A new approach to identify, classify and count drug-related events

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- In the literature data regarding the frequency of adverse drug events (ADEs), adverse drug reactions (ADRs) and medication errors (ME) are highly variable.
- Current definitions and schemes are not well suited for the evaluation and counting of ADEs, ADRs and MEs in common but complex clinical situations.

WHAT THIS STUDY ADDS

- New models and extended definitions that allow the classification and counting of ADEs, ADRs and MEs in simple and complex clinical cases have been developed.
- An exemplary set of patient cases illustrating the new models was constructed.
- A method to aid a detailed and comparable counting and reporting of drug effects was set up.

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AIMS

The incidence of clinical events related to medication errors and/or adverse drug reactions reported in the literature varies by a degree that cannot solely be explained by the clinical setting, the varying scrutiny of investigators or varying definitions of drug-related events. Our hypothesis was that the individual complexity of many clinical cases may pose relevant limitations for current definitions and algorithms used to identify, classify and count adverse drug-related events.

METHODS

Based on clinical cases derived from an observational study we identified and classified common clinical problems that cannot be adequately characterized by the currently used definitions and algorithms.

RESULTS

It appears that some key models currently used to describe the relation of medication errors (MEs), adverse drug reactions (ADRs) and adverse drug events (ADEs) can easily be misinterpreted or contain logical inconsistencies that limit their accurate use to all but the simplest clinical cases. A key limitation of current models is the inability to deal with complex interactions such as one drug causing two clinically distinct side effects or multiple drugs contributing to a single clinical event. Using a large set of clinical cases we developed a revised model of the interdependence between MEs, ADEs and ADRs and extended current event definitions when multiple medications cause multiple types of problems. We propose algorithms that may help to improve the identification, classification and counting of drug-related events.

CONCLUSIONS

The new model may help to overcome some of the limitations that complex clinical cases pose to current paper- or software-based drug therapy safety.

Introduction

Drugs are generally prescribed in the belief that the benefits outweigh the adverse effects attributable to the prescribed drugs. However, adverse drug effects have been recognized as a significant cause of morbidity and mortality [1–3]. Already in 1981 Kramer noted an up to 20-fold variation in the reported incidence of adverse drug-related events (1.5–35%) in hospitalized patients [4]. Differences in the intensity of surveillance, in definitions of adverse drug events and populations studied were identified as major contributing factors. Since then definitions have been refined and multiple schemes to clarify the relationship between errors, drug effects and adverse drug events (ADEs) have been published [5–9]. Still it appears that definitions and reported event rates vary as much as in 1981 [7, 10, 11]. This is disturbing as event rates are frequently used to identify priority areas for interventions and as a measure to evaluate the effectiveness of interventions.

In a study on medication safety in an emergency department (ED) we noticed that current definitions and algorithms may be too narrow and exclude whole classes of events that cannot be appropriately classified and counted [12, 13]. We especially noticed a restricted ability of current models to deal with complex interactions when multiple drugs contribute to a clinical event in a patient which may also be caused by an underlying disease. Based on these observations our research questions were:

- 1 Can we devise schemes and definitions that better accommodate the spectrum and complexity of possible adverse drug events?
- 2 Can we establish a counting mechanism for different types of adverse drug-related events and medication errors (MEs) that is suitable for clinical reality?

Methods

For a research project we examined and analyzed drug associated risk situations at the ED of a 749 bed adult tertiary care/level III and teaching hospital in Germany [12, 13]. For the current analysis we evaluated 752 consecutive adult non-traumatic patients admitted to the ED in September 2010. The patient records were reviewed for drug associated risk situations by an independent expert panel (FM, BP, BP-K, AS, HD and RM) including physicians specialized in internal medicine, emergency medicine and clinical pharmacology as well as pharmacists. Assessment was done in a two-step process, with each case being assessed at least by two of the authors (one physician, one pharmacist). All ADEs and MEs identified had to be confirmed by two independent board certified specialists (RM, HD). In the case of disagreement cases were discussed until consensus was achieved. The false negative rate of events or

errors overlooked by the first raters was determined to be 2.7% (95% CI: 1.7–9.8%). The ethics board of the Friedrich-Alexander-University of Erlangen-Nuremberg reviewed and approved the study protocol. The local data safety commissioner approved the technical infrastructure, the data handling and the pseudonymization procedures. A key task in the study was to classify and document MEs, ADEs and adverse drug reactions (ADRs) in a clinically meaningful manner and to address the causality for each event. We therefore performed a literature research for relevant definitions and found in line with Yu *et al.* 2005 [10] at least 12 different definitions for ADR [14–26], nine definitions for ADEs [3, 5, 7, 27–32] and five definitions for MEs [5, 17, 27, 28, 30, 33]. Besides, many more terms have been defined and used in publications (i.e. adverse effect, adverse event, adverse incident, adverse medication event, adverse reaction, critical event, critical incident, error, medical error, medication incident, near miss, potential adverse drug event, or sentinel event).

As a starting point we adopted the following definitions that we deemed widely used and most suitable for the purpose of our project:

- An ADR is defined as a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for modification of physiological function [23].
- An ADE is defined as an injury resulting from the administration of a drug [34]. This broad definition has been endorsed by the 2007 Institute of Medicine (IOM) report [7]. To allow a distinction from adverse events in general a causal link to a drug effect is required. For the purposes of our study we assumed the existence of an ADE if causality according to the WHO score was at least determined as possible or higher.
- A ME is defined as inappropriate use of a drug that may or may not result in harm [28].

As a first step we analyzed the formal relation of ADEs, ADRs and MEs, as it has been described by various authors. In 1995 Bates and colleagues [5] provided a frequently cited diagram detailing the relationship of MEs and ADEs (Figure 1). A key element of this diagram is a partial overlap of MEs and ADEs, indicating that some ADEs are related to error while others are not (according to the WHO definition the latter would be considered ADRs). This broad definition was also endorsed by the 2007 IOM report [7]. Aronson & Ferner extended the Venn diagram by including ADRs [35]. The diagram indicates that their definition of ADRs includes adverse drug-related events involving or not involving errors (which is equivalent to the definition used by Bates *et al.* for ADEs [34]). Aronson & Ferner [35] describe the sets 2, 3 and 4 as the equivalent to the Bates *et al.* definition of ADEs [34]. This aside, the inter-relations proposed by Bates *et al.* and Aronson & Ferner are rather similar.

Figure 1

Adaptation of some diagrams from the literature that are frequently cited to illustrate the relation of medication errors (ME), adverse drug events (ADE) and adverse drug reactions (ADR). The definition of ADR used by Aronson & Ferner and Ackroyd-Stolarz *et al.* includes events that involve MEs and thereby differs from that used in the present study. Aronson & Ferner prefer the use of the term adverse event (AE) with a definition given in [35]. They consider an ADE as the equivalent of the sets 2, 3 and 4 in their diagram

In contrast Ackroyd-Stolarz *et al.* define two different supersets [9], a set of injuries and a set of non-injuries. Thus, the ME set appears twice in both supersets. The injury superset contains MEs, ADEs and ADRs whereas the non-injury superset contains MEs and potential ADEs. In this diagram it is not disclosed what belongs into the set of 'drug related problems causing injuries that are not MEs or ADEs'. It could be interpreted to represent events such as intentional overdoses in cases of murder and suicide (which are frequently excluded when evaluating ADEs and MEs).

In our study we identified patients with one or more drug-related event(s). Typical event combinations found in these patients are described in the results section in tabular form. However, we soon noticed that neither the named definitions nor the models in Figure 1 are sufficient to establish a correct counting of events, symptoms and/or MEs in those complicated cases where several drugs plus diseases contribute to several clinical symptoms of the patient. As an example, we found it difficult to classify a gastrointestinal bleeding in a patient taking low dose aspirin with proper indication and receiving enoxaparin without proper clinical indication. Here we have one clinical event attributable to two drugs. The event could either

be an adverse drug reaction to the appropriately used aspirin or an ADE due to the effect of the inappropriately used enoxaparin (ME) or the combination of the above (two drugs contributing to one event). Therefore, we analyzed our data following the example of Yu *et al.* [10] in order to identify the smallest possible set of clinical cases that represents all major types of relations and that can be used as a basis to derive an appropriate classification and counting of drug-associated risk situations including ADEs, MEs and ADRs. Then, we used a combination of set theory and workflow diagrams to describe the complex relations found between events with the goal of correct atomic counts for ADEs, MEs and ADRs.

Results

Based on MEs and drug-related events identified in our set of 752 patients we assembled a set of events that can be used to describe the most important types of events as well as the nature of the underlying relationships (Table 1). Using this set of events we then extended the definition of different subtypes of ADRs and ADEs.

Table 1

Selected patient cases from the drug safety study at the ED of a municipal hospital. An asterisk (*) means that the event did not manifest within the study period, but would have been a possible outcome according to the prescribing information. Event 12 (+) was not explicitly examined in this study

Number	Problem	Outcome/possible outcome*	Description	Number of Drugs	Number of ADEs	Number of MEs	Number of ADRs	Number of diseases
1	Carvedilol (β-adrenoceptor blocker) prescribed at an adequate dose for the indication hypertension.	Symptomatic bradycardia	A clinical event attributable to the known effect of a drug (in the absence of MEs and other diseases contributing to the event)	1	1	0	1	0
2	L-thyroxine (thyroid hormone) prescribed at an inadequately high dose for the indication hypothyroidism.	Hyperthyroidism with symptomatic tachycardia	A clinical event attributable to the known effect of a drug (related to one or more MEs, but in the absence of other diseases contributing to the event)	1	1	1	0	0
3	Low dose aspirin (acetylsalicylic acid, non-steroidal analgesic) without plausible clinical indication. Later: previously unknown <i>Helicobacter pylori</i> infection detected.	Upper GI bleeding	Clinical event attributable to known effect of an inappropriately used drug as well as underlying comorbidity	1	1	1	0	1
4	Trimipramine (tricyclic antidepressant) prescribed without indication to a patient having a clear contraindication (urinary retention).	New onset of QT prolongation	Prescription of one drug involves two MEs leading to one clinical event related to the drug	1	1	2	0	0
5	Patient prescribed sulpiride (atypical neuroleptic agent) without indication.	Syncope and extrapyramidal signs	Two distinct clinical events attributable to one ME (pre-existing disease unlikely cause)	1	2	1	0	0
6	Administration of an overdose of metoprolamide (antiemetic dopamine antagonist) to a patient with known epilepsy.	Extrapyramidal symptoms* and acute seizure*	One drug involved in two MEs leading to two distinct clinical events	1	2	2	0	0
7	Xipamide (thiazide like diuretic) and torasemide (loop diuretic) prescribed to a patient with heart failure and hypertension.	Significant hypokalaemia	A clinical event attributable to two (or more) drugs causing one ADR in the absence of MEs (additive effects are possible but no prerequisite for the ADE)	≥2	1	0	1	0
8	Diltiazem (calcium antagonist) for hypertension. Simvastatin (statin) for hypercholesterolaemia. Both drugs given in doses formally allowed for this combination.	Elevation of creatine kinase (attributable to impairment of simvastatin metabolism by diltiazem)	A clinical event attributable to an interaction of two (or more) drugs causing one ADR in the absence of MEs (when either drug alone is tolerated well)	2	1	0	1	0
9	Prescription of two contraindicated drugs [isosorbide mononitrate (nitrate) and molsidomine (vasodilator)] in a patient with high grade aortic stenosis.	Decompensated heart failure	Two medication errors leading to one symptom with possible contribution of preexisting disease	2	1	2	0	1
10	Clonidine (antisympatonic, α ₂ -adrenoceptor agonist) prescribed to a patient with hypertension and melperone (neuroleptic, dopamine antagonist) prescribed without indication.	Severe drowsiness	A clinical event attributable to a ME as well as a classical ADE	2	1	1	1	0
11	A patient with depression is simultaneously prescribed mirtazapine (tetracyclic antidepressant) and tranylcypromine (neuroleptic MAO-inhibitor).	Serotonin syndrome*	A single mistake affects medication pathways leading to one or more clinical events	2	1	1	0	0
12	An indicated drug was not prescribed.	Possible outcome: Exacerbation of underlying disease+	An OEE of a drug pathway leads to an clinical event (OEE, omission error related event)	0	OEE	OEE	0	0

Figure 2

Proposed set theory diagram for clinical symptoms and medical decisions in the drug therapy process. Different subtypes of adverse drug events (ADEs): ADRs: Clinical symptom/event related to 1 medication pathway (drug) not involving a medication error ME: Case 1. ADR*: Clinical symptom/event related to ≥ 2 medication pathway(s) (drugs) not involving a ME. Cases 7 and 8. Mixed ADE: Clinical symptom/event related to ≥ 2 medication pathways of which ≥ 1 does involve ≥ 1 ME(s) and one is free of error. Case 10. ADE-ME*: Clinical symptom/event related to ≥ 1 medication pathway(s) (drugs) which involve(s) ≥ 2 MEs. Cases 4, 6 and 9. ADE-ME: Clinical symptom/event related to 1 medication pathway involving a single ME. Case 13. OEE: Omission error related event: Omission of drug therapy leading to a clinical event.

Figure 3

Top level medication pathway for one single drug at one dose. Several errors can happen. Time is represented in the third level and may lead to different assessment with regard to the prevalence of an ME (Figure 4)

The sample cases stand exemplarily for some much more complicated cases found in our study where three or more drugs in combination with or without MEs contribute to several clinical symptoms. To classify the sample cases we propose a combination of two Venn diagrams and a classification diagram which together may adequately represent and distinguish all relationships between MEs, ADEs and ADRs found in those cases (Figures 2 and 5).

The relevant point in Figure 2 is to distinguish between the basic sets of either symptoms or actions which contain the respective sets of ADRs, ADEs and MEs. The Venn diagrams acknowledge that ADRs and ADEs are essentially symptoms, clinical signs and test results which may be observed or biologically measured in a patient and belong to the basic set of all patient symptoms (green diagram). In contrast, MEs are activities related to a process or an action taken by a health care professional or patient and therefore belong to the basic set of all medical decisions and

actions undertaken to diagnose or treat a patient (red diagram). Both basic sets, in our opinion, do not have a common superset.

Splitting symptoms and decisions into two distinct basic sets requires a mechanism to describe relationships between those sets, symbolized by a blue arrow as a causality link (action causes event) in Figure 2. Therefore, we define a medication pathway (Figure 3) as the sum of all decisions and activities involved in the application of a single drug dose. Altering the dose, i.e. the flow rate of an intravenous infusion pump, would start a new medication pathway. We are aware that the drug ordering process may be an extremely complicated workflow of which only the top level activities such as drug prescription, preparation, application and monitoring are depicted in Figure 3. A medication pathway would also accommodate patient-related factors such as compliance. We consider errors as activities within a medication pathway. The number of

Figure 4

The observation period may alter the interpretation of events. Clinical example: A patient with hypertension develops two episodes of an II° AV block after taking a dose of metoprolol. Observer 1: One event (A). Conclusion: Administration of correct dose with correct indication causing an adverse drug reaction = 1 ADR (not preventable). Observer 2 (unaware of previous event): One event (B). Conclusion: Administration of correct dose with correct indication causing an adverse drug reaction = 1 ADR (not preventable). Observer 3 (aware of both events): Two events (A and B). Conclusion: (Event A) Administration of correct dose with correct indication causing an adverse drug reaction = 1 ADR (not preventable). (Event B) Administration of correct dose with correct indication but ignoring the previous ADR (which constitutes a contraindication for re-administration) = 1 ADE caused by a medication error (preventable)

possible errors or wrong actions along this pathway is by definition infinite.

With rare exceptions discussed further below errors of omission are primarily not related to a specific medication pathway. For matters of clarity an event not related to a specific drug or medication pathway should not be termed an ADE. Therefore, we would consider most omission error-related events (OEE) a different category of therapy-related events.

Some MEs may result in ADEs, but the majority of MEs may never have clinical consequences. Moreover, a small fraction of MEs may even inadvertently improve the clinical outcome. Furthermore, the assessment ME 'yes' or 'no' may well be time-dependent (Figure 4). For example, a drug metoprolol was given by the general practitioner for hypertension. The patient is later admitted to the ED and a II° atrioventricular block (typical ADR of metoprolol) is found in the ECG. If despite the occurrence of this ADR metoprolol is continued or reordered upon discharge from the ED this would be an ME and any related event would be considered an ADE resulting from an ME. The interpretation of the event may largely depend on the information available to the observer (e.g. the quality of documentation and the time period observed, Figure 4). So, any decision or action may be correct on the basis of the information available at the time the action was taken, but a retrospective analysis may show that it did or did not benefit or even harm the patient. With respect to the analysis of factors leading to an ADE a retrospective analysis may attribute the error/mistake to observer A who did not document the first ADE, or to observer B who ignored a documented ADR.

For ADRs, ADEs and MEs the blue arrow (causality link) in Figure 2 from actions to symptoms represents different options. To make those relationships between activities such as ME and the resulting events (the sets of ADEs and ADRs) explicit we propose a model which is able to mirror all relations observed in Table 1 and which permits the counting of the exact number of events for all three sets, e.g. MEs, ADEs and ADRs (Figure 5). In Figure 5, we start with the basic set of patient symptoms in the middle which comprise the sets of ADEs and ADRs (see also Figure 2). We represent the medical activities within different medication pathways from the outside which may or may not lead to events. One medication pathway can result in zero, one or several events, shown by arrows. Alternatively, an event may be caused only by the joint effect of several medication pathways. Along each medication pathway errors may occur. In addition it needs to be noticed that any event or symptom may be influenced or caused by one or more underlying disease(s) as well. With the model of Figures 2 and 5 we are able to count ADEs and ADRs within the set of symptoms and count MEs along the medication pathways in an unambiguous way.

That we can now apply to our sample patient cases. We start with those sample cases where just one single medication pathway is involved:

- Case 1 is a patient receiving one drug in the correct dose which leads to one ADR. In Figure 5 this would be medication pathway 1.
- Case 2: is a simple case: A patient receives a drug (thyroxine) in a dose which is too high and an ADE (symptomatic hyperthyroidism) is observed. In Figure 5 this would be represented by medication pathway 2 where one ME leads to ADE 2.
- Case 3 is pretty similar with the exception that the upper GI bleeding observed in the patient may be caused by the underlying disease (*Helicobacter pylori*) or from low dose aspirin. In Figure 5 this is represented by medication pathway 3 combined with the arrow from disease 1 to the ADE 3.
- Case 4: A patient with urinary retention is prescribed trimipramine which is contraindicated in this case (one ME) and without known indication (second ME). The patient has a new onset of QT prolongation. We have two MEs and one event. In Figure 5 we have medication pathway 4 with two ME along the line of which one is directly connected to the event while the other has not manifested (yet) leading to ADE 4.
- Case 5: A patient is prescribed sulpiride with no adequate indication. This results in a syncope and extrapyramidal signs. In this case one ME causes two distinct ADEs related to the same drug. In Figure 5 this is depicted by medication pathway 5 leading to events ADE 5 and ADE 6.
- Case 6: A patient with nausea but known epilepsy receives an overdose of metoclopramide, leading to a seizure and extrapyramidal symptoms. Here we have two

Figure 5

Relationship between medication errors (ME), medication pathways, clinical symptoms/events (ADEs, ADRs, ADRs*, mixed ADEs, ADE-MEs, ADE-MEs*) and diseases. Description in the text

MEs affecting the same medication pathway 6 which contributes to two distinct ADE-MEs (ADE 7 and ADE 8).

Next we have several cases where two medication pathways for different drugs are involved:

- Case 7 is a patient with heart failure receiving two diuretic drugs in whom hypokalaemia is detected by adequate monitoring. Thus two (or more) drugs which are both clinically appropriate lead to one ADR which involves no ME. Both drugs could have contributed to the hypokalaemia. In Figure 5, this is depicted with medication pathways 7 and 8 leading together to ADR* (ADR* because this is a shared side effect of more than one drug).
- Case 8 is a similar to case 7 (at the doses prescribed the combination was still allowed by the German drug labels, which implies that this should not be counted as an error). Here only the interaction between diltiazem and simvastatin produces the ADR of elevated creatine kinase (either drug alone would not have been sufficient or much less likely to cause the event). In Figure 5 this is

shown in medication pathways 9 and 10. Note the different type of arrow symbolizing the joint activity.

- Case 9 is a patient receiving two drugs which are each contraindicated in view of his high grade aortic stenosis. Thus two MEs occurred leading to one ADE, namely decompensated heart failure which of course could also be a result of the aortic stenosis itself. Here either drug alone could have caused the problem, but an additive effect is also plausible. In Figure 5 this is depicted by medication pathways 11 and 12.
- Case 10: The patient receives two drugs, one without known indication, resulting in one ADE. Thus two distinct medication pathways (one with an ME along the line) lead to one ADE. This is depicted in Figure 5, medication pathways 13 and 14.
- Case 11: A patient with depression is simultaneously prescribed mirtazapine and tranylcypromine (either drug alone would be well tolerated but the combination is contraindicated as it may cause a serotonin syndrome). Here a clinical event results from a single error that involved two medication pathways, 15 and 16.

In addition we considered two cases well known from clinical experience but excluded from or not observed during our study:

- Case 11b: Preparation of an overdosed heparin stock solution, which is used for several patients who subsequently suffer from bleeds. This is in principle a variation of case 11 with the difference that a single medication error leads to ADEs in more than one patient.
- Case 12 (excluded in current study): An indicated drug was not prescribed resulting in the aggravation of an existing disease or severe withdrawal symptoms. Possible outcome: OEE. Absence of a drug (effect) e.g. omission of a drug pathway leads to a clinical event.

In a more abstract way we arrive at the following relationships shown in Box 1.

Summarizing the results, we used clinical cases as a starting point to identify the possible sets of basic relationships of clinical decisions and actions on the one hand and clinical events and symptoms on the other hand (Box 1, Figures 3 and 5). The key element is to treat clinical events (ADEs and ADRs) and MEs as distinct entities which are related but not identical or mutually interchangeable. Furthermore, we extended the definitions of ADR and ADE in order to accommodate more complex events (ADRs, ADR*s, ADE-MEs, ADE-ME*s and mixed-ADEs). Using our model we now can establish independent 'atomic' counts of ADEs, ADRs and MEs for our study. We have tested the model with more complicated cases involving more drugs and events without yet detecting a conflict.

Discussion

When it comes to the implementation and comparison of measures to improve drug therapy safety, the precise classification of the events may be of as much importance as the actual counting of the events. The presently available definitions and classifications of events focus primarily on the simplest types of events (e.g. a single drug causing a single adverse reaction or a single prescribing error leading to a single ADE). However, patients frequently have more than one disease and take several drugs which all may combine in their effects (Figure 5 and Box 2). It was our aim to provide a framework that allows a clinically meaningful classification and the counting of more complex drug-related events.

We therefore tried to develop a model which allows the classification and counting of most drug-related risk situations in a meaningful manner. The first key element is to treat clinical events (ADEs and ADRs) and MEs as distinct entities which are related but not identical and not mutually interchangeable. To address this we recommend a clear cut between decisions/actions and the resulting events as seen in Figure 2, thus using another graphical

Box 1

Basic relationships between clinical decisions/actions and related clinical symptoms/events

- A single medication pathway free of error may contribute to (or may prolong) a single clinical symptom/event
- A single medication pathway free of error may contribute to (or may prolong) more than one clinical symptom/event
- Each step of a medication pathway may involve any number of medication errors
- A medication error may or may not contribute to (or may or may not prolong) a clinical event
- A single medication error may (or may not) contribute to (or may prolong) any number of clinical signs and events (in principle it may even affect more than one patient)
- Errors of omission cannot be related to a specific drug or medication pathway (and events related to an error of omission should not be counted as drug related events)
- A single medication pathway involving an error may contribute to (or may prolong) a single clinical symptom/event
- A single medication pathway involving an error may contribute to (or may prolong) more than one clinical symptom/event
- A medication pathway involves one or more medical/pharmaceutical decisions and actions which may or may not be associated with any number of medication errors
- Two or more drugs may only result in (or may prolong) clinical signs or events when combined
- A clinical sign or symptom may be the result of (or may be prolonged by) any combination of medication pathways involving errors and/or free of errors
- Any number of concomitant clinical conditions may contribute to or may modify any number of drug-related events

method to display the relationship between actions and events which by nature is unidirectional [36]. Furthermore we introduce extended definitions accounting for the fact that more than one drug and/or more than one error may contribute to a single event (Figure 3 details the interrelation of medication pathways and clinical events/symptoms in an individual patient).

Previous models and diagrams as shown in Figure 1 have their merits but may still make it difficult to count and distinguish ADEs, ADRs and MEs. Obviously, each such diagram is also dependent on the definitions used by the authors as seen in the original diagram given by Bates *et al.*

Box 2

Causality of clinical symptoms and events

- In an individual patient any drug may have any number of distinct drug effects that contribute to (or may prolong) any number of symptoms/events
- Any number of drug effects may combine to produce (or prolong) any number of events and symptoms
- Any number of concomitant clinical conditions may contribute to (or may modify) any number of drug-related events
- A medication pathway may involve any number of medication errors (e.g. wrong decisions and actions) that contribute to (or may prolong) any number of clinical events and symptoms
- A single medication error may affect more than one medication pathway

[5] where no ADRs are defined. In our viewpoint the upper group of diagrams in Figure 1 do not consider the different nature or basic set to which either ADEs and ADRs belong (patient symptoms) or to which MEs belong (actions or decisions). They do not give any hints how to count MEs in cases where either one drug causes two or more ADEs or ADRs or cases where several drugs together cause a single event. Later definitions such as [37] try to distinguish between drug-related problems causing an injury and those which do not. But again, MEs and ADEs/ADRs are mixed within one set. Also, in the latter diagram a question is: What is an ADE resulting in an injury which is an ME? Either, ADRs and ADEs are identical sets, assuming that any injury caused by a drug in normal or abnormal dose is an ADR (in which case one could be omitted) or the difference between ADRs and ADEs is that ADRs occur when applying regular drug doses. Thus, there would be no associated ME which makes the overlapping between ADEs and MEs dubious. We used the second approach to distinguish between ADRs and ADEs, although newer definitions also promote the first option, i.e. an ADR is defined as '*a response to a medicinal product which is noxious and unintended*' in Article 1 of Directive 2001/83/EC [38]. As mentioned above numerous ADR definitions (14–26 have been proposed and discussed [Aronson & Ferner [35]]). Despite its well described limitations we decided to stay with the traditional WHO definition to achieve best comparability of our results with other studies.

As Aronson & Ferner [35] correctly point out, confusion may arise when causality is not adequately accounted for or when different requirements for causality are used. In our understanding a causal association at least at the level of 'possible' is required to speak of an ADE, otherwise it would just be an adverse event, whatever the cause. Any much stricter definitions would leave a large proportion

of events attributable to drug effects unaccounted for. When too strict definitions are applied to clinical reality only events like hypoglycaemia under insulin (with no plausible alternative causes) would reach sufficiently high causality scores to be counted as drug-related events. To our best knowledge validated scores to assess causality for complex clinical situations (such as several contributing drugs) are missing. We tried to address this by introducing markups that allowed us at least to count and identify the complex events as described below. The WHO definition describes an ADR as '*... a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for modification of physiological function.*' [23]. Similarly, the new EC legislation uses the singular form only, one drug causing one ADR. This fails to account for the complexity of clinical reality where a clinical event may be attributable in equal parts to two or more different drugs. Moreover in some cases involving two or more drugs and one event either drug alone will not be able to cause the event, only the combination will lead to the effect (such as in case 7). Thus, if using the narrow single drug, single event definition of an ADR, a large proportion of ADRs will be recorded incompletely. To address this issue we have used a modified definition of an ADR (ADR*) because we would consider an event attributable to the joint or individual effect of two or more drugs used in a clinically appropriate manner a single ADR. For example, in the case an isolated hypotension occurs during the combined use of bisoprolol and amlodipine there will be no clinically meaningful way to dissect this ADR* further into subevents attributable to either drug alone.

It may be also a problem to define when a drug effect should be described and counted. The definitions mentioned above do not comprise a threshold, i.e. when to count an asymptomatic elevation of an enzyme or an asymptomatic slight bradycardia. There may certainly be clinical situations in which certain effects have to be accepted, i.e. neutropenia in a patient treated with cytotoxic agents for leukemia. As discussed further below, causality and strength of the causal association as well as the thresholds that define a noteworthy clinical event or that distinguish mediocre therapy from a medication error require consideration when defining and counting events. To our best knowledge consensus has not yet been reached in this area.

In the literature information regarding the complexity and composition of ADEs is rarely found. It is therefore very difficult to estimate the proportion of ADEs that can (and should) be identified using standardized automated procedures and software tools (especially as software-based interaction tools are usually focused on 1 to 1 interactions).

As a rule of thumb it has long been recognized that the larger a study and the more standardized (predefined lists of events) or electronically automated (software-based interaction checks) a study is, the lower the reported event

rates will be [4]. This may explain why events that are easy to detect, such as hypoglycaemia caused by insulin or bleeding related to warfarin, usually dominate the list of reported ADEs [2]. Moreover, considering the long lists of proven frequent side effects of many other commonly used drugs, why do we identify or report ADRs related to these drugs so much less frequently? Do we have a problem with the tools used to detect ADEs or are the ADR rates reported in the prescribing information obsolete for most drugs? Here, the clinical complexity which leads to low causality ratings for the contribution of individual drugs to the clinical situation may indeed lead to a chronic underestimation of drug effects to morbidity and mortality [39]. In clinical reality a large proportion of drug-related events may occur in rather complex clinical settings which may make it difficult to dissect the contribution of an individual drug (effect) and to attribute a high level of causality to any single drug effect. Despite an accumulating wealth of studies in different clinical settings we still do not know the relative proportions of simple and complex ADEs. Knowing this would be of importance to choose the correct tools for the detection of events as well as the most appropriate measures to improve drug therapy safety. Our extended definitions may also help to identify the proportion of events that may not be suitable for classification by commonly used causality [40, 41] or preventability [42] scores.

For each medication pathway the diagram in Figure 5 may be used to determine the number of ADEs/ADRs involved and the number of MEs involved. We have not been able to find another publication proposing a similar split into separate diagrams for symptoms and decisions.

There are numerous publications with regard to where in a medication pathway an ME may occur. Yu *et al.* [10], for example, used a case of a patient allergic to penicillin who received just this drug to distinguish various types of errors. But even this seemingly straightforward test case may be subject to interpretation. In our opinion there is a major point in detecting how drugs contribute to an event. A specific event such as QT prolongation may be much more likely drug-related (thus an ADE or ADR) if the patient takes several drugs which are able to evoke this side effect. This multiplicity is often not considered.

In the present study a symptomatic hypotensive episode occurred in a patient taking nine drugs with hypotensive effects, which made the overall contribution of the patient's drug therapy to the hospitalization highly probable. Still, using standard scoring systems the causal contribution of the individual drugs could only be scored as possible.

Events involving errors

We deem it most essential to achieve a correct classification of all MEs in our study, because those are the drug associated problems which can be influenced either by improved training and teaching of drug safety or with the

help of computer based clinical decision support systems. Causality aside, counting and assessing MEs may be the most difficult and controversial task in the evaluation of drug therapy safety. The line between medical error and mediocre therapy or poor documentation is frequently rather blurred. Event numbers will be determined by the definitions of error as well as by the scrutiny of the observers. Comparisons of error rates are meaningful only when definitions of errors as well as method of detection and the underlying time frame are precisely defined. Detection of MEs requires adequate documentation of reasoning and actions as well as clinical events and diagnoses. In other words, the better the documentation the more errors can be detected. Therefore, a low error rate can be an indicator of excellent clinical treatment as well as lousy documentation or very narrow definitions of error. When a patient on warfarin presents with a very low INR and bleeding some physicians will record this as warfarin 'overdose' and document a ME. In many cases, however, it will only constitute a simple ADR (WHO) when the dose and the monitoring interval were adequate in principle. It is important to note that a single mistake may involve more than one medication pathway and/or may contribute to several adverse events. Take the example of a patient in a nursing home who is given the medication box containing the pills for her neighbour. Here a single mistake may, with enough bad luck, result in several adverse effects and it may even affect more than one patient.

Timing and documentation of MEs

The involvement of a time line may add further complexity to the interpretation of events. The association of an event with a medication error may depend on the time frame and the perspective of the observer (Figure 4). An action which, at a specific point of time, was correct may no longer be correct and has to be considered an ME at a later stage. This happened several times in our study, because we took an inventory of ADEs, ADRs and MEs at three points in time, namely when the patient was seen by a physician before transport to the ED, on arrival in the ED and finally on discharge from the ED. Considering this at a timeline, an ADR may well later be associated with an ME (thus converting to an ADE) when the ADR was noticed as such, but no appropriate measure (i.e. discontinuing the medication) was taken or, even worse, the previous GP drug order was re-established on discharge from the ED. The case of a patient receiving citalopram who presents with a profound QT prolongation and in whom the prescription of citalopram is continued for weeks may illustrate a further issue. Here repeated errors do not cause a new symptom but rather prolong an existing symptom/event. How to count a clinical event/symptom that is perpetuated rather than initiated by one or more MEs? In the present example we have a simple ADR that turns into a mixed ADE (e.g. it changes its nature and associated tags such as preventability etc.). But should we record it as two

distinct events or one event involving x errors? Based on these considerations we propose a hierarchical presentation of events: We have one ADE that is related to an ADR as well as an ME-ADE resulting from x medication errors. Now, take a similar patient who is given her initial dose of citalopram without obtaining a prior ECG, and in whom we find a significant QT prolongation in the first ECG captured shortly after medication. It is not possible to tell whether this is an ADR or and ME-ADE. Not taking the ECG prior to administration of the first dose may be considered an error in a broader sense, but we still do not know the underlying truth. The QTc interval may have been already prolonged prior to the administration of the drug, in this case one may count it as an medication error (ME), but it would be unclear if it is also an ADE-ME. In case the QTc interval was normal before administration of the drug one could speak of an ADR. A conservative approach for publications would be to provide the number of events that could not be adequately classified due to missing documentation.

It is well known from the analysis of catastrophic events such as plane crashes that it usually takes a chain of several errors and wrong actions until the final event occurs. Consider a patient with a penicillin allergy where the admitting physician fails to document the allergy. Another physician fails to follow up on the blank (missing) allergy information and prescribes penicillin. The penicillin is then administered by a further physician who leaves the room just after starting the infusion. The patient subsequently dies of an allergic shock. Here we have a single event attributable to at least three errors.

Finally, a further dimension of complexity is added when considering the possible intention underlying an obviously wrong action. For good reason, many studies exclude intentional overdoses (murder and suicide) from their count of errors or ADEs [2]. It makes a huge difference if hypoglycaemia is related to an unintentional overdosing due to wrong calculation of the required insulin units or an intentional overdosing in an attempted suicide.

Errors of omission

OEEs in a narrow sense (e.g. not giving an indicated drug or even 'underdosing' [43]) constitute a special class of errors that is especially difficult to evaluate. Events caused by OEEs do, by definition, not involve a drug but rather the absence thereof. Failure to prescribe a statin in a patient with a history of myocardial infarction and no contraindications relates to a whole group of potential medication pathways for eligible drugs (statins) whereas one specific medication pathway according our definition involves just one specific drug (simvastatin).

A prototypical classification problem arises with the failure to prescribe an anti-emetic drug in a patient receiving emetogenic cisplatin chemotherapy: The event severe vomiting is a clear side effect (ADR) of cisplatin, yet it occurred because the recommended anti-emetic therapy (with a drug like ondansetron) was forgotten (OEE related

to the 'cisplatin' medication pathway as well as to the set of anti-emetic drugs not given).

Meaningful evaluation and counting of errors of omission requires a degree of documentation rarely achieved outside clinical trials. Reasons for not giving a drug despite a possible indication are plentiful and not all are easy to document. Some clear cut cases aside (such as failure to administer adrenaline to a patient with allergic shock who has no contraindications) it is frequently debatable what constitutes an OEE. A key limitation is the lack of a gold standard or definite clinical evidence in many therapeutic indications. Does 'not prescribing' a drug endorsed by a class C (expert opinion only) recommendation in a guideline constitute an OEE, and will this be viewed differently with regard to drugs that improve survival or only symptoms? Moreover, how to evaluate an OEE when drug therapy and surgical therapy are considered clinically equal alternatives? It may be prudent to evaluate OEEs and other MEs separately. Alternatively, one should try to differentiate OEEs that can be related to a specific medication pathway from those that are of global nature. Insufficient control of blood pressure in a substantial proportion of our population (that is at least in part attributable to insufficient pharmacotherapy) may serve as an example that global OEEs are common and clinically relevant.

Limitations of our model

The price of increased precision is complexity. Obviously, some of the simplicity of commonly used models [5, 35] is lost with our combination of Figures 2 and 5. In our case, the relationship between ADRs/ADEs and MEs is primarily only represented in the blue arrow in Figure 2 and made explicit in the second, medication pathway based model in Figure 5.

Our model does not consider in detail, where in the medication pathway an error may occur. Some of those errors may even be difficult to summarize in a medication pathway. Some OEEs involving drug therapy can be visualized in the global model but not in the model based on an individual patient (Figure 5) because in those cases there do not exist explicit underlying medication pathways and there are infinite reasons why a decision or action may not have taken place.

Our model is intended to increase the precision of our terminology, but it does not yet allow the weighing of factors contributing to an event. To address relative contributions of drugs and underlying diseases as well as the dynamics of evolving events a different approach such as the application of Markov chains may be needed [44, 45].

In conclusion, one or more medication pathways involving or not involving errors may or may not contribute in any combination dependently or independently to any number of clinical symptoms and events which are also influenced by the underlying medical conditions of the patients. We have tried to make this explicit with a graphic representation which comprises two Venn

diagrams and a medication pathway representation. We were able to map all drug risk situations encountered in a clinical drug safety study and to achieve an unambiguous count of ADEs, ADRs and MEs and would like to emphasize the temporary aspects of counting MEs depending on the temporary knowledge about the patient and his conditions.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf and declare TB, HD and RM had support from the German Ministry of Health for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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