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Focus on pharmacogenomics, phytonutrient-drug interactions and COVID-19 vaccines: Perspectives on ADRs, ADEs, and SEDs

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INTRODUCTION

Adverse drug events (ADEs), drug-induced toxicity and side effects are a significant concern. ADEs are known to pose significant morbidity, mortality, and cost burdens to society. ADEs are estimated to be the fourth leading cause of death in the United States—ahead of pulmonary disease (before the COVID-19 pandemic), diabetes, AIDS, pneumonia, accidents, and automobile deaths (USFDA-1) [S]. However, there is a lack of strong evidence to determine their precise impact. For example, FDA receives over 1 million adverse event and medication error reports annually, which considerably helps in monitoring post-market surveillance data. However, FDA Adverse Event Reporting System (FAERS) data do not necessarily include all known safety information for a reported medication; therefore, all other pertinent information should be considered before making any drug-related treatment decisions (USFDA-2) [S].

FAERS provides a web-based public dashboard for practitioners, healthcare professionals and the public to look for information reported to FDA by the pharmaceutical industry, healthcare providers and consumers. The primary intent of creating FAERS was to improve data access and establish transparency. However, caution is warranted before interpreting the data because reports on certain drugs or biologics may not reflect the cause of the ADEs by the concerned agents (USFDA-2) [S]. Other data constraints could be: (i) duplicate or incomplete reports; (ii) mere inclusion of a report does not pinpoint causation; (iii) unverified information in the reports; (iv) reports not necessarily reflecting rates of incidences. In 2020 alone, over 1.1 million reports were received compared to over 2.19 million in 2019 and 2.15 million in 2018. In the 2020 total reports, over 591 000 reports were expedited and over 473 000 reports were non-expedited. Approximately 42 000 were direct reports (voluntarily submitted directly to FDA through the MedWatch program by consumers and healthcare professionals) (USFDA-3) [S]. In this regard: (i) expedited report connotes at least one adverse effect that is not currently described in the product labeling and for which the patient outcome is serious; (ii) non-expedited means reports that do not meet the criteria for expedited reports, including cases that are reported as serious and expected, non-serious and unexpected, and non-serious and expected (USFDA-3) [S].

The landmark 1999 Institute of Medicine (IOM) report, *To Err is Human* implicated ADEs in 7000 annual deaths at an estimated cost of $2 billion (USFDA-4) [S]. Similarly, a second landmark study from 1995 suggested that approximately 28% of ADEs were preventable through optimization of medication safety and

distribution systems, provision and dissemination of timely patient and medication information, and staffing assignments (Leape et al., 1995) [R]. Subsequent investigations suggest these numbers are most likely conservative estimates of the morbidity and mortality impact of ADEs (James, 2013) [R]. This concern, however, has not been resolved as demonstrated in a 2015 report from the National Patient Safety Foundation, *Free from Harm: Accelerating Patient Safety Improvement Fifteen Years After To Err Is Human* (Natl. Saf. Found., 2015) [R]. The report found ADEs play a role in 50% of surgeries and that more than 700 000 outpatients are treated annually in emergency departments for a drug-induced adverse event and that 120 000 of these cases require hospitalization.

In 2001, the US Department of Health and Human Services estimated 770 000 people were injured or died each year in hospitals from ADEs, which cost up to $5.6 million each year per hospital excluding the other accessory costs (e.g., hospital admissions due to ADEs, malpractice and litigation costs, or the costs of injuries) (USDHHS, 2001) [S]. Nationally, hospitals spend $1.56–$5.6 billion each year to treat patients who suffer ADEs during hospitalization (USDHHS, 2014) [S]. In response, the Department of Health and Human Services issued the *National Action Plan for Adverse Drug Event Prevention* (ADE Action Plan) in 2014 that identified the means to measure and prevent ADEs and described future goals to improve patient safety (USDHHS, 2014) [S].

Analysis of ADEs, ADRs, side effects and toxicity

A recent report suggested that ADEs and/or side effects of drugs occur in approximately 30% of hospitalized patients (Wang et al., 2015) [R]. The American Society of Health-System Pharmacists (ASHP) defines medication mishap as unexpected, undesirable, iatrogenic hazards or events where a medication was implicated (ASHP-advisory-1) [R]. These events can be broadly divided into two categories: (i) medication errors (i.e., preventable events that may cause or contain inappropriate use), (ii) ADEs (i.e., any injury, whether minor or significant, caused by a medication or lack thereof). Another significant ADE-generating category that can be added to the list is lack of incorporation of pre-existing condition(s) or pharmacogenetic factors. This work focuses on ADEs; however, it should be noted that ADEs may or may not occur secondary to a medication error.

The lack of more up-to-date epidemiological data regarding the impact of ADEs is largely due to challenges with low ADE reporting. ASHP recommends that health systems implement adverse drug reaction (ADR) monitoring programs to (i) mitigate ADR risks for specific patients and expedite reporting to clinicians involved in the care of patients who do experience ADRs and (ii) gather pharmacovigilance information that can be reported to pharmaceutical companies and regulatory bodies (ASHP-advisory-1) [R]. Factors that may increase the risk for ADEs include polypharmacy, multiple concomitant disease states, pediatric or geriatric status, female gender, genetic variance, and drug factors, such as class and route of administration. The Institute for Safe Medication Practices (ISMP advisory, 2018) [S] defines high-alert medications as those with high risk for harmful events, especially when used in error (ISMP advisory, 2018) [S]. Examples of high-alert medications include antithrombotic agents, cancer chemotherapy, insulin, opioids, and neuromuscular blockers. Meta-analysis of intervention studies is also underway to reduce ADRs in certain populations (see the following table for reference).

The following table provides the most recent CDC estimates (updated June 7, 2018) on ADEs, hospitalizations and/or emergency department (ED) visits. Corresponding references are provided in the last column of the table:

ADEs (age groups)	ADEs from specific medicines	No. of ED visits/year (approx.)	No. of hospitalizations/ year	References
Total		@1.3 million	450 000	https://www.cdc.gov/medicationsafety/adult_adversedrugevents.html[a] @https://www.ncbi.nlm.nih.gov/pubmed/27893129
Elderly (65+ years)	Blood thinners, diabetic medications, seizure medications and heart medicines[b]	450 000		https://www.cdc.gov/medicationsafety/adult_adversedrugevents.html[a]
Children (17 years or younger)		200 000		https://www.cdc.gov/medicationsafety/parents_childrenadversedrugevents.html[c]

Note: Meta-analysis of Interventions to Reduce ADRs in Older Adults: https://onlinelibrary.wiley.com/doi/abs/10.1111/jgs.15195.

[a] *Approximately 150 000 adults are treated in EDs each year because of adverse events from antibiotics.*

[b] *https:/www.cdc.gov/medicationsafety/adverse-drug-events-specific-medicines.html.*

[c] *Finding and eating or drinking medicines, without adult supervision, is the main cause of emergency visits for ADEs among children less than 5 years old. Approximately 60 000 children less than 5 years old are brought to EDs each year because of unsupervised ingestions. Nearly 70% of ED visits for unsupervised medication ingestions by young children involve 1- or 2-year-old children.*

Terminology

ADEs may be further classified based on expected severity into adverse drug reactions (ADRs) or adverse effects (also known as side effects). ASHP defines ADRs as an "unexpected, unintended, undesired, or excessive response to a drug" resulting in death, disability, or harm (Edwards & Aronson, 2000 [R]; Ferner & Aronson, 2010 [R]; Gray et al., 2018 [M]; Eva Montané & Santesmases, 2020 [R]). The World Health Organization (WHO) has traditionally defined an ADR as a "response to a drug which is noxious and unintended, and which occurs at doses normally used"; however, another proposed definition, intended to highlight the seriousness of ADRs, is "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" (Edwards & Aronson, 2000) [R]. Under all definitions, ADRs are distinguished from side effects in that they generally necessitate some type of modification to the patient's therapeutic regimen. Such modifications could include discontinuing treatment, changing medications, significantly altering the dose, elevating or prolonging care received by the patient, or changing diagnosis or prognosis. ADRs include drug allergies, immunologic hypersensitivities, and idiosyncratic reactions. In contrast, side effects, or adverse effects, are defined as "expected, well-known reactions resulting in little or no change in patient management" (ISMP advisory, 2018) [S]. Side effects occur at a predictable frequency and are often dose-related, whereas ADRs are less foreseeable (Edwards & Aronson, 2000 [R]; ISMP [S]; Cochrane et al., 2013 [R]).

Two additional types of ADEs are drug-induced diseases and toxicity. Drug-induced diseases are defined as an "unintended effect of a drug that results in mortality or morbidity with symptoms sufficient to prompt a patient to seek medical attention, require hospitalization, or both" (Tisadale et al., 2018) [R]. In other words, a drug-induced disease has elements of an ADR (i.e., significant severity, elevated levels of patient care) and adverse effects (i.e., predictability, consistent symptoms). Toxicity is a less precisely defined term referring to the ability of a substance "to cause injury to living organisms as a result of physicochemical interaction" (Wexler et al., 2014) [R]. This term is applied to both medication and non-medication types of substances, while "ADRs," "side effects," and "drug-induced diseases" typically only refer to medications. When applied to medication use, toxicity typically refers to use at higher-than-normal dosing or accumulated supratherapeutic exposure over time, while ADRs, side effects, and drug-induced diseases are associated with normal therapeutic use.

Although the title of this series is "Side Effects of Drugs," this volume provides emerging information for all ADEs including ADRs, side effects, drug-induced diseases, toxicity, and other situations less clearly classifiable into a particular category, such as effects subsequent to drug interactions with other drugs, foods, and cosmetics. Pharmacogenetic considerations have been incorporated in several chapters as appropriate and subject to the availability of literature.

ADRs are described in *Side Effects of Drugs Annual* (SEDA) using two complementary systems, EIDOS and DoTS (Aronson & Ferner, 2003 [R]; Callréus, 2006 [R]; Aronson & Ferner, 2010 [R]). These two systems are illustrated in Figs 1 and 2 and general templates for describing reactions in this way are shown in Figs 3–5. Examples of

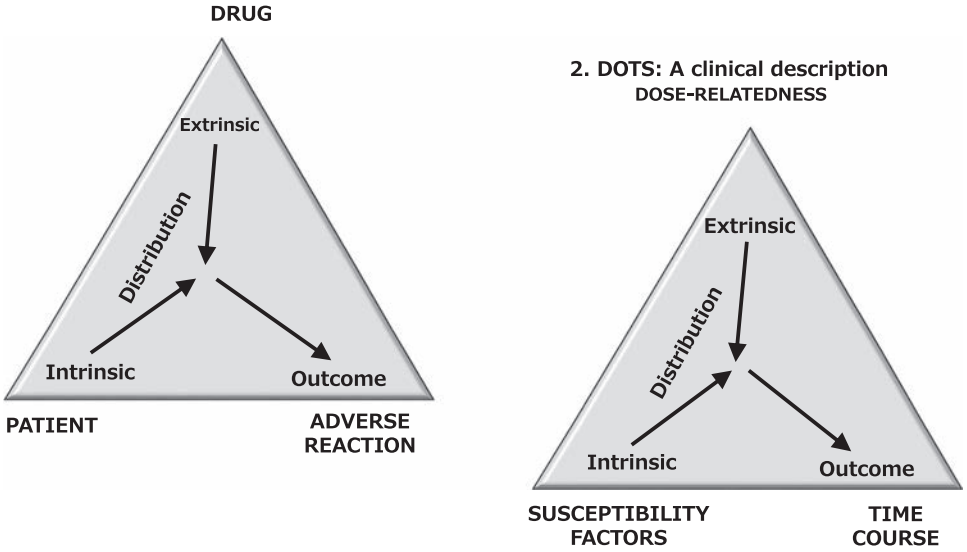

FIG. 1 Describing adverse drug reactions using two complementary systems. Note that the triad of drug-patient-adverse reaction appears outside the triangle in EIDOS and inside the triangle in DoTS, which leads to a scenario as depicted in Fig. 2.

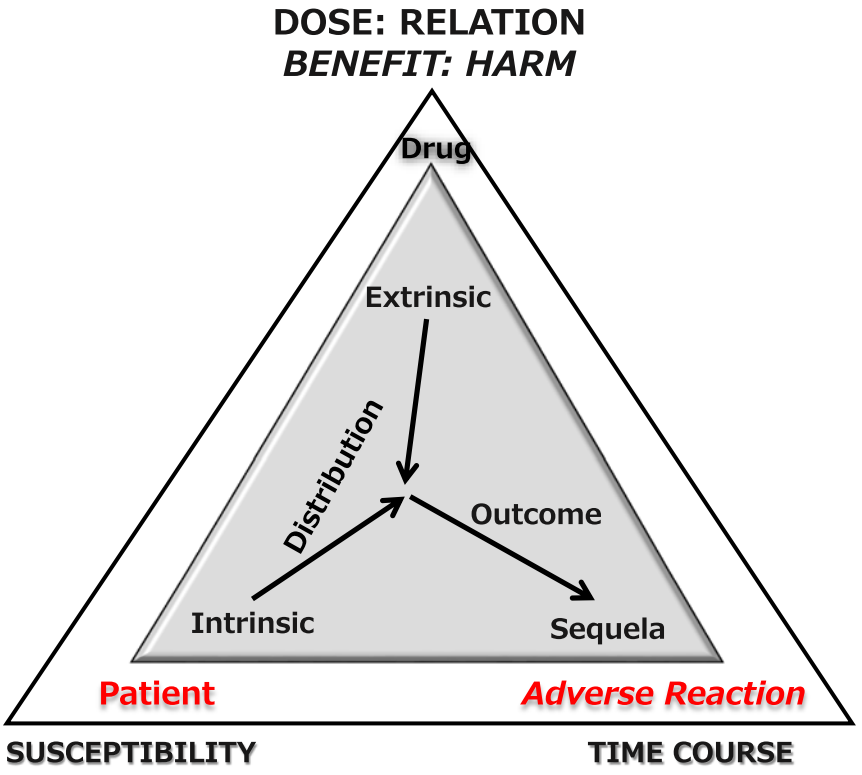

FIG. 2 How the EIDOS and DoTS systems relate to each other. Here, the two triangles in Fig. 1 are superimposed to show the relation between the two systems. An adverse reaction occurs when a drug is given to a patient. Adverse reactions can be classified mechanistically (EIDOS) by noting that when the Extrinsic (drug) species and an Intrinsic (patient) species, are co-Distributed, a pharmacological or other effect (the Outcome) results in the adverse reaction (the Sequela). The adverse reaction can be further classified (DoTS) by considering its three main features—its Dose-relatedness, its Time-course, and individual Susceptibility.

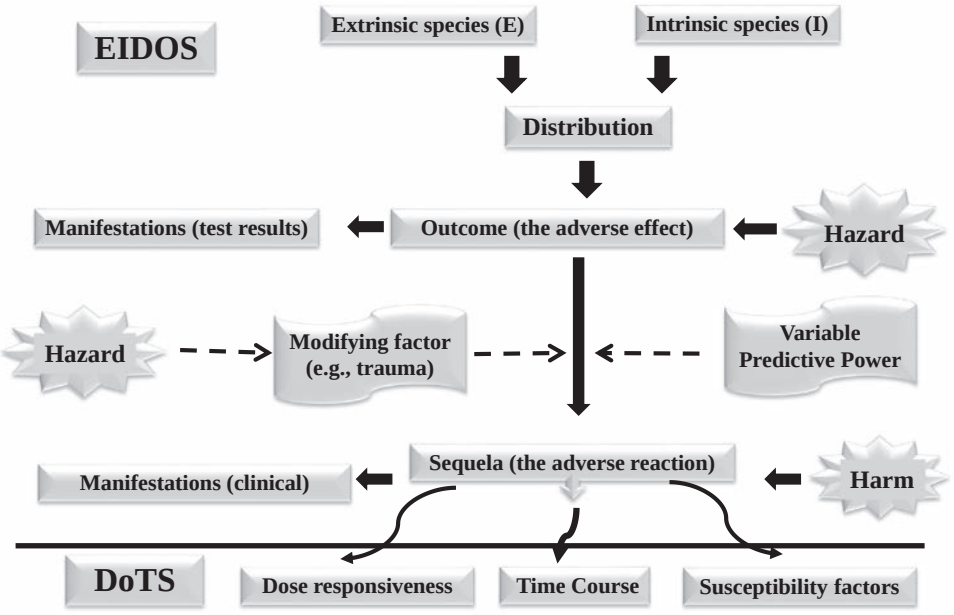

FIG. 3 A general form of the EIDOS and DoTS template for describing an adverse effect or an adverse reaction.

their use have been discussed elsewhere (Callréus, 2006 [R]; Aronson et al., 2009 [R]; Calderón-Ospina & Bustamante-Rojas, 2010 [R]; Ferner & Aronson, 2010 [R]; Aronson & Ferner, 2010 [R]). As clinicians are becoming more cognizant about different types of adverse effects, ADEs, and ADRs, reports in this arena are growing faster than one can imagine; a few recent highly relevant reviews are listed for reference (Category [R]: Alghamdi, et al., 2019; White & Thomson Reuters Accelus, 2015; Davies & O'Mahony 2015; Mouton et al., 2015; Bouvy, et al., 2015; Coleman & Pontefract, 2016; Castillon et al., 2019; Patton & Borshoff, 2018; Eva

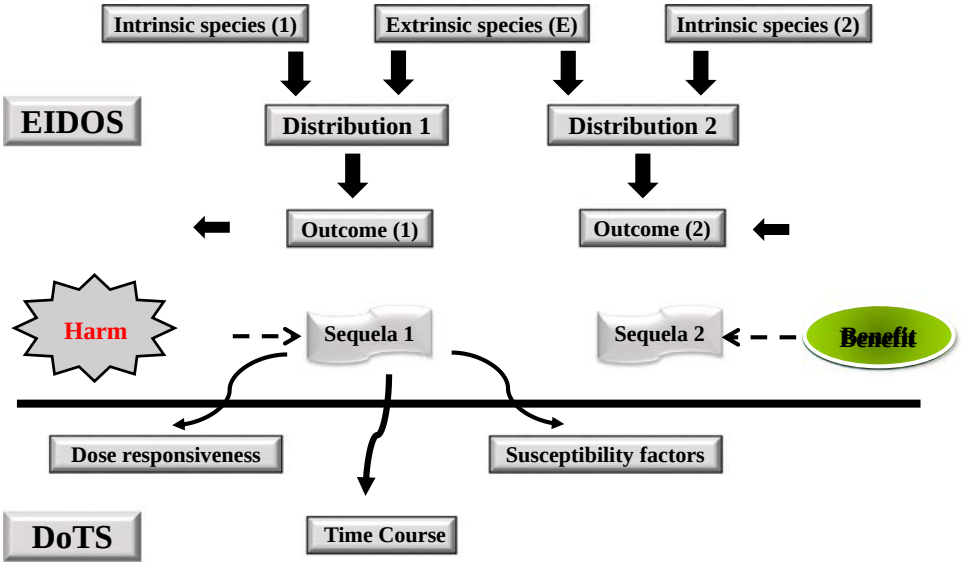

FIG. 4 A general form of the EIDOS and DoTS template for describing two mechanisms of an adverse reaction or (illustrated here) the balance of benefit to harm, each mediated by a different mechanism.

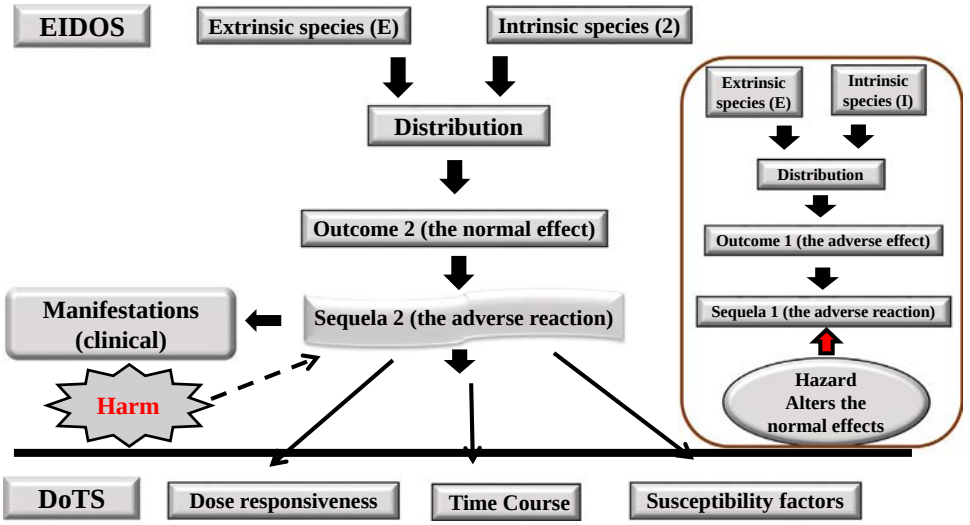

FIG. 5 A general form of the EIDOS and DoTS template for describing an adverse drug interaction.

Montané & Santesmases, 2020); (Gray et al., 2018 [M]; Lovegrove et al., 2019; [M]; Kojima et al., 2019 [M]); (Bénard-Laribière et al., 2015 [C]).

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EIDOS

The EIDOS mechanistic description of ADRs [17] has five elements:

- The Extrinsic species that initiates the reaction (Table 1)
- The Intrinsic species that it affects
- The Distribution of these species in the body
- The (physiological or pathological) Outcome (Table 2), which is the adverse effect
- The Sequela, which is the adverse reaction

- *Extrinsic species*
  This can be the parent compound, an excipient, a contaminant or adulterant, a degradation product, or a derivative of any of these (e.g. a metabolite) (for examples see Table 1).
- *Intrinsic species*
  This is usually the endogenous molecule with which the extrinsic species interacts; this can be a

TABLE 1 The EIDOS mechanistic description of adverse drug effects and reactions

Feature	Varieties	Examples
E. Extrinsic species	**1.** The parent compound	Insulin
	2. An excipient	Polyoxyl 35 castor oil
	3. A contaminant	1,1-Ethylidenebis [l-tryptophan]
	4. An adulterant	Lead in herbal medicines
	5. A degradation product formed before the drug enters the body	Outdated tetracycline
	6. A derivative of any of these (e.g. a metabolite)	Acrolein (from cyclophosphamide)
I. The Intrinsic species and the nature of its Interaction with the extrinsic species		
(a) Molecular	**1.** Nucleic acids	
	(a) DNA	Melphalan
	(b) RNA	Mitoxantrone
	2. Enzymes	
	(a) Reversible effects	Edrophonium
	(b) Irreversible effect	Malathion
	3. Receptors	
	(a) Reversible effect	Prazosin
	(b) Irreversible effect	Phenoxybenzamine
	4. Ion channels/transporters	Calcium channel blockers; digoxin and Na^+-K^+-ATPase
	5. Other proteins	
	(a) Immunological proteins	Penicilloyl residue hapten
	(b) Tissue proteins	*N*-acetyl-p-benzoquinone-imine (paracetamol [acetaminophen])
(b) Extracellular	**1.** Water	Dextrose 5%
	2. Hydrogen ions (pH)	Sodium bicarbonate
	3. Other ions	Sodium ticarcillin
(c) Physical or physicochemical	**1.** Direct tissue damage	Intrathecal vincristine
	2. Altered physicochemical nature of the extrinsic species	Sulindac precipitation
D. Distribution	**1.** Where in the body the extrinsic and intrinsic species occur (affected by pharmacokinetics)	Antihistamines cause drowsiness only if they affect histamine H_1 receptors in the brain
O. Outcome (physiological or pathological change)	The adverse effect (see Table 2)	
S. Sequela	The adverse reaction (use the Dose, Time, Susceptibility [DoTS] descriptive system)	

TABLE 2 Examples of physiological and pathological changes in adverse drug effects (some categories can be broken down further)

Type of change	Examples
1. Physiological changes	
(a) Increased actions	Hypertension (monoamine oxidase inhibitors); clotting (tranexamic acid)
(b) Decreased actions	Bradycardia (beta-adrenoceptor antagonists); QT interval prolongation (antiarrhythmic drugs)
2. Cellular adaptations	
(a) Atrophy	Lipoatrophy (subcutaneous insulin); glucocorticosteroid-induced myopathy
(b) Hypertrophy	Gynecomastia (spironolactone)
(c) Hyperplasia	Pulmonary fibrosis (busulfan); retroperitoneal fibrosis (methysergide)
(d) Metaplasia	Lacrimal canalicular squamous metaplasia (fluorouracil)
(e) Neoplasia	
– Benign	Hepatoma (anabolic steroids)
– Malignant	
– Hormonal	Vaginal adenocarcinoma (diethylstilbestrol)
– Genotoxic	Transitional cell carcinoma of bladder (cyclophosphamide)
– Immune suppression	Lymphoproliferative tumors (ciclosporin)
3. Altered cell function	IgE-mediated mast cell degranulation (class I immunological reactions)
4. Cell damage	
(a) Acute reversible damage	
– Chemical damage	Periodontitis (local application of methylenedioxymetamfetamine [MDMA, 'ecstasy'])
– Immunological reactions	Class III immunological reactions
(b) Irreversible injury	
– Cell lysis	Class II immunological reactions
– Necrosis	Class IV immunological reactions; hepatotoxicity (paracetamol, after apoptosis)
– Apoptosis	Liver damage (troglitazone)
5. Intracellular accumulations	
(a) Calcification	Milk-alkali syndrome
(b) Drug deposition	Crystal-storing histiocytosis (clofazimine) Skin pigmentation (amiodarone)

nucleic acid, an enzyme, a receptor, an ion channel or transporter, or some other protein.

- *Distribution*
  A drug will not produce an adverse effect if it is not distributed to the same site as the target species that mediates the adverse effect. Thus, the pharmacokinetics of the extrinsic species can affect the occurrence of adverse reactions.
- *Outcome*
  Interactions between extrinsic and intrinsic species in the production of an adverse effect can result in physiological or pathological changes (for examples see Table 2). Physiological changes can involve either increased actions (e.g. clotting due to tranexamic acid) or decreased actions (e.g. bradycardia due to β-adrenoceptor antagonists). Pathological changes can involve cellular adaptations (atrophy, hypertrophy, hyperplasia, metaplasia and neoplasia), altered cell function [e.g. mast cell degranulation in immunoglobulin E (IgE)-mediated anaphylactic reactions] or cell damage (e.g. cell lysis, necrosis or apoptosis).
- *Sequela*
  The sequela of the changes induced by a drug describes the clinically recognizable ADR, of which there may be more than one. Sequelae can be classified using the DoTS system.

DoTS

In the DoTS system (SEDA-42, xxv–xlvii), ADRs are described according to the Dose at which they usually occur, the Time-course over which they occur, and the Susceptibility factors that make them more likely, as follows:

- *Relation to dose*
  - Toxic reactions (reactions that occur at supratherapeutic doses)
  - Collateral reactions (reactions that occur at standard therapeutic doses)
  - Hypersusceptibility reactions (reactions that occur at subtherapeutic doses in susceptible individuals)
- *Time course*
  - Time-independent reactions (reactions that occur at any time during a course of therapy)
- *Time-dependent reactions*
  - Immediate or rapid reactions (reactions that occur only when drug administration is too rapid)
  - First-dose reactions (reactions that occur after the first dose of a course of treatment and not necessarily thereafter)
  - Early tolerant and early persistent reactions (reactions that occur early in treatment then either abate with continuing treatment, owing to tolerance, or persist)
  - Intermediate reactions (reactions that occur after some delay but with less risk during longer-term therapy, owing to the 'healthy survivor' effect)
  - Late reactions (reactions the risk of which increases with continued or repeated exposure)
  - Withdrawal reactions (reactions that occur when, after prolonged treatment, a drug is withdrawn or its effective dose is reduced)
  - Delayed reactions (reactions that occur at some time after exposure, even if the drug is withdrawn before the reaction appears)
- *Susceptibility factors*
  - Genetic (e.g. variations in expression of certain drug-metabolizing enzymes)
  - Age (newborn, pediatric, young adult, adult and old age)
  - Sex (gender differences, hormonal variations)
  - Physiological variation (e.g. weight, pregnancy)
  - Exogenous factors (e.g. the effects of other drugs, devices, surgical procedures, food, phytochemicals and nutraceuticals, alcoholic beverages, smoking, miscellaneous other behavioral and lifestyle-related, etc.)
  - Diseases (ongoing but latent with no clinical signs, pre-existing and obvious)
  - Environmental factors (drinking water containing trace chemicals, breathing polluted air)

WHO classification

Although not systematically used in SEDA, the WHO classification, used at the Uppsala Monitoring Center, is a useful schematic to consider in assessing ADRs and adverse effects. Possible classifications include:

- Type A (dose-related, "augmented"): more common events that tend to be related to the pharmacology of the drug, have a mechanistic basis, and result in lower mortality
- Type B (non-dose-related, "bizarre"): less common, unpredictable events that are not related to the pharmacology of the drug
- Type C (dose-related and time-related, "chronic"): events that are related to the cumulative dose received over time
- Type D (time-related, "delayed"): events that are usually dose-related but do not become apparent until significant time has elapsed since exposure to the drug
- Type E (withdrawal, "end of use"): events that occur soon after the use of the drug
- Type F (unexpected lack of efficacy, "failure"): common, dose-related events where the drug effectiveness is lacking, often due to drug interactions

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PHARMACOGENOMIC CONSIDERATIONS

It has long been known that individuals respond differently to the same medication, regardless of dose, and that these differences may result in ADRs. In addition to well-recognized clinical factors, such as age, sex, kidney and liver function, drug-drug interactions, and comorbid conditions, genetic variation also explains some, or the majority, of the variability in drug response. Heritability is the amount of variation that is explained by genetics, and the heritability of drug responses ranges from 25% to 79% (Roden et al., 2011) [R]. Therefore, genetics explains a proportion of every drug response, and in some cases, genetics explains the majority of drug response. The study of how genetics affects drug response is called pharmacogenetics or pharmacogenomics. These terms are used interchangeably, but typically pharmacogenetics refers to the study of one or a few genes, whereas pharmacogenomics refers to the study of many genes or the entire genome. A primary goal of this field is to characterize the relationship

between genetic variations and drug responses, and the role of genetic variations in the development of ADRs is now well recognized. Greater use of pharmacogenomics may replace, in part or in full, the "one-size-fits-all" approach to drug prescription in favor of a more tailored pharmacological approach. The ultimate goal of clinical pharmacogenetic testing is to use a patient's genetic profile to maximize the efficacy of the medication while minimizing the risk of ADRs. This is the promise of individualized or personalized medicine.

The genetic variations between individuals may be described by polymorphisms in their genetic code, also known as genetic variants. These variations may be caused by the insertion or deletion of a few nucleotides, entire gene deletions, copy number variations or, more typically, are the result of single nucleotide polymorphisms (SNPs). SNPs are variations in a single nucleotide within a gene that may result in the production of a protein with a different amino acid sequence and altered activity or expression. Depending on the kind of protein that is affected by the polymorphisms, drug pharmacokinetics or pharmacodynamics may be altered. Polymorphisms in proteins such as drug-metabolizing enzymes or transporters may affect drug absorption, metabolism, distribution, and excretion. Polymorphisms in proteins such as membrane and intracellular receptors may affect drug binding to the receptor and hence the pharmacodynamics. Polymorphisms in proteins such as human leukocyte antigens (HLAs) may affect immune reactions and hypersensitivity to drugs. These pharmacogenetic variants are quite common. It is estimated that 99% of individuals carry at least one actionable pharmacogenetic variant (Chanfreau-Coffinier et al., 2019) [R]. Changes in drug pharmacokinetics and pharmacodynamics affect both the efficacy of the drug and the development of ADRs. With respect to ADRs, of particular interest in the field of pharmacogenomics is the role of polymorphisms in drug-metabolizing enzymes, ion transporters, and HLA.

Enzymes and transporters

The cytochrome P450 (CYP) enzymes metabolize 70–80% of all drugs in clinical use, and many genetic variants significantly affect CYP enzyme function and expression, thereby affecting pharmacokinetics and risk of ADEs (Zanger & Schwab, (2013) [R]. Other drug-metabolizing enzymes with variation-inducing toxicity include *N*-acetyl transferase type 2 (NAT2), thiopurine methyltransferase (TPMT), dihydropyrimidine dehydrogenase (DPYD), uridine diphosphateglucuronosyl transferases (UGTs), and organic anion transporters (OATs). Pharmacogenomic analyses have also shown the association of mutations in *KCNH2* and *SCN5A*, which encode cardiac ion channels and their components, with long QT syndrome (LQTS) induced by several drugs, including antibiotics, antipsychotics, chemotherapeutics, antiemetics, opioid analgesics, and anti-arrhythmics (Niemeijer et al., 2015) [R]. Examples of the genetic variants with the primary gene and the associated drug with adverse effects are shown in Table 3.

TABLE 3 Examples of genes in which genetic polymorphisms lead to increased risk of drug-induced adverse reactions

Gene	Drug	Comments
CYP2D6	Tricyclic antidepressants	Increased risk of adverse effects in *CYP2D6* poor metabolizers
TPMT	Thiopurines	Increased risk of myelosuppression in individuals with deficient or intermediate *TPMT* activity
DPYD	Fluoropyrimidines	Increased risk for toxicity in DPYD intermediate or poor metabolizers
SLCO1B1	Simvastatin	Increased myopathy risk with low or intermediate function SLCO1B1
CYP2D6	Codeine	Potential for toxicity in *CYP2D6* ultrarapid metabolizers
CYP2C9	Phenytoin	Increased risk of SJS/TEN in CYP2C9 poor or intermediate metabolizers
CYP2C19	SSRIs	Increased risk of adverse effects in CYP2C19 poor metabolizers
CYP2C19	Clopidogrel	Increased risk of adverse effects in CYP2C19 poor and intermediate metabolizers
UGT1A1	Atazanavir	Increased probability of hyperbilirubinemia in UGT1A1 poor metabolizers

Human leukocyte antigens

The HLA family comprises over 200 genes, forming the human major histocompatibility complex (MHC). Associated ADRs may occur through direct or indirect interaction of the drug with a specific HLA allele, thereby initiating an immune response and causing an adverse effect. These HLA-mediated reactions are typically hypersensitivity reactions, but they also include drug-induced injury to such organs as the liver, kidney, skin, muscle, and heart. As these reactions are dependent upon the presence of specific HLA alleles, the phenotype or ethnicity of an individual is of particular interest in determining if a medication may cause unwanted effects.

Due to the risk of ADRs, HLA genotyping is commonly done prior to prescribing several medications. In the case of abacavir, screening for the presence of *HLA-B*5701* is required by American and European regulatory authorities prior to the initiation of treatment. Similarly, genetic screening for *HLA-B*1502* and

TABLE 4 Examples of HLA allele variants and associated drug-induced adverse reactions

Reaction	Drug	HLA variant(s)
Hypersensitivity	Abacavir	*HLA-B*5701*
Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and severe cutaneous adverse reactions	Allopurinol	*HLA-B*5801*
Hypersensitivity and SJS/TEN	Carbamazepine	*HLA-B*1502*, *HLA-A*3101*
Hepatotoxicity	Lapatinib	*HLA-DRB1*07:01*
Hypersensitivity and SJS/TEN	Oxcarbazepine	*HLA-B*15:02*
Hepatotoxicity	Pazopanib	*HLA-B*57:01*
SJS/TEN	Phenytoin	*HLA-B*1502*

*HLA-B*5801* before administration of carbamazepine or allopurinol has become commonplace in several Asian countries and in patients with Asian ancestry. Several drug-induced reactions have been associated with specific variants in the HLA genes and several examples are shown in Table 4. The HLA Adverse Drug Reaction Database also provides an up-to-date listing of HLA alleles and the associated adverse drug reactions (Ghattaoraya et al., 2016) [R].

Pharmacogenetic testing

The cost of genetic testing is declining rapidly. Pharmacogenetic tests can be performed for as little as a few hundred dollars, and health insurance companies are readily reimbursing the costs (Empey et al., 2021) [R]. The turnaround time to receive results from tests typically ranges from 48 h to 2 weeks, and tests can be performed using a saliva sample, blood sample, or a buccal swab. Health systems that are currently implementing pharmacogenetic testing use a variety of different genetic testing platforms and assays (Luzum et al., 2017) [R]. Available pharmacogenetic tests can be found in the Genetic Testing Registry® curated by the National Center for Biotechnology [S]. The amount of evidence required for the clinical use of pharmacogenetic testing is widely debated, and decisions regarding the clinical use of pharmacogenetic testing depend upon the relative frequency of the genetic variation in the affected population, the disease phenotype, and the severity of the outcome/reaction (Luzum et al., 2021) [R].

Types of genomic testing that are used in pharmacogenomic research are as follows:

1. Candidate gene association studies (CGAS)

   There are approximately 30 000 genes and 1 000 000 independent genetic variants in the human genome. CGAS analyze only a few genetic variants or genes. The candidate genetic variants and genes are selected based on a priori knowledge that the genes have a role in pharmacology (e.g. pharmacokinetics or pharmacodynamics) and that the variants affect protein function and/or expression. By only analyzing a few genetic variants or genes, the major limitation of CGAS is that they can miss many other potentially important genes or variants in the genome.
2. Genome-wide association studies (GWAS)

   GWAS overcome that limitation of CGAS by analyzing all ~30 000 genes and ~1 000 000 independent variants in the genome. Although GWAS were initially used as a means to better understand human disease, this method has increasingly been used to study the genetic basis for ADRs. It is likely that as costs and application limitations decrease, the whole genomic analysis will become the preferred method. As a GWAS makes ~1 000 000 statistical tests, rigorous corrections for statistical significance must be employed to limit the potential for false-positive associations in GWAS. Therefore, the major limitation of GWAS is low statistical power, and thus very large sample sizes are required. Large sample sizes are particularly challenging for pharmacogenomic GWAS, as it is difficult to identify thousands of patients all treated with the same drug for the same indication and with whole genome analyses completed. Large sample sizes are particularly challenging if the ADR is rare. Despite these challenges, hundreds of pharmacogenomic GWAS have now been published, and all GWAS studying the association with response to a drug can be found in the publicly available GWAS catalog (Buniello et al., 2019) [R].
3. Next-generation sequencing methods

   A limitation of both CGAS and GWAS is that they only analyze certain locations in the genome where variants are a priori known to be present, which is approximately 1 in every 300 nucleotides. Therefore, CGAS and GWAS do not analyze all nucleotides in the genome, nor can they identify novel mutations associated with drug response. Sequencing overcomes that limitation by analyzing the complete nucleotide sequence. The human genome includes ~3 billion pairs of nucleotides, and thus massively parallel (or "next-generation") sequencing is necessary to sequence a human genome within a feasible amount of time (which can now be completed in as fast as 1 day). While whole genome sequencing is currently possible and may be preferential, the processing power for analysis of the ~3 billion nucleotides is prohibitive for the majority of users. As a result, a subset of the genome, the exome, or all exons (protein-coding regions), is typically analyzed in whole exome sequencing (WES). This technique

allows identification of any variations within this section of the genome; a major drawback, however, is that any variations in other areas of the genome such as in introns (regulatory coding regions) are not included. Specific to pharmacogenetics, sequencing is most useful for identifying rare genetic mutations, such as those associated with LQTS.

Resources for pharmacogenetic information

In addition to the resources mentioned earlier, several other resources exist for pharmacogenetic information. The Pharmacogenomics Knowledgebase (PharmGKB®) is the best resource because it is a central location for almost all pharmacogenetic information, including clinical and variant annotations, links to the primary literature, and clinical and regulatory recommendations from around the world (Whirl-Carrillo et al., 2021; PharmGKB) [R]. The most commonly used guidelines by pharmacogenetic implementers (Luzum et al., 2021) [R] are by the Clinical Pharmacogenetics Implementation Consortium (CPIC), which can be found on the CPIC website, or PharmGKB®. The US FDA provides two different pharmacogenetic resources: the "Table of Pharmacogenomic Biomarkers in Drug Labeling" [R] and the "Table of Pharmacogenetic Associations" (USFDA Table) [S]. Information on pharmacogenetic implementation can be found on the Implementing Genomics in Practice (IGNITE) website [S]. The Pharmacogene Variation Consortium (PharmVar) is a central repository for pharmacogenetic variation that focuses on haplotype structure and allelic variation (PharmVar). The Pharmacogenomics Global Research Network (PGRN) catalyzes and leads research in precision medicine for the discovery and translation of genomic variation influencing therapeutic and adverse drug effects [S].

Conclusion

The availability of genetic testing technology and increasing knowledge about genetic variation-associated ADRs have elevated the role of pharmacogenomics in designing the drug regimen tailored to the individual patient ("individualized" or "personalized medicine"). An individual's genetic profile would, therefore, help to determine what medication would be most appropriate along with the most effective dosing regimen to increase the drug effectiveness and reduce the probability of ADRs. The cost of conducting genetic testing to identify polymorphisms that influence drug response has been declining, and reimbursement rates by health insurance companies are improving. Although pharmacogenetic testing is becoming more widespread in application, it is not expected that this approach will eliminate standard therapeutic monitoring or measurement of other phenotype variables, but rather supplement it. It is known that adverse reactions may be affected by other factors such as drug-drug interactions, drug-food, and drug-dietary supplement interactions, besides age, gender, ethnicity, and comorbidities. In the future, it is likely that there will be a blending of the different methods to provide the most appropriate therapeutic approach. Additional information on this topic can be found in these reviews (Osanlou et al., 2019 [R]; Cacabelos et al., 2019 [R]; Ray et al., 2020 [R]; Woo et al., 2020 [R]).

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IMMUNOLOGICAL/HYPERSENSITIVITY REACTIONS

Immunological reactions to drugs are diverse and varied. Nearly five decades ago, Karl Landsteiner's ground-breaking work "The Specificity of Serological Reactions" set the standard in experimental immunology. Several new discoveries in immunology in the 20th century, such as, 'CD' receptors (cluster of differentiation), recognition of 'self' vs 'non-self', a large family of cytokines and antigenic specificity became instrumental in describing immunological reactions. The most widely accepted classification divides immunological reactions (drug allergies or otherwise) into four pathophysiological types:

A. Type I hypersensitivity: (anaphylaxis, immediate type)

B. Type II hypersensitivity: (antibody-mediated cytotoxic reactions, cytotoxic type)

C. Type III hypersensitivity: (immune complex-mediated reactions, toxic-complex syndrome)

D. Type IV hypersensitivity: (cell-mediated immunity, delayed-type hypersensitivity)

Although this classification was proposed more than 30 years ago, it is still widely used today (Coombs & Gell, 1975 [R]; Schnyder & Pitcher, 2009 [R]; Boyman et al., 2014 [E]).

Type I reactions (IgE-mediated anaphylaxis; immediate hypersensitivity)

In type I reactions, hypersensitivity is induced when IgE antibodies are produced by B cells against an antigen. These IgE antibodies bind to mast cells and blood basophils, sensitizing them to subsequent exposures in which they release pharmacological mediators (histamine, 5-hydroxytryptamine, kinins, and arachidonic acid derivatives) which cause the allergic response. The development of such a reaction depends exclusively upon exposure to the same assaulting agent (antigen, allergen, or metabolite) for the second time and the severity depends on the level of exposure. The clinical effects (Schnyder & Pichler, 2009) [R] are due to smooth muscle contraction, vasodilatation, and increased capillary permeability. The symptoms include faintness, lightheadedness, pruritus, nausea, vomiting, abdominal pain, and a feeling of impending doom (angor animi). The signs include urticaria, conjunctivitis, rhinitis, laryngeal edema, bronchial asthma, pulmonary edema, angioedema, and anaphylactic shock. In addition, takotsubo cardiomyopathy can occur as well as Kounis syndrome (an acute coronary episode associated with an allergic reaction). Not all type I reactions are IgE-dependent; however, adverse reactions that are mediated by direct histamine release have conventionally been called anaphylactoid reactions but are better classified as non-IgE-mediated anaphylactic reactions. Cytokines, such as inteleukin (IL)-4, IL-5, IL-6 and IL-13, either mediate or influence this class of hypersensitivity reaction. Representative agents that are known to induce such reactions include gelatin, gentamicin, kanamycin, neomycin, penicillin, polymyxin B, streptomycin and thiomersal (Coombs & Gell, 1975 [R]; Schnyder & Pichler, 2009 [R]; Boyman et al., 2014 [E]). In this regard, it is not uncommon that drugs and their metabolites can form complexes with serum or tissue proteins and provoke a multitude of immunological reactions including type I. A classic example would be how metabolites of sulfamethoxazole mount such reactions.

Type II reactions (cytotoxic reactions)

Type II reactions involve circulating immunoglobulins G (IgG) or M (IgM) (or rarely IgA) binding with cell surface antigens (membrane constituent or protein) and interacting with an antigen formed by a hapten (drug or metabolite) and subsequently fixing complement. The complement is then activated leading to cytolysis. Type II reactions often involve antibody-mediated cytotoxicity directed to the membranes of erythrocytes, leukocytes, platelets, and probably hematopoietic precursor cells in the bone marrow. Drugs that are typically involved are methyldopa (hemolytic anemia), aminopyrine (leukopenia), and heparin (thrombocytopenia) with mostly hematological consequences, including thrombocytopenia, neutropenia, and hemolytic anemia (Coombs & Gell, 1975 [R]; Schnyder & Pitcher, 2009 [R]; Boyman et al., 2014 [E]).

Type III reactions (immune-complex reactions)

In type III reactions, the formation of an immune complex and its deposition on tissue surface serve as primary initiators. Occasionally, immune complexes bind to endothelial cells and lead to immune complex deposition with subsequent complement activation in the linings of blood vessels. Circumstances that govern immune complex formation or immune complex disease remain unclear to date, and it usually occurs without symptoms. The clinical symptoms of a type III reaction include serum sickness (β-lactams), drug-induced lupus erythematosus (quinidine), and vasculitis (minocycline). Type III reactions can result in acute interstitial nephritis or serum sickness (fever, arthritis, enlarged lymph nodes, urticaria, and maculopapular rashes) (Coombs & Gell, 1975 [R]; Schnyder & Pitcher, 2009 [R]; Boyman et al., 2014 [E]).

Type IV reactions (cell-mediated or delayed hypersensitivity reactions)

Type IV reactions are initiated when a hapten-protein antigenic complex sensitizes T lymphocytes (T cells). Upon re-exposure to the immunogen, the activity of the sensitized T cells usually results in severe inflammation in the affected areas. Type IV reactions are exemplified by contact dermatitis while pseudoallergic reactions may resemble allergic reactions clinically but are not immunologically mediated. Examples of type IV reactions include asthma and rashes caused by aspirin and maculopapular erythematous rashes due to ampicillin or amoxicillin in the absence of penicillin hypersensitivity. This reaction may also be caused by sulfonamides and sulfites, anticonvulsants (phenytoin, carbamazepine, and phenobarbital), non-steroidal anti-inflammatory drugs (NSAIDs—aspirin, naproxen, nabumetone, and ketoprofen), antiretroviral agents and cephalosporins (Coombs & Gell, 1975 [R]; Schnyder & Pitcher, 2009 [R]; Boyman et al., 2014 [E]; Brown, 2004 [R]).

Other types of reactions

Classification of drugs into particular types of hypersensitivity reactions may be challenging because the presentations of hypersensitivity can be quite different. For example, a study of pediatric hypersensitivity

reactions to NSAIDs showed combinations of symptoms of urticaria, angioedema, anaphylaxis, and respiratory involvement. In this case, the authors classified NSAID hypersensitivity into three categories: NSAID-induced urticarial/angioedema, NSAID-exacerbated cutaneous disease, NSAID-exacerbated respiratory disease, and single NSAID-induced urticarial/angioedema and/or anaphylaxis. At the molecular level, these differences can be partially explained by local or systemic effects induced by histamine and leukotriene metabolites (Johansson et al., 2001 [S]; Dispenza, 2009; Descotes & Choquet-Kastylevsky, 2001 [r]; Corominas et al., 2016 [E]; Velicković et al., 2015 [A]; Yip et al., 2017 [R]).

Several types of ADRs do not easily fit into the general classification scheme. These include most cutaneous hypersensitivity reactions (such as toxic epidermal necrolysis), 'immune-allergic' hepatitis and hypersensitivity pneumonitis. Another difficulty is that allergic drug reactions can occur via more than one mechanism; picryl chloride in mice induces both type I and type IV responses. Several articles are included in this review to serve as a pointer to this field (Arikoglu et al., 2016 [R]; Blanca-Lopez et al., 2019 [R]; Agúndez et al., 2019 [R]; Wheatley et al., 2015 [R]). Miscellaneous other types of drug reactions are listed throughout this manuscript in other sections (Leon et al., 2018 [R]; Ramsbottom et al., 2018 [R]; Just et al., 2020 [R]; Malki & Pearson, 2020 [R]).

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VACCINE-INDUCED ADVERSE EFFECTS

Although not the primary subject of this series, increased interest in adverse effects induced by vaccinations merits the inclusion of this section. Adverse effects can be induced by the active immunological agent of the vaccine, by adjuvants, and/or by other components such as preservatives. However, in nearly all cases, the concentration of preservatives is well below the threshold toxicological dose, suggesting the majority of adverse effects are due to the immunological agents of the vaccine and/or adjuvants.

The most common side effects of vaccines are associated with the immunological activation of the innate immune response by adjuvants. Indeed, these effects are necessary to induce inflammation that results in better vaccine take. Proposed mechanisms of action include the sustained release of antigen at the site of injection (the depot effect), upregulation of cytokines and chemokines, cellular recruitment to the site of injection, increased antigen uptake by antigen-presenting cells, activation of antigen-presenting cells followed by their migration to lymph nodes, and activation of inflammasomes (Awati et al., 2013 [R]; Toussirot & Bereau, 2015 [R]). Their mechanism of action is often complex and varied. However, the side effects are localized and often short in duration (Di Pasquale et al., 2015 [R]; D'Alo et al., 2017 [R]).

Adjuvants are mostly used for vaccines that are not self-replicating, including inactivated whole pathogen vaccines, subunit vaccines, and purified antigens. Since their discovery in the early part of the 20th century, adjuvants have been licensed components of more than 30 vaccines from different manufacturers (Di Pasquale et al., 2015 [R]; D'Alo, et al., 2017 [R]). As vaccine development has progressed away from live attenuated vaccines to recombinant vaccine methodologies, adjuvant usage has increased.

There are several safety concerns around adjuvanted vaccines (reviewed by D'Alo, et al., 2017) [R]. A local inflammatory response can include temporary pain and inflammation at the site of injection that lasts several days. However, studies so far have not demonstrated a statistically significant increase in immune-mediated diseases such as Guillain-Barré syndrome in vaccinated individuals. Similarly, macrophagic myofasciitis was hypothesized to be induced by aluminum in vaccines but was refuted upon further study by the WHO Global Advisory Board on Vaccine Safety. Long-term side effects from adjuvants have not been noted.

The vaccine adjuvants that include alum (aluminum salts), AS04 (combination of aluminum hydroxide and monophosphoryl lipid A), and AS03 (squalene, DL-alpha-tocopherol, and polysorbate80, used with influenza vaccines primarily) are used to induce inflammation in conjunction with vaccines. Alum, the most commonly used vaccine adjuvant in use for over 70 years, has been implicated in some type I hypersensitivity reactions. Monophosphoryl lipid A (MPA) has been implicated in one case of anaphylaxis to a pollen extract vaccine. AS03-adjuvanted H1N1pdm09 vaccine was associated with an enhanced rate of anaphylaxis (8 cases per million doses administered) (Sorriano et al., 2012) [R]. Overall, it is not clear that the rare hypersensitivity reactions can be decoupled from the efficacy of the adjuvant at inducing the proper immune response to accompanying antigens.

The hypersensitivity reactions to preservatives and stabilizers of vaccines were reviewed in a recent article. Gelatin, which is used to stabilize several vaccines, is known to cause both type I and type IV hypersensitivity reactions. Thimerosal has been reported to cause similar hypersensitivity reactions in patients who pre-developed hypersensitivity due to previous exposure via cosmetics such as contact lens solution or makeup (Mondino et al., 1982) [R], although most patients with pre-existing allergy tolerated thimerosal-containing vaccines (Leventhal et al., 2012) [R]. A single report exists for formaldehyde causing hypersensitivity reactions (Kuritzky & Pratt, 2015) [c].

Within the past decade, autoinflammatory/autoimmunity syndrome induced by adjuvants (ASIA) in susceptible patients has been proposed as a result of exposure to foreign materials such as vaccine adjuvants. ASIA syndrome is defined as an adjuvant exposure that induces autoimmunity, and several of the adverse effects described in the Table 4 may fall under the ASIA umbrella. Implanted foreign materials such as silicone breast implants and stents are thought to induce ASIA by acting as an adjuvant promoting autoimmunity. Vaccines may contain adjuvants capable of inducing similar responses, although the literature in this area is sparse. Genetic predisposition such as HLA-DRB1*01 or HLA-DRB4 may render patients more likely to have an ASIA syndrome following vaccination (Perricone et al., 2013) [R].

Adverse effects may also be induced by the primary antigens of the vaccine, the most common types of which are shown in Table 5 (D'Alo et al., 2017) [R]. This table reflects only those adverse effects confirmed through a robust meta-analysis. These adverse effects may be related to the antigenic features of the causative agent itself or may duplicate adverse effects caused by the infections themselves.

COVID-19 pandemic

The creation and use of vaccines for COVID-19 was novel in many regards. The extraordinary implementation of accelerated approvals for COVID-19 vaccines

TABLE 5 Adverse effects associated with particular vaccines

Adverse effect	Features	Candidate vaccines
Hypotonic hyporesponsive episode	Poor muscle tone, hyporesponsiveness, loss of skin color, within 48 h of vaccination, for a period of 6–30 min (Buettcher et al., 2007) [R]	Pertussis vaccine (Goodwin et al., 1999 [S]; Monteiro et al., 2010 [A]; Czajka et al., 2004 [M])
Multiple sclerosis	Chronic immune-mediated inflammation in the central nervous system (Langer-Gould et al., 2014) [c]	None—possible links have not been demonstrated in meta-analyses (Mailand & Frederickson, 2017 [R]; Farez & Correale, 2011 [R])
Apnea in pre-term newborns	Absence of breathing for longer than 20 s or shorter breathing pause accompanied by bradycardia, cyanosis, or pallor (Eichenwald et al., 2016) [S]. These are age- and complication-related effects	Diphtheria-tetanus-whole cell pertussis, *H. influenza* B, hepatitis B virus, inactivated poliovirus, meningococcal C conjugate (Sen et al., 2001 [c]; Cooper et al., 2008 [C]; Lee et al., 2006 [C]; Botham et al., 1997 [c]; Botham et al., 1994[c]; Sanchez et al., 1997 [c])
Vasculitides	Inflammation of blood vessels cause tissue or organ injury (Lee et al., 2006 [c]; Watts et al., 2011 [R])	Influenza vaccine and cutaneous vasculitides [(Hehn et al., 2003) [R] Influenza vaccine and giant cell arteritis (Sorriano et al., 2012) [c] Hepatitis B virus vaccine and polyarteritis nodosa (de Carvalho et al., 2008) [c]
Arthritis/ arthralgia	Articular pain. post-vaccination arthritis/arthralgia is self-limiting and moderate in intensity (Perricone et al., 2013 [R]; Sukumaran et al., 2015 [R]; Schattner et al., 2005 [R])	None—possible links have not been demonstrated (Toussirot & Bereau, 2015) [R]
Immune thrombocytopenic purpura	Platelet count below 100 000/μL and small areas of hemorrhage due to induction of antibodies against platelet antigens. Mild cases are typically not reported (Rejjal et al., 1993 [c]; Mantadakis et al., 2010 [R]; O'Leary et al., 2012 [R])	Hepatitis A and varicella zoster vaccines (Meyboom et al., 1995) [R] MMR (Mantadakis et al., 2010) [R]

(such as Emergency Use Authorization in the United States on a never-before-used scale), the use of more novel vaccine strategies (such as mRNA and adenovirus vector vaccines), and their very widespread administration has not only engendered concern for potential side effects not identified in safety trials, but also provided an opportunity to contrast side effects from the two different vaccine types. It is important to recognize that clinical trials have limited efficacy in the detection of rare side effects, such as those that are fewer than one case in 10 000; post-market surveillance is necessary to identify them. Several studies have investigated post-market adverse effects of COVID-19 vaccines since the last volume of this publication.

Interestingly, the rare adverse effects listed in Table 5 have not been associated with COVID-19 vaccination. A comprehensive review assessed side effects of provisionally approved vaccines in the United Kingdom: BNT162b2 and ChAdOx1 NCoV-19 (Menni et al., 2021) [C]. The most common side effects for both types of vaccine included pain, swelling, tenderness, itch, swollen armpit glands, redness, warmth, and bruising consistent with activation of the innate immune system and inflammation. Allergic reactions were rare for both types of vaccine, but included rash (0.2–0.4%), skin burning (0.7–1.7%), and red welts on face and lips (0.2%). Systemic side effects were more frequently observed after administration of a second dose for BNT162b2 or if the first dose was given following infection with COVID-19. Similar results were found in other studies; side effects were also more frequent in younger patients (Wi et al., 2021) [C].

In the United States, post-market surveillance of vaccines is conducted via the Vaccine Adverse Event Reporting System (VAERS), which gathers information from healthcare providers for the COVID-19 vaccine and for other vaccines. The United States requires reporting of serious adverse effects whether or not they are causally linked to the vaccine, including life-threatening adverse effects, persistent incapacity, or substantial disruption of normal life functions, congenital or birth defects, multisystem inflammatory syndrome, and any cases of COVID-19 post-vaccination that led to hospitalization or death. However, causal relationships between vaccination and the adverse effects are not determined and the system is limited in that reporting is incomplete and may contain errors. With these limitations in mind, the US Centers for Disease Control has reported VAERS data related to COVID-19 vaccines (CDC, 2021) [S]. Anaphylaxis was observed at a rate of 2–5 per million vaccinations in the United States. Some have suggested that polyethylene glycol used to create the lipid nanoparticles containing mRNA for RNA vaccines may be the cause, as approximately 72% of people have antibodies against polyethylene glycol (Yang et al., 2016) [E].

Forty-four confirmed reports of thrombosis with thrombocytopenia syndrome were identified in people

receiving the adenoviral vaccine marketed by Johnson and Johnson; two confirmed cases were identified following vaccination with mRNA (Moderna). One hundred and seventy-six reports of Guillain-Barré syndrome were identified in the VAERS in the United States following vaccination with the adenovirus-based vaccine. Interestingly the adenoviral-based vaccines do not contain adjuvants, suggesting a potential inherent risk in the adenoviral delivery system itself. Myocarditis and pericarditis after COVID-19 vaccination were reported 1377 times in individuals aged 30 years and younger, with most cases following mRNA vaccination (Pfizer or Moderna) (Nassar et al., 2021 [c]; Shay et al., 2021 [c]). Mechanisms for induction of myocarditis are unclear. The CDC is currently assessing the potential for a causal relationship between vaccination and these adverse effects.

Analysis of side effects of vaccines for COVID-19 must be assessed concomitantly against the effects of the infection itself. A recent review assessed outcomes of COVID-19 infection (Liu et al., 2021) [R]: immune-mediated injury contributes to COVID-19 injury, which is caused by perpetuated inflammatory responses that are similar to autoimmune diseases suggesting that SARS-CoV-2 might trigger autoimmune response through molecular mimicry. Evidence for this includes overactivation of innate immune cells, decreased T-cell numbers, increased cytokines, production of autoantibodies, and clinical conditions including immune-mediated hemolysis, decreased white blood cell counts, cytokine storm syndrome, macrophage activation syndrome, and procoagulant condition. Links between COVID-19 and various autoimmune diseases have been postulated, including multiple sclerosis (Palao et al., 2020 [R]; Domingues et al., 2020 [c]; Yachou et al., 2020 [R]), vasculitides (Mondal et al., 2020 [R]; Becker, 2020 [R]), type III hypersensitivity, and arthralgia (Roncati et al., 2020) [A]. Fortunately, vaccination has much fewer negative consequences than natural infection for COVID-19.

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ANALYSIS OF TOXICOLOGICAL REACTIONS

Potentiation reactions

This type of reaction occurs when either one non-toxic chemical interacts with another non-toxic chemical or one non-toxic chemical interacts with another toxic chemical at low doses (subtoxic, acutely toxic) resulting in a greater level of toxicity. An alternate interpretation could be when two drugs are taken together and one of them intensifies the action of the other. In such scenarios, if the final result is high toxicity, then the final outcome is called potentiation (increasing the toxic effect of 'Y' by 'X'). Results usually lead to unanticipated level of cell death in the form of apoptosis, necrosis, apocrosis (or necroptosis, aponecrosis), autophagy or mitophagy. Theoretically, it can be expressed as: $x + y = M$ $(1 + 0 = 4)$.

(i) When chronic or regular alcohol drinkers, consume therapeutic doses of acetaminophen, it can lead to alcohol-potentiated acetaminophen-induced hepatoxicity (cause: ethanol-induced massive CYP2E1 induction in the liver)

(ii) Administration of iron supplements in patients on doxorubicin therapy may cause potentiation of doxorubicin-induced cardiotoxicity (cause: hydroxyl radical formation and redox cycling of doxorubicin)

(iii) Phenergan®, an antihistamine, when given with a pain-killing narcotic such as Demerol® can intensify the narcotic effect; reducing the dose of the narcotic is advised

(iv) Ethanol potentiation of CCl_4-induced hepatotoxicity

(v) The combination of phenytoin and calcium-channel blockers should be used with caution

(vi) Several H1 antagonists (e.g., desloratadine, loratadine, and fexofenadine) and H2 antagonists (e.g., famotidine, cimetidine, ranitidine) markedly potentiate analgesia of opioids (e.g., morphine, fentanyl and nalbuphine)

(vii) Potentiation of warfarin by dietary supplements and foods such as garlic, ginger, ginkgo, and grapefruit

Synergistic effect

Synergism is somewhat similar to potentiation. When two drugs are taken together that are similar in action, such as barbiturates and alcohol, which are both depressants, an effect exaggerated out of proportion to that of each drug taken separately at the given dose may occur (mathematically: $1 + 1 = 4$). Normally, taken alone, neither substance would cause serious harm, but if taken together, the combination could cause coma or death. Another example is when smokers are exposed to asbestos, resulting in the development of lung cancer.

Additive effect

Additive effect is defined as a consequence that follows exposure to two or more agents which act jointly but do not interact; the total effect is the simple sum of the effects of separate exposure to the agents under the same conditions. This could be represented by $1 + 1 = 2$:

(i) A barbiturate and a tranquilizer given together before surgery to relax the patient

(ii) The toxic effect on bone marrow resulting after AZT + ganciclovir or AZT + clotrimazole administration

Antagonistic effects

Antagonistic effects occur when two drugs/chemicals are administered simultaneously or one closely followed by the other with the net effect or the final outcome of the

reaction being negligible or zero. This could be expressed by 1 + 1 = 0. An example might be the use of a tranquilizer to stop the action of LSD.

- **(i)** When ethanol is administered to a methanol-poisoned patient
- **(ii)** NSAIDs administered to diuretics (hydrochlorothiazide/furosemide) reduce effectiveness of diuretics
- **(iii)** Certain β-blockers (INDERAL®), taken to control high blood pressure and heart disease, counteract β-adrenergic stimulants such as albuterol®
- **(iv)** St. John's wort in combination with drugs such as digoxin, indinavir, nifedipine and alprazolam

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PHYTONUTRIENT–DRUG INTERACTIONS

Introduction

The use of phytonutrients, dietary supplements and herbal medicines has increased markedly in recent years,

with over 50% of adults in the United States regularly using these products. Due to the diverse nature of the bioactive and novel constituents in these products, a potential exists for unintended interactions with drugs. Interactions between constituents in these products and drugs may be considered similar to drug-drug interactions due in part to the involvement of the same or similar mechanisms.

It should be kept in mind that the potential for drug-phytonutrient interactions increases with the number of phytonutrients and drugs consumed, and the number of drugs used daily increases with age. The average elderly person routinely uses 9–13 different drugs daily, and approximately three-fourths of these individuals concurrently consume phytonutrients (Agbabiaka et al., 2018) [R]. Thus, the elderly are most susceptible to experience adverse events.

In general, herbal remedies are better tolerated and exhibit fewer adverse effects than synthetic medications (Izzo et al., 2016) [R]. However, serious adverse events have been described due to phytonutrient-drug interactions. Nutraceutical-drug interactions can generally be classified as being pharmacokinetic or pharmacodynamic in nature (Yeung et al., 2018 [R]; Briguglio et al., 2018 [R]). Pharmacokinetic interactions describe and denote how a phytonutrient/herbal product can influence the absorption, distribution, metabolism and excretion of a drug or group of drugs. Pharmacodynamic interactions describe how a phytonutrient/herbal product alters the actions of drugs when used concurrently and is the result of the pharmacokinetic interactions. Several examples involving potentiation and antagonism are noted in the section "Analysis of Toxicological Reactions."

Mechanisms

Research studies have focused on the mechanisms associated with phytonutrient-drug interactions. Most phytonutrients that interact with drugs have been shown to involve inhibition or induction/activation of CYP metabolizing isoenzymes, and/or the upregulation or downregulation of efflux transporter P-glycoprotein (P-gp) or influx organic anion transporting polypeptides (OATPs) (Agbabiaka et al., 2018; Izzo et al., 2016 [R]; Yeung et al., 2018 [R]; Briguglio et al., 2018 [R]; Posadki et al., 2012 [R]; Feltrin & Simoes, 2019 [R]). Initial mechanistic studies focused on the role of CYPs, while more recent studies have described the importance of intestinal and hepatocellular transporter proteins (Feltrin & Simoes, 2019 [R]; Murtaza et al., 2019 [R]). It should be noted that phytonutrient-drug interactions mechanistically may concomitantly involve both CYP isoenzymes as well as transporters. Furthermore, in recent years the pregnane X receptor (PXR) has been shown to be one of the most important transcriptional factors involved in the regulation of phase I and phase II drug-metabolizing enzymes and drug transporter proteins and polypeptides (Hogle et al., 2018) [R]. PXR has been implicated in multiple phytonutrient-drug interactions.

The most definitive information regarding mechanisms of action has been derived from studies with specific phytonutrients and phytochemicals. Unfortunately, most dietary supplements and herbal remedies contain multiple ingredients that may interact with drugs in an additive, synergistic or inhibitory manner. The amounts of specific phytochemicals in a preparation also play an important role in determining if a potential interaction will occur and be clinically relevant. Herbal extracts may not be comparable in composition due to many factors including methods of preparation, lack of standardization, plant part used, age at harvest and geographical location. Furthermore, high genetic inter-individual variability exists which can markedly influence whether an interaction occurs and to what extent (Liu et al., 2015 [R]; Werba et al., 2018 [R]).

Various studies have reviewed the literature regarding case study reports and pharmacokinetic studies involving phytonutrient-drug interactions (Izzo et al., 2016 [R]; Posadzki et al., 2015 [R]; Murtaza et al., 2017 [R]; Tsai et al., 2012 [R]; Ge et al., 2014 [R]; Asher et al., 2015 [R]). It should be noted that the results of in vitro mechanistic studies do not always agree with the results of in vivo clinical observations. Clinically observed effects may not be observed in spite of in vitro effects on metabolizing enzymes and/or transporters (Briguglio et al., 2018 [R]; Feltrin & Simoes, 2019 [R]; Murtaza et al., 2019 [R]).

Two of the most common phytonutrients associated with the report of serious drug interactions are St. John's wort (*Hypericum perforatum*), which contains hyperforin, and grapefruit (*Citrus paradise*), which contains furanocoumarins (Asher et al., 2015 [R]; Wilson & Mulik, 2018 [R]). Hyperforin acts as an inducer of cytochromes, most notably CYP3A4, and P-gp via activation of PXR (Feltrin & Simoes, 2019 [R]; Murtaza et al., 2019 [R]; Hogle et al., 2018 [R]). Furanocoumarins act as inhibitors of cytochromes and can also modulate P-gp (Feltrin & Simoes, 2019 [R]; Murtaza et al., 2019 [R]).

Various other phytonutrients for which less frequent interactions with drugs have been reported include ginkgo, ginger, ginseng, garlic, valerian, curcumin, cranberry, Echinacea, and Camellia (green tea) (Izzo et al., 2016 [R]; Briguglio et al., 2018 [R]; Posadki et al., 2012 [R]; Feltrin & Simoes, 2019 [R]; Liu et al., 2015 [R]; Tsai et al., 2012 [R]; Ge et al., 2014 [R]; Awortew et al., 2018 [R]; Awortwe et al., 2019 [R]; Asher et al., 2017 [R]; Wilson et al., 2016 [R]). The most common drugs that are involved in interactions with

phytonutrients due to their metabolism by CYPs and/or transport by P-gp and OATPs include anticoagulants, hormones such as insulin, and cardiovascular drugs (most notably digoxin) with fewer interactions being reported that involve antineoplastic and immunosuppressive agents, neuroactive drugs and anti-infective agents.

Various studies have examined and reported on the potential for hepatotoxicity due to phytonutrient-drug interactions (Wang et al., 2016 [R]; Parvez & Rishi, 2019 [R]). The most probable mechanism for the occurrence of hepatotoxicity involves the formation of reactive metabolites that react with cellular components like proteins, DNA, and membranes, subsequently resulting in the overproduction of reactive oxygen species, oxidative stress and cellular dysfunction. Fortunately, the most potentially hepatotoxic herbals such as *Evodia, Rheum, Senecio, Angelica* and *Psoralea* species are not commonly used.

Finally, adverse effects of drugs that are frequently overlooked involve the impact of drugs on micronutrients/nutrients and the production of nutritional deficiencies (Amadi & Mgbahurike, 2018 [R]; Gurley et al., 2018 [R]). In some cases, it is the drug that causes nutrition-related untoward effects. Several examples are provided. Long-term use of proton pump inhibitors can result in severe iron deficiency anemia (Dado et al., 2017) [R], hypomagnesemia (William & Danziger, 2016) [R], and hypocalcemia (Liamis et al., 2009) [R]. Other drugs that can cause hypocalcemia include aminoglycoside antibiotics, antiepileptics, bisphosphonates and cisplatin (Liamis et al., 2009) [R]. Furthermore, proton pump inhibitors, H2-receptor antagonists and metformin can cause vitamin B-2 deficiency, resulting in megaloblastic anemia and neurological disorders (Chapman et al., 2016 [R]; Miller, 2018 [R]). Other examples can be provided. It is important for the clinician to keep in mind that adverse effects beyond those of a toxicological nature can occur in response to various drugs.

Conclusions

A rapidly growing body of information is available regarding phytonutrient/nutrient-drug interactions. Based on the widespread use of phytonutrients, dietary supplements, and herbal medicines as well as the plethora of drugs used in modern medicine, the occurrence of interactions is not unexpected. However, the number of serious life-threatening interactions is relatively small. This is, in part, due to the growing understanding of most prominent mechanisms as well as likely involvement of clinically relevant drugs and nutraceuticals. Healthcare professionals must ascertain phytonutrient/dietary supplement/herbal medicine product use histories and be aware of the common pharmacokinetic and pharmacodynamic interactions that can affect therapeutic outcomes of drugs. In addition, the fact that drugs can interfere with and cause deficiencies of various essential nutrients should also be kept in mind.

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GRADES OF ADVERSE DRUG REACTIONS

Drugs and chemicals may exhibit ADRs (or adverse drug effects) that may include unwanted (side effects), uncomfortable (system dysfunction), or dangerous effects (toxic). ADRs are a form of manifestation of toxicity that may occur after overexposure or high-level exposure or, in some circumstances, ADRs may also occur after exposure to therapeutic doses but often an underlying cause (pre-existing condition) is present. In contrast, 'side effect' is an imprecise term often used to refer to a drug's unintended effects that occur within the therapeutic range (Merck Manual). Risk-benefit analysis provides a window into the decision-making process prior to prescribing a medication. Patient characteristics such as age, gender, ethnic background, pre-existing conditions, nutritional status, genetic pre-disposition or geographic factors, as well as drug factors (e.g., type of drug, administration route, treatment duration, dosage, and bioavailability), may profoundly influence ADR outcomes. Drug-induced adverse events can be categorized as unexpected, serious or life-threatening.

ADRs are graded according to intensity, using a scheme that was originally introduced by the US National Cancer Institute to describe the intensity of reactions to drugs used in cancer chemotherapy (NCI, 2006). This scheme is now widely used to grade the intensity of other types of adverse reactions, although it does not always apply so clearly to them. The scheme assigns grades as follows:

- Grade 1 ≡ mild
- Grade 2 ≡ moderate
- Grade 3 ≡ severe
- Grade 4 ≡ life-threatening or disabling
- Grade 5 ≡ death

Then, instead of providing general definitions of the terms "mild," "moderate," "severe," and "life-threatening or disabling," the system describes what they mean operationally in terms of each adverse reaction, in each case the intensity being described in narrative terms. For example, hemolysis is graded as follows:

- Grade 1: Laboratory evidence of hemolysis only (e.g. direct antiglobulin test; presence of schistocytes)

- Grade 2: Evidence of red cell destruction and $\geq 2\,g/dL$ decrease in hemoglobin, no transfusion
- Grade 3: Transfusion or medical intervention (e.g., steroids) indicated
- Grade 4: Catastrophic consequences (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)
- Grade 5: Death

Not all adverse reactions are assigned all grades. For example, serum sickness is classified as being of grade 3 or grade 5 only; i.e., it is always either severe or fatal.

The system is not as good at classifying subjective reactions. For example, fatigue is graded as follows:

- Grade 1: Mild fatigue over baseline
- Grade 2: Moderate or causing difficulty performing some activities of daily living
- Grade 3: Severe fatigue interfering with activities of daily living
- Grade 4: Disabling

Attribution categories can be defined as follows:

(i) Definite: The adverse event is clearly related to the investigational agent(s)
(ii) Probable: The adverse event is likely related to the investigational agent(s)
(iii) Possible: The adverse event may be related to the investigational agent(s)
(iv) Unlikely: The adverse event is doubtfully related to the investigational agent(s)
(v) Unrelated: The adverse event is clearly not related to the investigational agent(s)

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FDA PREGNANCY CATEGORIES/ CLASSIFICATION OF TERATOGENICITY

The FDA has established five categories to indicate the potential of a drug to cause birth defects if used during pregnancy. The categories are determined by the reliability of documentation and the risk-to-benefit ratio. They do not take into account any risks from pharmaceutical agents or their metabolites in breast milk. The pregnancy categories are:

Category A

Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy and there is no evidence of risk in later trimesters.

Example drugs or substances: levothyroxine, folic acid, magnesium sulfate, liothyronine.

Category B

Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

Example drugs: metformin, hydrochlorothiazide, cyclobenzaprine, amoxicillin, pantoprazole.

Category C

Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Example drugs: tramadol, gabapentin, amlodipine, trazodone, prednisone.

Category D

There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Example drugs: lisinopril, alprazolam, losartan, clonazepam, lorazepam.

Category X

Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

Example drugs: atorvastatin, simvastatin, warfarin, methotrexate, finasteride.

Category N

FDA has not classified the drug.

Example drugs: aspirin, oxycodone, hydroxyzine, acetaminophen, diazepam.

Examples of drugs approved since June 30, 2015, showing various new pregnancy and lactation subsections in their labels:

- Addyi (flibanserin)—indicated for generalized hypoactive sexual desire disorder (HSDD) in premenopausal women
- Descovy (emtricitabine and tenofovir alafenamide fumarate)—indicated for HIV-1 infection
- Entresto (sacubitril and valsartan)—indicated for heart failure
- Harvoni (ledipasvir and sofosbuvir)—indicated for chronic hepatitis C virus (HCV) infection
- Praluent (alirocumab)—indicated for heterozygous familial hypercholesterolemia or patients with atherosclerotic heart disease who require additional lowering of LDL-cholesterol
- Vosevi (sofosbuvir, velpatasvir and voxilaprevir)—indicated for chronic HCV infection
- Nerlynx (neratinib)—indicated for early stage HER2-overexpressed breast cancer, following adjuvant trastuzumab-based therapy
- Rituxan Hycela (rituximab and hyaluronidase human)—indicated for follicular lymphoma, diffuse large B-cell lymphoma (DLBCL), and chronic lymphocytic leukemia (CLL)
- Mydayis (amphetamine mixed salts)—indicated for attention deficit hyperactivity disorder (ADHD)
- Kevzara (sarilumab)—indicated for rheumatoid arthritis
- Radicava (edaravone)—indicated for amyotrophic lateral sclerosis (AML)
- Imfinzi (durvalumab)—indicated for urothelial carcinoma

On December 3, 2014, the FDA issued a final rule for the labeling of drugs during pregnancy and lactation, titled "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling"; this rule is also informally known as the "Pregnancy and Lactation Labeling Rule (PLLR)."

The rule changes the content and format for drug labeling information and the new labeling requirements include:

- *Elimination of the pregnancy letter categories (A, B, C, D, and X)*
  - *Text provides specific information in each section to assist with making benefit-risk decisions when medication is needed*
- *Labeling sections are changed*
  - *Old: Pregnancy, Labor and Delivery, Nursing Mothers*
  - *New: Pregnancy (includes L&D), Lactation (includes nursing mothers), Females and Males of Reproductive Potential*
- *Requirement that the label is updated as new information becomes available*

The PLLR changes are effective as of June 30, 2015. Prescription medications and biologics approved after this date will use the new format while older material will have a 3-year phase-in for the new labeling. These changes are not applicable to over-the-counter (OTC) products.

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Clinicians are suggested to be aware of the information contained in the following literature originating from regulatory agencies:

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CONCLUSION

ADEs, including ADRs, side effects, drug-induced diseases, toxicity, pharmacogenetic, immunologic, drug-drug, drug-gene, and drug-phytonutrient interactions represent a significant burden to patients, healthcare systems, and society. It is the goal of SEDA to summarize and evaluate important new evidence-based information to guide clinicians in the monitoring, assessment and prevention of ADEs in their patients. This work not only provides a summary of this essential new data but also suggests how it may be interpreted and possible implications for practice.