Electronic Supplementary Material 1: Glossary of Selected Terms Related to Drug-Drug Interactions

The Evidence Workgroup (listed as authors above) developed definitions for terms that specifically relate to the evaluation of drug-drug interactions. Some of these terms were created de novo by the workgroup, while others were adapted from definitions in the published literature.

**Adverse event:** Harm in a patient administered a drug but not necessarily caused by a drug [1].

**Adverse drug event:** Harm caused by the use of a drug [1, 2].

**Adverse drug reaction:** Harm directly caused by a drug at normal doses [1].

**Clinically relevant potential DDI:** A potential DDI associated with safety concerns related to either toxicity or loss of efficacy that warrant the attention of healthcare professionals and/or systems involved in the medication therapy process. This definition excludes theoretical interactions such as: i) metabolic inhibition of a minor clearance pathway (< 30% total clearance) for a medication with a wide therapeutic index; ii) metabolic induction of minor clearance pathway; and iii) competitive inhibition between two substrates sharing a common elimination pathway.

**Drug-drug interaction (DDI):** A clinically meaningful alteration in the exposure and/or response to a drug (object drug) that has occurred as a result of the co-administration of another drug (precipitant drug) [3-5]. Response can refer to either precipitating an adverse event or altering the therapeutic effect of the object drug.

**High-alert medications.** High-alert medications are drugs that bear a heightened risk of causing significant patient harm when used in error. Although mistakes may or may not be more common with these drugs, the consequences of an error are clearly more devastating to patients. Use these lists to determine which medications require special safeguards at your practice site to reduce the risk of errors [6].

**Medication error:** Inappropriate use of a drug that may or may not result in harm [1, 8].

**Narrow therapeutic index (NTI) drug:** Drugs for which even a small change in their levels of exposure may lead to serious safety concerns or therapeutic failure related to either toxicity or loss of efficacy. For example: i) <100% (<2-fold) INCREASE in AUC for the object drug may lead to potentially serious exposure-related adverse event(s); or ii) <50% DECREASE in AUC for the object drug may result in a loss of efficacy with potentially serious therapeutic consequences (e.g., failure of contraception, or virologic failure due to subtherapeutic drug levels). NTI drugs often require serum concentration monitoring. Examples of NTI drugs are class I/III anti-arrhythmic agents, colchicine, immunosuppressive agents, digoxin, ergot derivatives, ethinyl estradiol/progestin oral contraceptives, lithium, phenobarbital, phenytoin, theophylline, and warfarin.

**Object drug:** The drug being affected by the drug-drug interaction. Sometimes called victim drug.

**Perpetrator drug:** See precipitant drug.

**Pharmacodynamic drug-drug interactions (PD DDI):** Drug-drug interactions in which the response to the object drug is modified by the precipitant drug, without changes in object drug concentration/exposure.

**Pharmacokinetic drug-drug interactions (PK DDI):** Drug-drug interactions in which the concentration/exposure of the object drug is altered by the precipitant drug.

**Potential drug-drug interaction (PDDI):** Co-prescription or co-administration of two drugs known to interact, and therefore a DDI could occur in the exposed patient [4, 5]. PDDIs are usually detected with computerized CDS [8].
Precipitant drug: The drug causing the drug-drug interaction. Sometimes called perpetrator drug.

Serious adverse event (SAE): An adverse event resulting from a DDI that results in any of the following patient outcomes [9]:

1. Death;
2. Life-threatening event (the patient is at substantial risk of dying at the time of the adverse event, or use or continued use of the drug might have resulted in the death of the patient);
3. New or prolonged hospitalization (new admission to the hospital or prolongation of existing hospital stay);
4. Disability or permanent damage (substantial disruption of a patient's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent, or permanent change, impairment, damage, or disruption in the patient's body function/structure, physical activities, and/or quality of life);
5. Required intervention to prevent permanent impairment or damage (medical or surgical intervention was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure);
6. Other serious important medical events (the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes).

This excludes idiosyncratic effects such as pancreatitis, hepatotoxicity, blood dyscrasias, and anaphylaxis.

Seriousness: A measure of the extent to which an adverse reaction can or does cause harm [10]. For example, ventricular tachycardia or hepatic impairment of any intensity is serious, while discoloration of the urine by rifampicin, even if very pronounced (i.e., severe), is not serious [10].

Severity: A measure of the extent to which the reaction develops in an individual. Severity may be more accurately described as intensity. Practically, when one is discussing the severity of an adverse reaction, they are referring to seriousness. More precisely, however, severity and seriousness are different concepts. A severe reaction need not be serious [10].

Side effect: A usually predictable or dose-dependent effect of a drug that is not the principal effect for which the drug was chosen; the side effect may be desirable, undesirable, or inconsequential [1, 10].

Victim drug: See Object drug.

References

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1 The terms “mild”, “moderate”, and “severe” are often used to describe the severity (intensity) of an adverse reaction [10]. However, there are no satisfactory definitions of these terms, and using any one of them to describe a particular adverse reaction implies a value judgment, which may differ from patient to patient and from prescriber to prescriber. Furthermore, some of the terms used to define “severe” actually mean “serious” [10].