Article title: Application of the Pareto principle to identify and address drug therapy safety issues

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(A) Supplementary details to the methods section

1. Definitions

Medication errors

A medication error (ME) was defined as “inappropriate use of a drug that may or may not result in harm” [22]. This included: Application or prescription of a contraindicated drug or contraindicated combination of drugs, application or prescription of a drug without any plausible clinical indication, clinically relevant underdosing or overdosing, failure to monitor drug concentration or effects according to the prescribing information, or continued application or prescription of a drug causing clinically relevant side effects in the patient in spite of available less harmful alternative. Errors with little or no potential for harm as well as guideline-backed off-label use were not considered ME.

Adverse drug events

Adverse drug events (ADE) were defined as injuries “resulting from the administration of a drug” [23], further specified as clinically relevant symptom or symptom complex or a clinically relevant abnormality in the electrocardiogram or clinical laboratory assessment, resulting from administration of one or more drugs, regardless of whether ME were causally involved.

Interdependence between ME, ADE and concurrent disease(s)

Current key models for assessment of drug-associated risk situations are hampered by logical inconsistencies and often cannot be used to deal with the complexity of real clinical cases [21]. Therefore, we developed a new approach for identification, classification and counting of drug-related risk situations and applied this method to the current study [21]. In short, we defined a “medication pathway” as the sum of all decisions and activities involved in the application of a single drug (main components: drug prescription, drug preparation, drug application and drug monitoring). This pathway may be repeated over time, e.g., at the application of a second dose of a drug. At all stages of the pathway, ME may occur. A single medication pathway may contain more than one ME, e.g., a contraindicated drug (ME1) could be given intravenously instead of intra-articularly (ME2). One medication pathway may causally be involved in one or more distinct ADE, e.g., haloperidol may cause both hyperkinesia and exanthema. On the other hand, more than one medication pathway may
be involved in one ADE, e.g., concomitant administration of several antihypertensive drugs may cause symptomatic hypotension. In extension, more than one medication pathway involving more than one ME may contribute to one or more ADE. In addition, concomitant disease may play a role. E.g., administration of acetylsalicylic acid and clopidogrel (two medication pathways) in a patient with implantation of a drug-eluting stent for coronary heart disease (disease 1), and gastritis as concomitant disease (disease 2) may cause upper gastrointestinal bleeding (one ADE). Acetylsalicylic acid may have contributed to disease 2 (gastritis), and the gastritis in turn may have contributed to upper gastrointestinal bleeding. The complexity of the situation is increased even more by time (repeated administration of the same drug or administration of several drugs at different time points being involved in one or more ADE). For more details concerning a systematic approach of how to deal with the complexity of real-life cases, we would like to refer to our previous publication [21].

2. **Screening for events and errors and data handling**

Demographic, clinical and laboratory data as well as drug prescriptions were documented in the commercial Good-Clinical-Practice certified study documentation system secuTrial® (iAS GmbH, Berlin, Germany).

The complete charts of 752 non-traumatologic patients presenting consecutively at the ED of Fürth hospital in September 2010 were screened for ADE and ME. The identification of ADE and ME was organized as a two-step process. In the first step, all patient charts were screened by a medical doctor and a pharmacist. In the second step, all detected ADE and ME were confirmed by two board-certified specialists specialized in internal and critical care medicine (HD) or in clinical pharmacology (RM). To determine the rate of false negatives, 75 cases initially evaluated to be without ADE were reevaluated. The rate of false-negatives was 2.7% (95% confidence interval [CI]: 1.7-9.8%) [20]. The software MMI PHARMINDEX PLUS (Medizinische Medien Informations GmbH, Neu-Isenburg, Germany) was used as primary reference data base for prescribing information data on prescribed drugs.

Study data including medication, diagnoses, ME and ADE were recorded in secuTrial®. For each ME, the concerned drug(s) was/were documented as well as the location(s) where the drug(s)
was/were prescribed or given (at home, drugs given during emergency transport, in the ED, at transfer from the ED, or at discharge from the ED). The location where the ME was first recognized as drug-related problem was recorded. For each ADE, the clinical symptoms were documented as well as the drug(s) causally associated and the location(s) where the drug(s) was/were prescribed or given. The location where it was discovered that the clinical symptoms were drug-related was recorded. If an ME or ADE was explicitly documented (e.g., gastrointestinal bleeding under acetylsalicylic acid), if the medication involved in ME or ADE was explicitly stopped (e.g., acetylsalicylic acid paused), or if adequate measures were taken (e.g., addition of potassium for furosemide-induced hypokalemia), this was accepted as adequate recognition of the error or event. If a medication was stopped without any documentation (e.g., home medication not available at admission and not prescribed at inpatient transfer), this was assessed as unclear recognition. If a drug was continued without further notice despite being involved in an ME or ADE, this was assessed as not recognized.

3. Preventability and Schumock criteria

According to Schumock GT et al., an ADR is preventable if ≥ 1 of the following questions can be answered with yes [24]:

1. Was the drug involved in the ADR not considered appropriate for the patient’s clinical condition?

2. Was the dose, route, and frequency of administration not appropriate for the patient’s age, weight and disease state?

3. Was required therapeutic drug monitoring or other necessary laboratory tests not performed?

4. Was there a history of allergy or previous reactions to the drug?

5. Was a drug interaction involved in the reaction?

6. Was a toxic serum drug level documented?

7. Was poor compliance involved in the reaction?
**Supplementary Figure 1.** Original wall chart showing the guideline-driven use of enoxaparin and heparin for primary prophylactic use of venous thromboembolism. This chart was posted on the walls of the emergency department of Fürth hospital.
Supplementary Figure 2. Original wall chart presenting QT-prolonging drugs and proposing a management of QT prolongation. This chart was posted on the walls of the emergency department of Fürth hospital.
(C) References


