

Nevertheless, there are many possible reasons why a predominantly pharmacological effect may be less easy to demonstrate and may not be detected in a clinical trial. The delayed discovery of cough induced by ACE inhibitors years after their introduction, is an example. A high background frequency or unspecificity of the event may blur the relation with the drug; the mechanism may be unrelated to the therapeutic action of the drug; the effect may only develop after prolonged administration of the drug. In the example of cough and ACE inhibitors a clear dose response-relationship could not be demonstrated, suggesting the existence of a sensitive subpopulation. As is reviewed below, a variety of pharmacological ('type A') effects occur mainly in special situations or patients with increased susceptibility, for example, demographic determinants, pre-existent disturbances of drug handling, special physiological states, or concomitant use of other medicines or drugs (interactions) (table IV).

2.1.1 Organ Selective Injury

There are many medicines that are generally well tolerated, but exert selective toxic effects on one particular organ, tissue or structure, for instance because of accumulation or the production of toxic metabolic intermediates in the particular tissue. Examples are aminoglycoside and ototoxicity or chloroquine-induced retinopathy ('bull's eye').

2.1.2 Late Effects

There are many examples of type A effects that take months or even years of drug use to develop (e.g. tardive dyskinesia induced by antipsychotics). Their detection may be difficult because of the absence of a suggestive time relationship.

Carcinogenicity is a special form of late effect. Fortunately, many potential carcinogenic or mutagenic drugs are eliminated during preclinical testing. Nevertheless, there are several examples of medicines that were found to be associated with an increased risk of the development of malignant diseases, for instance, diethylstilbestrol (vaginal carcinoma after maternal exposure), oral contraceptives (hepatic carcinoma), phenacetin (carcinoma of the urinary tract), immune suppressants such as azathioprine or cyclosporin (malignant lymphoma),

Table III. Type A adverse effects ('drug actions'): methods of study

Clinical trial
Spontaneous reporting
Experiments
Hospital studies
Prescription event monitoring
Follow-up studies

Table IV. Type A adverse effects occurring in special situations or patients with increased susceptibility

Organ selective injury
Late effects
carcinogenicity, mutagenicity
Interactions
Risk situations:
childhood
the elderly
renal failure
haemodialysis
pregnancy
lactation

or the contrast dye thorium dioxide (widely used in the past and associated with renal carcinoma and leukaemia).[10]

2.1.3 Risk Groups

There are many different physiological or pathological states that predispose to the development of basically pharmacological effects. Pregnancy, lactation, childhood, elderly, decreased renal clearance or haemodialysis, all have characteristic features which may allow medicines to exhibit effects that would otherwise be rare or could not occur. The notorious teratogenicity of thalidomide is a clear example. Because trial patients are selected, clinical trials are unlikely to yield information regarding such special populations. Other methods of detection, for example those used for type B adverse effects, may be needed.

2.1.4 Interactions

Since many medicines may interact in many different ways, medicine-medicine, medicine-food or medicine-drug (e.g. alcohol) interactions play an important role in pharmacovigilance. Because of their pharmacological mechanism, interactions can often be classified as type A effects. Sometimes drugs react physicochemically when exposed outside the body, for example, when injected into an intravenous line. Although not a truly pharmacological effect, this phenomenon of pharmaceutical incompatibility is included here.

2.2 Type B Adverse Effects: Patient Reactions

The second major category, the type B adverse effects, refers to the phenomenon that a medicine is well tolerated by the (vast) majority of users, but occasionally elicits an 'allergic' reaction (allos = different) (tables V and VI). Often and characteristically, type B effects are acute, unexpected and severe. Often there is a characteristic sensibilisation period of about 10 days, but a fairly long latency period may also occur. Such reactions may be as rare as 1 in 5000 or even 10 000 patients and yet may be very important, for the merit of the medicine and from the public health point of view. Type B adverse effects are a major reason for withdrawal of medicines from the market. Characteristically, there is little or no dose relationship: the reaction is not more frequent or more severe in patients using higher doses. Therefore, in figure 1, type B effects are depicted to be opposite type A effects.

Type B adverse effects are either immunological or nonimmunological forms of hypersensitivity and occur in patients with an, often unknown or unrecognised, predisposing condition. Immunoallergic reactions may have complex pathology and take many forms, ranging from nonspecific rashes to specific reactions such as cholestatic hepatitis, agranulocytosis or autoimmune syndromes (see table VII). Several drugs are known directly – that is, without the involvement of an antigen-antibody reaction – to release mediators of inflammation (no-

Table V. Type B adverse effects ('patient reactions')

Immunoallergic reactions
Metabolic intolerance
Idiosyncrasy
rare (<1%)
unexpected
causality uncertain
mechanism uncertain
no dose relationship
not reproducible experimentally
characteristic, serious
suggestive time relationship
low background frequency

Table VI. Type B adverse effects ('patient reactions'): methods of study

Spontaneous reporting
Prescription event monitoring
Case control surveillance
Large databases/record linkage

tably histamine) and elicit pseudoallergic reactions, for instance morphine-induced urticaria or aspirin (acetylsalicylic acid)-mediated bronchospasm. The notion of 'intolerance' usually refers to patients with an excessive response to a normal dose of a medicine, for example, because of a slow metabolism. The response is qualitatively normal but quantitatively excessive. In the case of idiosyncrasy (a word indicating that the reaction is determined by the constitution of the patient), on the other hand, the response is also qualitatively different. Among the many examples are haemolytic reactions in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency and, possibly, phenylbutazone-related aplastic anaemia. Type B adverse effects are notoriously difficult to study experimentally and often the mechanism is not known or not fully clarified. Diagnostic tests are rarely available and in the individual patient the connection often remains unproved. There are several examples that a medicine was withdrawn because of an idiosyncratic reaction, whereas the underlying mechanisms was never elucidated (a striking example was the practolol-associated sclerosing peritonitis).

That type B adverse effects, in spite of so much difficulty, are often readily detected, is explained by the situation that these effects often occur in a suggestive time relationship with drug exposure, are characteristic and have a low background frequency. In this light it is understandable why spontaneous reporting, the major system used by national pharmacovigilance centres, has been found to be especially effective in detecting type B adverse effects (table VI).[11] Other methods for studying type B effects are prescription event monitoring, case control surveillance and record linkage (e.g. by using large automated databases).[9,12]

2.3 Type C Adverse Effects: 'Statistical Effects'

Since the controversy regarding increased cardiovascular mortality in patients with diabetes mellitus using oral hypoglycaemic drugs emerging from the prestigious University Diabetes Group Diabetes Program report in the early seventies, numerous connections have been assumed to exist between drug exposure and disease frequency.[13] Another example is the increased overall occurrence of malignant diseases observed in clofibrate-users in a large multinational study of the prevention of ischaemic heart disease.[14] Such type C adverse effects can be defined as the increased occurrence of a given disease in patients using a particular drug, as compared with the (relatively high) background frequency in unexposed patients (table

Table VII. Examples of immunological adverse drug reactions

Skin
Urticaria
Maculopapular rash
Erythema nodosum
Eczema
Lichenoid eruptions
Vasculitis
Stevens-Johnson syndrome
Toxic epidermal necrolysis
Blood
Thrombocytopenia
Agranulocytosis
Haemolytic anaemia
Aplastic anaemia
Liver
Cholestatic hepatitis
Hepatocellular hepatitis
Kidney
Interstitial nephritis
Glomerulonephritis
Lung
Pneumonitis (eosinophilic, alveolar, interstitial)
Systemic
Anaphylaxis
Vasculitis
Serum sickness
Systemic lupus erythematosus

Table VIII. Type C adverse effects ('statistical effects')

Increased frequency of 'spontaneous' disease
high background frequency
less typical for a drug reaction
no suggestive time relationship
often long latency
mechanism unknown
difficult to reproduce experimentally

VIII). The association is essentially one of statistical disproportionality. The possibility of confounding is a notorious problem. Compared with type B adverse effects, type C effects have a higher background frequency and a less obvious time relationship. Type C adverse effects, like type B adverse effects, are often difficult to study in experimental models and (at first) the mechanism often is unknown. Later on the mechanism may become understood, as happened for example in the case of increased risks of biliary stones or thromboembolic disease in women using oral contraceptives.

Because of the probability of coincidence and the absence of a suggestive time relationship or a specific marker, in these patients the involvement of the drug often remains uncertain or doubtful. Therefore, spontaneous reporting is of limited use for the detection and study of type C effects (table IX). Prescription event monitoring, on the other hand, may be of value, provided that the adverse event collection takes place after the latency period and the sample size is large enough.

Although follow-up (cohort) studies are theoretically the method of choice to study a medicine, the required population size and study duration often pose scientific, logistic, ethical and financial problems. Also, the acquisition of a suitable control population may be cumbersome. Although experiences with case control surveillance and nested case control studies using large linked databases are promising, the study of type C adverse effects remains a major challenge to pharmacovigilance and pharmacoepidemiology.

3. Therapeutic Ineffectiveness

The healing power of medicines is inherently limited and especially in chronic and serious diseases insufficient effectiveness is frequently encountered. Sometimes ineffectiveness is dose related and sometimes it is not. Although perhaps not an adverse effect in the true sense of the word, ineffectiveness is obviously an unintended and potentially harmful response. About half of medicine-related hospital admissions are because of ineffectiveness.[3] Effect evaluation – especially for long term use – is therefore undoubtedly one of the tasks of pharmacovigilance.

Ineffectiveness, especially when unexpected, can be secondary to inappropriate use (e.g. wrong dose, wrong duration or wrong indication) (table X). Furthermore, unexpected ineffectiveness can be an important warning sign in pharmacovigilance, for example, concerning an interaction, a pharmaceutical defect, a counterfeit product, tolerance or resistance development (table XI). The importance of alertness for counterfeit drugs can be illustrated by a recent report of the WHO Data Base on Counterfeit Pharmaceuticals, in which 751 cases of counterfeiting were reviewed, occurring in developing as well as developed countries.[15,16] In rare instances ineffectiveness is caused by metabolic insensitivity of the patient (i.e. the opposite of intolerance), for example in the case of hereditary coumarin resistance (a rare autosomal, dominant condition).

4. Noncompliance and Inappropriate Use

As is indicated in the definition of the WHO, any type A, B or C adverse effect can occur during entirely appropriate medicine use. This is a matter of bad luck or a calculated risk. The distinction

Table IX. Type C adverse effects ('statistic effects'): methods of study

Follow-up studies (cohort)
Case control studies
Prescription event monitoring
Large databases/record linkages
Spontaneous reporting is of limited use

Table X. Therapeutic ineffectiveness

Pharmaceutical defects and counterfeit
Inappropriate use (noncompliance)
Interactions
Resistance
Tolerance

between appropriate and inappropriate use of a medicine may be less obvious, however, than one might think. It is our experience, for example, that in the history of a patient with a serious adverse reaction, with hindsight often a moment can be found when an unfortunate decision was made, a precaution disregarded or a warning sign overlooked.

When medicine is not taken properly, the risk of adverse effects – type A in particular – is likely to increase, in frequency and in severity. Inappropriate medicine use (i.e. not or not fully in accordance with the approved instructions for use) may have many different shapes and causes, ranging from unrealistic promotion or a wrong attitude of the patient, to 'off-label' use (common in children) or medication error.[17-19] When a drug is used in a way that is contrary to the instructions for use, the adverse effects may legally have a different position and therefore be difficult to deal with in drug regulation. Regulatory management of analgesic nephropathy, for example, has been delayed in several countries because it only occurs after inappropriate use of the analgesic (excessive doses for excessive periods of time). In recent years it has become understood that the vast grey area of suboptimal use of medicines is of great importance in pharmacovigilance. Since about 50% of medicine-related problems leading to hospital admission were found to be avoidable,[3] there is much to be gained from preventive measures in this area. Inappropriate medicine use, however, is often difficult to study (table XII). Sometimes the information in the case reports sent to a spontaneous reporting system already suggest that there is something wrong, for example, that too high a dose or a wrong indication is involved. Often active study is needed, however, to unmask inappropriate use as the cause of a problem, for example an inquiry or a hospital study.

5. Dependence and Addiction; Tolerance and Rebound

Dependence in its various forms often can be seen as noncompliance in the extreme: the indication is often not (or no longer) valid and there is a strong tendency to increase the dose beyond the maximum and to a prolonged duration of use. The potential of inducing dependence is in many cases an inherent feature of the drug, which should be included in pharmacovigilance. The triad dependence, tolerance development and withdrawal reaction is pharmacologically of special interest. A withdrawal or a rebound reaction can be seen as a virtual pharmacologic effect. The drug stimulates the body to take counteractions which, during readaptation after discontinuation of the exposure, may in turn have detrimental results. Mechanistically, there is a similarity with the phenomenon of enzyme induction and what happens after the drug is stopped.

As a rule, opioids and sedative drugs can cause dependence. The fact that there was ignorance for a long time about the addicting properties of benzodiazepine derivatives, in spite of its far reaching consequences, illustrates the importance of dependence as a focus of pharmacovigilance. Another example, the question of whether deterioration in a patient's condition after stopping an antidepressive drug is a relapse of depression or is a mistaken withdrawal reaction, has still to be unravelled.[20] Dependence is not restricted to psychotropic drugs,

Table XI. Inappropriate drug use

Wrong dose
Wrong duration
Wrong route
Wrong indication
Wrong expectations
'off label' use and noncompliance
failure of information or monitoring
neglect of precautions
medication administration error

Table XII. Inappropriate use: methods of study

spontaneous reporting
prescription event monitoring
questionnaire
cross sectional studies
follow-up studies

however, but may – often unexpectedly – occur with a variety of other medicines, such as nasal decongestants ('nose drop nose'), laxatives, or minor analgesics. Analgesic nephropathy, a sequel of the prolonged abuse of the latter drugs, is still a major concern of pharmacovigilance.[21]

Dependence is notoriously difficult to study. So long as the patient gets the drug, the doctor prescribes it and the pharmacist dispenses it, all seem happy, until the addiction is out of control. In routine monitoring of drug addiction, spontaneous reporting plays a major role. For better information to become available, active data collection is required, which may be difficult because of the strategy of denial often built up by such patients.

6. Overdose and Poisoning

From dependence, with the notorious associated tendency of patients to increase the amounts taken, it is a small step further to overdose or poisoning. Poisoning may be relative or absolute, may be recreational, iatrogenic, intentional or accidental, and may be acute or chronic.

From poisoning, which constitutes excessive pharmacological effects, it is only one step to the type A adverse effects where we started and thereby we have come full circle.

In many countries, a national poison control system is operational, at the same time ensuring proper treatment of poisoning and monitoring the toxic potential of new medicines. Acute poisoning can be seen as an unintended human experiment, which may be very interesting from the pharmacological point of view. There are several examples of medicines that were found to exert a toxic effect in overdose, which was predictive of an adverse effect during chronic therapeutic use. In many countries, poisoning was originally regarded as separate from therapeutic drug use and, also for legal reasons, beyond the scope of drug regulation. According to Dutch law, for example, a medicine had to be safe 'when used as recommended'. Worldwide there is now a tendency towards increased collaboration or even integration of poison control and pharmacovigilance.

7. 'Indirect' Adverse Effects

Apart from therapeutic administration, medicines can, throughout the process of production, distribution and destruction, give rise to health hazards in a variety of ways. A production error could lead to contamination of the environment with a toxic intermediary or waste product. Widely used drugs that are excreted unchanged or as an active metabolite may be traceable in the surface water. Antibacterial use in, for instance the bioindustry, may lead to bacterial resistance development. These types of indirect harmful effects of medicines have not been included in the classification in figure 1.

8. Implications

Drug related problems have a variety of different causes, ranging from adverse effects and interactions to ineffectiveness, inappropriate use, counterfeiting, dependence and poisoning. Between the appropriate use and overt misuse of medicines there is a vast grey area of suboptimal use, which may decrease safety. Pharmacovigilance is concerned with all aspects of the use of medicines that have consequences with regard to safety, efficacy and rational use.

There is not one method that can be used to study all aspects of all medicines and there probably never will be. Traditionally there are 2 major systems for ongoing 'open question' vigilance: spontaneous reporting (especially for the detection of type B adverse effects) and poison control (mainly concerned with acute poisoning). Different problems often need different methods of study. As a rule such studies need to be specifically designed for the question or purpose and are limited in scope, size and duration. There is a limited number of methods available for the study of marketed med-

icines, each with specific advantages and limitations, as is illustrated in tables II, VI, VIII and XI.[6,15] New approaches are under development, combining aspects of monitoring and formal study, for example, case control surveillance or data mining or nested case control studies using large automated databases.

The classification proposed in this paper (figure 1) covers the entire scale of medicine-related problems, taking into account their basic characteristics and distinctions, and is generally applicable. It may serve as an educational structure for a good understanding by practitioners and scientists (e.g. clinicians, pharmacists, pharmacologists and epidemiologists) of the complex problems relating to drug treatment. In addition, it may be useful for the proper choice of a study method and for the design of rational and efficient strategies for the scientific study of medicines after approval.

References

1. Drug Monitoring. The role of the hospital. WHO Technical Report Series 425. World Health Organization, Geneva, Switzerland, 1969
2. Edwards IR, Biriell C. Harmonisation in pharmacovigilance. Drug Saf 1994; 10: 93-102
3. Nelson KM, Talbert RL. Drug-related hospital admissions. Pharmacotherapy 1996; 16: 701-7
4. Imbs JL. Pouyanne P, Haramburu F, et al. Iatrogenie médicamenteuse: estimation de sa prévalance dans les hôpitaux publics français. Thérapie 1999; 34: 21-7
5. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients. JAMA 1998; 279: 1200-5
6. Rawlins MD, Thompson JW. Mechanisms of adverse drug reactions. In: Davies DM, editor. Textbook of adverse drug reactions. IVth ed. Oxford: Oxford University Press, 1991: 18-45
7. Inman WHW, editor. Monitoring for drug safety. 2nd ed. Lancaster: MTP Press, 1986
8. Royer RJ. Mechanism of action of adverse drug reactions: an overview. Pharmacoepidemiol Drug Saf 1997; Suppl. 3: S43-S50
9. Meyboom RHB, Egberts ACG, Edwards IR, et al. Principles of signal detection in pharmacovigilance. Drug Saf 1997; 16: 355-65
10. Dukes MNG, editor. Meyler's side effects of drugs. 13th ed. Amsterdam: Elsevier Science Publishers, 1996
11. Meyboom RHB, Gribnau FWJ, Hekster YA, et al. Characteristics of topics in pharmacovigilance in the Netherlands. Clin Drug Invest 1996; 4: 207-19
12. Strom BL, editor. Pharmacoepidemiology. 2nd ed. Chichester: John Wiley & Sons, 1994
13. The committee for the assessment of the biometric aspects of controlled trials of hypoglycaemic agents. Special Report. JAMA 1975; 213: 583
14. Committee of Principle Investigators. A cooperative trial in the primary prevention of ischaemic heart disease using clofibrate. Br Heart J 1978; 40: 1069
15. Kimura K. WHO Data Base on Counterfeit Pharmaceuticals. World Health Organization, Geneva, 1998
16. Counterfeit Drugs. Guidelines for the development of measures to combat counterfeit drugs. Department of Essential Drugs and Other Medicines. World Health Organization, Geneva, Switzerland, 1999
17. Conroy S, Choonara I, Impicciatore P, et al. Survey of unlicensed and off label drug use in paediatric wards in European countries. BMJ 2000; 320: 79-82
18. Phillips DP, Christenfeld N, Glynn LM. Increase in US medication-error deaths between 1983-1993. Lancet 1997; 351: 643-4
19. Kohn LT, Corrigan JM, Donaldson MS, editors. To err is human. Building a safer health system. Committee on Quality of Health Care in America. National Academy Press, Washington DC, 1999
20. Medawar C. The antidepressant web. Int J Risk Saf Med 1997; 10: 75-127
21. De Broe ME, Elseviers MM. Analgesic nephropathy. N Engl J Med 1998; 338: 446-52

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