A Need for a Practical Taxonomy

Over the last ten years many important studies have been published on the problem of adverse drug events (ADEs) and have suggested ways for reducing their incidence.1–7 Recently there have even been articles touting successful efforts of reducing ADEs.8–10 Most of these efforts have relied on computer assistance.9,10

Our group at the Salt Lake City Veterans Health System and the University of Utah Medical Center has spent the last eight months analyzing over one thousand reports of ADEs. We agree that computer-assisted methods of reducing adverse events show tremendous promise but are under-developed and
underutilized. Our experience in operationalizing key definitions has highlighted significant barriers to eventual automation of comprehensive ADE surveillance methods. The promise of computer-assisted methods is threatened by inconsistencies and vagueness that currently surround the definition and classification of ADEs and their attributes.

This paper briefly describes the range of definitions in the literature, highlights the vagueness inherent in classifications of ADEs, and proposes guidelines for definitions and classifications of ADEs to be used in future research.

The Range of Definitions

Definitions and their interpretations vary with the focus of investigation, which has ranged from effect characterization to reduction of harm. The World Health Organization (WHO) has been a leader in the surveillance of ADEs. A prime aim of the WHO and regulatory bodies such as the Food and Drug Administration (FDA) is pharmacovigilance. Among other things pharmacovigilance involves 1) cataloguing the types and rates of side effects of a drug to inform its use and 2) determining whether a drug is suitable for use on the market. This goal of effect characterization is in contradistinction to the goals of quality management (QM) at the level of the provider or system. In QM the goal is harm reduction through early detection, heightened awareness, and primary prevention. Most current research in ADEs is oriented towards QM rather than premarketing or postmarketing surveillance.

The WHO provides definitions for two types of events: adverse drug reactions (ADRs) and adverse drug events. An ADR was originally defined in 1972 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 functions.” In late 2000 this definition was revised to “an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.”

On the other hand, the WHO continues to define an ADE as “any untoward occurrence that may be present during treatment with a pharmaceutical product but which does not necessarily have a causal relation to the treatment.” This definition reveals the WHO’s orientation towards premarketing and postmarketing surveillance instead of QM. One famous ADE is violent death associated with HMG-CoA reductase inhibitors. Initial studies found that these cholesterol-reducing agents did not improve mortality as reduced cardiovascular deaths were offset by increased violent deaths. There was never a documented causal relationship between violence and the pills and subsequent studies showed there was no association. However, a function of postmarketing surveillance is to pick up adverse events that may have a causal link with drugs, so this definition of ADE has its place.

Researchers in computer-assisted QM in this country started by adopting the WHO definition of ADR but used the name ADE. Classen et al. defined an ADE as a “noxious and unintended and occurs at doses used in man for prophylaxis, diagnosis, therapy, or modification of physiologic functions.” Later Bates et al. expanded the definition to an “injury resulting from medical intervention related to a drug.” This definition drops the restrictions of use and dose but maintains the requirement of at least a weak causal link. However Bates’ illustrations of his definition expand ADE beyond injury caused by a drug (an ADR) to injury related to the use of a drug including the omission of doses and disease breakthrough. Bates’ definition appears to have been adopted by the Institute of Medicine in 1999. Although other studies use variations on these two definitions, we know of no recent American study on the incidence or prevention of ADEs that uses the WHO definition of ADE and drops the requirement of a causal link.

The adoption of WHO terminology by QM has resulted in the vagueness of the label ADE. In the international literature an ADE may be 1) an injury caused by a drug (an injury of commission), 2) an injury related to the under use or lack of use of a drug but caused by the disease (an injury of omission), or 3) an injury that may have no causal relationship to drug therapy.

So what is the correct definition of an ADE? The definition offered by Bates is acceptable. However, a definition is only a small component of the taxonomy of ADEs. Any definition will require further operationalization as to what types of events are to be included or excluded from consideration and how to describe those events.
What is a Drug Event?

There are several questions that need to be answered about an event. What is the relation of disease, drug effect, and adverse event? What is the intent of the prescriber and the patient? Is a suite of diagnoses related to a drug a single event or multiple events?

Relationship of Events to Drug or Disease Effect

Few papers explicitly lay out the types of events they report on. Even papers touting definitions rarely describe the range of drug and disease effects that were included in the analysis.

When viewed in terms of causality, the types of events in are roughly organized from events that have the tightest to weakest causal link to drug therapy. (Causality will be explored further below.)

This classification has more than academic interest as different interventions in the system of healthcare are likely to differentially prevent the various types of ADEs. The type of events selected for study will depend on the design and goals of the study. Whatever the selected set of events may be, we recommend classifying each reported ADE into one of the categories in Table 1. This explicit reporting will allow for better understanding of study results and will facilitate study comparisons among studies.

Special Cases of Intent

Most definitions in the literature do not address the intent of the patient or the prescriber. Some critics of ADE research who do not participate in this research complain that studies are too broad. They claim that, of course, there will be some hypokalemia or hypotension from diuretic use; that this is a normal expectation of therapy that is titrated between adverse and desired effects. Others have complained that patient-directed therapy should not be included in ADE surveillance and prevention strategies, as healthcare systems are not “responsible” for these types of events.

We believe that healthcare systems should address harm for all the cases of intent detailed in Table 2. Clearly classifying and reporting ADEs in these special cases will help quantify the burden of harm and perhaps highlight the importance of further research in these under-appreciated areas.

We have operationalized titration events as those where the offending drug was or should have been discontinued, as the harm to benefit ratio was intolerable.

Multiplicity of Events

Often more than one syndrome result from the use of a drug. An angiotensin II receptor antagonist may cause renal insufficiency that may lead to edema, congestive heart failure, myocardial infarction and death. In this case renal insufficiency is the proximal event—the syndrome closest to the physiologic effect of the drug and often the first syndrome to manifest itself. The other diagnoses are corollary or downstream events. The proximal event may be separated by hours, days, or weeks from the corollary events.

In the case of multiple corollary syndromes the investigator has the option of reporting each syndrome as a separate event or lumping all the syndromes together as a single event.

We recommend not inflating results by reporting multiple corollary syndromes as separate ADEs. However, unrelated syndromes with different pathophysiologic bases should be reported as a separate ADE. For example aminoglycosides can cause both rash and nephrotoxicity.

When an Event is an Adverse Event

It is not clear from reading most studies what outcomes were considered adverse events. For example,
some studies may report hypokalemia as any value under the lower limit of normal whereas others may require a value 60% of the low normal value. Clearly the frequency and seriousness of adverse events can vary markedly among these studies. Another area of concern involves common clinical syndromes such as constipation. Is constipation no stool for 72 hours, hard stool, or patient report of constipation? Again, variation in definitions may greatly affect frequency and seriousness of adverse events. These examples highlight the importance of prospectively defining explicit parameters for adverse event determination.

Another reason for prospectively setting explicit parameters for adverse events is to promote uniformity in the determination of events for a given study. For example, the first month of the study the investigator may decide that hypokalemia is any value below normal but may choose another threshold the following month.

**Scales and Descriptions of Seriousness**

One of the most important characteristics of an ADE is its severity or seriousness. After all, we are interested in ADEs because they cause trouble; we want to know how much trouble they cause or how much trouble interventions prevent.

The WHO prefers the term seriousness over severity. Severity describes the intensity of symptoms whereas seriousness described the risk to the patient; for example, severe nausea is not as serious as ventricular fibrillation. We agree that the term seriousness is preferable but resign ourselves to the preferred use of severity in the American literature.

Various scales of seriousness have been used in the literature. Many investigators follow the lead of the pharmacovigilance community and classify severe or serious ADEs as those that result in death; a life-threatening condition; initial or extended hospitalization; persistent or significant disability; cancer; and congenital abnormalities. The next level down on the scale is described as significant or moderate which is an event that requires treatment. The lowest level are mild or insignificant events.

The chief trouble with scales is that one can always find cases that fall within the serious category but are intuitively insignificant and others that may fall into an intermediate or low category but are intuitively serious. For example, hospitalizations may be extended for relatively minor events depending on the day of the week or other coincident social factors. On the other hand, we have seen a hundred-fold overdose of a GPIIb/IIIa inhibitor cause only minor bleeding but it did not prolong hospitalization because the patient required monitoring for other reasons. Was this a mild, self-limited reaction?

Another shortcoming of scales is that they can be very subjective. We frequently find ourselves arguing whether a dose of medication was life threatening. Scales that may be less subjective are quite complicated and may present practical problems in a large study.

We recommend that individual outcomes be reported rather than levels on a scale. Of course, seriousness may vary greatly within such outcomes as admission or unit transfer. However, this approach to reporting gives more information to policy makers and other researchers who may want to target a particular type of event.

Individual outcomes may also serve as indicators of cost to the healthcare system. Admissions, unit transfers, procedures, etc. are of interest to those who might actually implement strategies reported in the literature that prevent ADEs.

**Error**

Since the publication of the Institute of Medicine report *To Err is Human,* there has been a heightened interest in error analysis. However we find that this area presents multiple problems.

**Inappropriate Application of James Reason’s Conceptual Framework**

The work of Reason on human error is also being used to classify adverse drug events. According to Reason, there are two kinds of errors. The first kind is
an error of execution—a slip or lapse—that occurs when the action is not performed as intended, e.g., the default dosage is selected in a computerized order entry system. The other kind is an error in planning where the action is completed as intended but the desired effect is not achieved, as the plan was faulty, e.g., kidney function was not considered when the drug was ordered and the resulting overdose caused harm.

In the medical literature Reason’s classification is often misunderstood as being associated with systems when the unit of analysis is the person. For example, when a nurse gives the wrong dose of a medication, some authors may classify the error as an error of execution because the intention of the physician was not acted out. However, the nurse may have intended to give the dose but incorrectly calculated how many pills were required to make up the prescribed dose. In that case, the error was really an error of planning on the part of the nurse. We find it presumptuous to assume that the physician is the only thinking being in the drug therapy process and that allied providers are appendages or automatons that carry out orders. We find more useful the error classification scheme of the National Coordination Council Medication Error Prevention Program’s Taxonomy for Medication Errors.18 The section on errors provides a fairly complete analysis of the type of error that is more descriptive than just planning vs. execution.

The Difficulty of Finding Omissions

Some investigators have stressed error analysis in conjunction with the study of ADEs.1 These authors have described both errors of omission (failure to act) and errors of commission (where action was inappropriate).

The investigator must be especially careful of reporting results that include errors of omission. The problem is in determining the denominator or determining the total number of errors of omission. Errors of commission are relatively easier to spot than missed opportunities to act. Capturing a representative sample of omitted acts requires a meticulous examination of the record by content experts in the fields of interest. Few studies or surveillance programs can afford broad surveillance of omissions.

Judging Errors

Finally, an act or plan must be determined to be erroneous relative to a standard. Standards must be agreed upon for each type of potential error. Consensus among a couple of investigators is less desirable than an evidenced-based standard or practice guideline.

Practice standards are difficult to come by even by well-funded national committees. For this reason it is preferable to use criteria-based error classification schemes such as the NCC MERP taxonomy. This scheme covers a narrow spectrum of drug prescription and administration problems. Studies that wish to address higher-level errors should be sufficiently narrow in scope so as to have a literature-based standard for each type of error investigated.

Causality

Once an event is identified, it is important to describe the strength of the causal relationship with the suspect drug.

Scales

There are several standardized schemata for the attribution of causality. These all have their particular strengths and weaknesses, the analysis of which lies outside the scope of this paper. Many of the scales or algorithms have been validated.14,19 It is important to match the method to the study. One popular scale is that developed by Naranjo et al.14 However, this scale was validated using case reports in the literature and not real-world surveillance. Moreover, only traditional WHO-style ADRs are logically assessable with this scale; the scale does not apply to ADEs resulting from omissions.

Difficulty with Disease-associated Harm

Attribution of cause in the case of ADRs is less problematic than cases where a disease precipitates or contributes to harm. In an ADR the suspect drug often adds a new physiologic process to the patient, which results in harm. However, in the case of a disease breakthrough or failure to prophylax, it is often difficult to tell whether the drug was at fault or whether the disease would have progressed despite any therapy.

Distinct and Corollary Syndromes

As covered above, a drug intervention may be associated with corollary syndromes. The proximal event may be separated by days or weeks from the final event. The strength of the causal relationship will
vary with each of these syndromes and should be assessed separately especially if reported as separate syndromes.

**Weight of Contribution**

Closely allied with the attribution of cause is whether the drug exacerbated a condition or precipitated it. This type of information about the relationship of a drug to an event helps to qualify which events are not pure drug events, thus the harm or seriousness of the event cannot be wholly attributed to drug therapy.

Likewise the corollary outcomes such as admission or treatments may be strongly or weakly dependent on the effects of a drug. Instead of a subjective weighting, we recommend classifying whether the adverse event was the sole, necessary or sufficient cause of the outcome in question.

**Conclusion**

ADE research continues to be plagued with vague definitions and inconsistent classifications. Although this paper provides some guidelines for making more sense of ADEs, the approach to classification of ADEs should be tailored to the research design and questions. But whatever the classification system, it should be as explicit as possible and reported along with the research findings to facilitate a better understanding of the findings and comparisons with others studies.

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**References**