Drug-related problems:
definitions and classification

When reviewing literature on drug-related problems, most studies are difficult to compare because of variations in definitions and classification. A uniform definition and classification system for drug-related problems would solve this. A proposal for such a system is described in this article.

PMLA van den Bemt PhD

Professor ACG Egberts

Drugs are a dualistic therapeutic tool. They are intended to cure, prevent or diagnose diseases, signs or symptoms, but the shadow side is that improper use can be the cause of patient morbidity and even mortality. While in the 1960s the interest in adverse drug reactions increased greatly after the thalidomide disaster (which can be considered as the final trigger for the establishment of formal programmes of drug approval and subsequent surveillance), only in recent years has attention shifted toward the problem of medication errors [1]. Literature is now expanding rapidly for both adverse drug reactions and medication errors.

In general, problems related to the use of approved drugs can be summarised with the term "drug-related problems" [2]. When reviewing the literature on drug-related problems (DRPs), one quickly discovers that most studies are difficult to compare because of variations in definitions and classification of DRPs [3, 4]. A uniform definition and classification system for drug-related problems would solve these difficulties.

Definitions

DRPs can be divided into intrinsic and extrinsic toxicity. Intrinsic toxicity is caused by the interaction of the pharmaceutical, chemical and/or pharmacological characteristics of the drug itself and the human biosystem. Intrinsic toxicity is therefore synonymous with adverse drug reactions (ADRs). An ADR is defined by the World Health Organization (WHO) as "any response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function" [5]. Previously unknown drug-drug interactions and lack of therapeutic effect [6] are included in this definition. Mechanistically there are two types of ADRs: Type A and Type B [2].

Type A reactions are pharmacological effects as much as therapeutic actions are, the essential difference being that they are unintended. Examples are constipation during the use of morphine and peptic ulcer induced by NSAIDs. Type A effects are by far the most prevalent. As a rule, there is a dose-response relationship: Type A ADRs are more frequent and more severe when higher doses are taken.

Type B reactions, in contrast, refer to the phenomenon that a medicine is well tolerated by the (vast) majority of users but elicits an idiosyncratic reaction in predisposed patients. Type B effects are often unexpected (ie from pharmacology), rare and severe. Type B reactions have historically been the major reason for the withdrawal of medicines from the market. Characteristically there is no dose-response relationship. Type B effects are either immunological or non-immunological forms of hypersensitivity and occur in patients with a predisposing condition, which is often unknown or unrecognised. Stevens-Johnson Syndrome and anaphylactic shock are two examples of Type B reactions.

Extrinsic toxicity refers to the problems caused by the handling of the drug either by the healthcare professional or by the patient. The drug is not used in the proper way: a medication error has been made. A medication error is defined as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient or consumer [7]. Therefore, medication errors do not necessarily need to result in harm to the patient. In contrast, ADRs always involve some form of harm. Known drug-drug

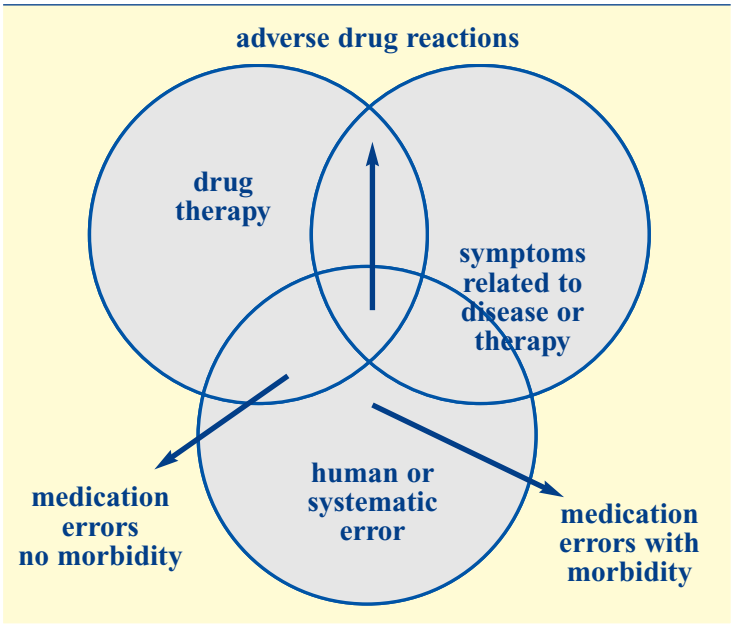

Table 1: Classification of prescribing errors

Administrative and procedural errors
- general (e.g. readability)
- patient data (e.g. patient mix-up)
- ward data and prescriber data
- drug name
- dosage form and route of administration

Dosage errors
- strength
- frequency
- dosage too high/low
- no maximum dosage in "at need" prescription
- length of therapy
- directions for use

Therapeutic errors
- indication
- contra-indication
- monitoring
- drug-drug interaction
- incorrect monotherapy
- (pseudo) duplicate therapy (duplicate therapy would be e.g. inderal [contains propranolol] and propranolol; pseudo duplicate therapy would be e.g. omeprazol and pantoprazol [two drugs from same therapeutic category])

interactions can be seen as medication errors because the drugs were prescribed not taking into account the interaction.

Finally, the term "adverse drug events" is frequently encountered in literature. These are defined as injuries occurring during drug therapy, but this association may not necessarily be causal. They comprise both ADRs and medication errors [8-10]. The relationship between the various definitions is depicted in Figure 1.

Classification of intrinsic toxicity

ADRs can be classified using the WHO adverse reaction terminology [11]. According to this, ADRs are divided into 32 system-organ classes (e.g. skin). The class forms the first part of the code (e.g. 0100 for skin). The second part is formed by the so-called "preferred term," a code that describes the ADR more specifically (e.g. 0001 for acne). Together both codes form the exact classification of the ADR, so 0100-0001 would refer to the skin reaction acne. A classification of seriousness is also often necessary. This can be achieved by applying the WHO Critical Terms List [12], which are ADR-codes related to possibly serious conditions. In practice, this classification is more useful than the more legal definition of serious: death, invalidity or (a longer duration of) hospitalisation. Finally, it is important to do a causality assessment of ADRs, for which various systems exist [13].

Another ADR terminology coding system, the Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART), was used together with the WHO coding system and the International Classification of Diseases (ICD) to create the Medical Dictionary for Drug Regulatory Affairs (MedDRA). This terminology is increasingly being used in the pre- and post-marketing phases of the medicines regulatory process [14].

Classification of extrinsic toxicity

Medication errors can be divided into five main classes: prescribing, transcription, dispensing, administration (including non-compliance) and "across settings" (errors occurring on the interface between different healthcare settings – for example, between hospital and ambulatory care) [3, 7, 15].

Prescribing errors are those occurring in the process of selecting and prescribing a drug and on monitoring of therapy. Table 1 shows a subclassification of types of prescribing errors [16].

Transcription errors occur when transcribing or interpreting a medication order of the physician. In literature, no subclassification of transcription errors can be found: an order is either transcribed correctly or not.

When the pharmacy makes an error, it is called a dispensing error. For example, the wrong drug or strength can be dispensed or a preparation error may occur [17]. A subclassification of dispensing errors can be found in Table 2. Errors made in the last stage of the drug distribution

process are administration errors. These errors are made by nurses or doctors in hospital or by the patient in the ambulatory setting (non-compliance). Table 3 shows the subclassification [18].

A bit of an exotic class of medication errors are the "across settings" errors, which are not mentioned as such in international literature. Yet studies have been performed on this class of errors, which occur, for example, when patients are admitted to or discharged from hospital. As in transcription errors, no subclassification is made.

As is the case with ADRs, medication errors can be classified in classes of seriousness. This can be done by using a modified version of the classification of the National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP) [7, 19]. This classification is illustrated in Table 4.

Conclusion

By choosing uniform definitions and classification of DRPs, results of studies can be communicated unambiguously. The same goes for reports in medication error reporting systems. The classification system presented in this article is not definite. Although it has proven value in Dutch studies on drug safety [20], it is subject to further improvement. Nevertheless, it may certainly constitute a firm basis for a uniform classification system. The authors welcome reactions to this proposal.

Authors

PMLA van den Bemt, PhD
Professor ACG Egberts
Division of Pharmacoepidemiology and Pharmacotherapy
Utrecht Institute for Pharmaceutical Sciences
Utrecht University
PO Box 80082
3508 TB, Utrecht, The Netherlands
p.m.l.a.vandenbemt@ pharm.uu.nl
a.c.g.egberts@pharm.uu.nl

Table 2: Classification of dispensing errors

- for wrong patient or for wrong ward
- wrong drug
- wrong dosage form
- wrong strength
- wrong time

Table 3: Classification of administration errors

- omission (drug not administered)
- unordered
- wrong preparation
- wrong dosage form
- wrong route of administration
- wrong administration technique
- wrong dosage
- wrong time (at least 60 minutes early/late)
- compliance/adherence

Table 4: Classification of medication errors in classes of seriousness

A
An error has been made, but the medication did not reach the patient

B
An error has been made, and the medication reaches the patient, but no harm is done
B1
medication not administered
B2
medication administered but no harm

C
An error has been made which results in an increased frequency of monitoring, but no harm is done

D
An error has been made, and harm is done
D1
temporary damage necessitating treatment
D2
temporary damage resulting in an increased length of hospital stay
D3
permanent damage
D4
patient nearly dies

E
An error has been made which results in the death of the patient

References

1. Kohn L, Corrigan J, Donaldson M, Ed. To Err Is Human: Building a Safer Health System. Committee on Quality of Health Care in America. Institute of Medicine. Washington, DC, National Academy Press, 1999.
2. Meyboom RHB, Lindquist M, Egberts ACG. An ABC of drug-related problems. Drug Safety 2000;22:415-23. Erratum in: Drug Safety 2000;23:99.
3. Bemt van den PMLA, Egberts ACG, De Jong-van den Berg LTW, Brouwers JRBJ. Drug-related problems in hospitalized patients – a review. Drug Safety 2000;22:321-33.
4. Mil van JW, Westerlund LOT, Hersberger KE, Schaefer MA. Drug-related problem classification systems. Ann Pharmacother 2004;38:859-67.
5. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet 2000;356:1255-9.
6. Meyboom RHB, Lindquist M, Flygare AK, Biriell C, Edwards IR. The value of reporting therapeutic ineffectiveness as an adverse drug reaction. Drug Safety 2000;23:95-9.
7. National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP), www.nccmerp.org (approached May 2006).
8. Leape LL. Preventing adverse drug events. Am J Health-Syst Pharm 1995;52:-379-82.
9. Nebeker JR, Barach P, Samore MH. Clarifying adverse drug events: a clinician's guide to terminology, documentation and reporting. Ann Intern Med 2004;140:795-801.
10. Morimoto T, Gandhi TK, Seger AC, Hsieh TC, Bates DW. Adverse drug events and medication errors: detection and classification methods. Qual Saf Health Care 2004;13:306-14.
11. International monitoring of adverse reactions to drugs. Adverse reaction terminology. Uppsala: WHO Collaborating Centre for International Drug Monitoring, 2002.
12. WHO adverse reaction terminology – critical term list. Uppsala: The Uppsala WHO Monitoring Centre, 2002.
13. Meyboom RHB, Hekster YA, Egberts AC, et al. Causal or casual? The role of causality assessment in pharmacovigilance. Drug Saf 1997;17:374-89.
14. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). Drug Saf 1999;20:109-17.
15. Shojania KG. Safe medication prescribing and monitoring in the outpatient setting. CMAJ 2006;174:1257-8.
16. Fijn R, Van den Bemt PMLA, Chow M, et al. Hospital prescribing errors: epidemiological assessment of predictors. Br J Clin Pharmacol 2002;53:326-31.
17. Kelly WN. Pharmacy contributions to adverse medication events. Am J Health-Syst Pharm 1995;52:385-90.
18. Allan EL, Barker KN. Fundamentals of medication error research. Am J Hosp Pharm 1990;47:555-71.
19. Bemt van den PMLA, Fijn R, Voort van der PHJ, Gossen AA, Egberts ACG, Brouwers JRBJ. Frequency and determinants of drug administration errors in the intensive care unit. Crit Care Med 2002;30:846-50.
20. Van den Bemt PMLA. Drug Safety in Hospitalised Patients [thesis]. Groningen University, 2002.