

ADVERSE DRUG REACTIONS



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LEARNING OBJECTIVES

1. Distinguish adverse drug reactions (ADRs) from adverse drug events.
2. Devise methods for ADR detection, and classify an ADR when it presents.
3. Discover various worldwide ADR reporting methods and learn how to report ADRs in the United States.
4. Detect populations most at risk of, and apply pharmacovigilance principles to prevent ADRs.

INTRODUCTION

An adverse drug reaction (ADR) is an unwanted, undesirable effect of a medication that occurs during usual clinical use. Adverse drug reactions occur almost daily in health care institutions and can adversely affect a patient's quality of life, often causing considerable morbidity and mortality. Much attention has been given to identifying the patient populations most at risk, the drugs most commonly responsible, and the potential causes of ADRs. An increase in the number of drugs on the market, an aging

population, and an upward trend in polypharmacy are contributing factors to the prevalence of ADRs worldwide.

Adverse drug reactions may cause patients to lose confidence in or have negative emotions toward their physicians and seek self-treatment options, which may consequently precipitate additional ADRs. Around 5% of all hospital admissions are the result of an ADR, and around 10%–20% of inpatients will have at least one ADR during their hospital stay (Kongkaew 2008; Lundkvist 2004; Pirmohamed 1998). The actual incidence of ADRs may be even greater because some ADRs mimic natural disease states and may thus go undetected and/or unreported. Although some ADRs present as minor symptoms, others are serious and cause death in as many as 0.1%–0.3% of hospitalized patients (Lazarou 1998; Pirmohamed 1998). Adverse drug reactions should be quickly identified and managed to limit their detrimental effects on the patient.

The cost of managing ADRs can be high, whether they occur in the inpatient or the outpatient setting. Because the clinical diagnosis of an ADR is not always obvious, practitioners often order additional laboratory tests or procedures to investigate the cause of a patient's

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- Medication errors
- National Patient Safety Goals
- Pharmacologic treatment of allergic reactions
- General medication precautions and monitoring for high-risk medications
- Medication reconciliation process

ADDITIONAL READINGS

The following free resources are available for readers wishing additional background information on this topic.

- U.S. Food and Drug Administration (FDA). [FDA Adverse Event Reporting System \(FAERS\)](#) [homepage on the Internet].
- American Society of Health-System Pharmacists. [ASHP guidelines on adverse drug reaction monitoring and reporting](#). *Am J Health Syst Pharm* 1995;52:417-9.

ABBREVIATIONS IN THIS CHAPTER

ADE	Adverse drug event
ADR	Adverse drug reaction
BOOST	Better Outcomes for Older Adults Through Safe Transitions
FAERS	FDA Adverse Event Reporting System
ISMP	Institute for Safe Medication Practices
NCC MERP	National Coordinating Council for Medication Error Reporting and Prevention
TJC	The Joint Commission

symptoms. Practitioners may also prescribe pharmacotherapy for conditions caused by an unrecognized ADR, further increasing costs and the risk of additional ADRs. If the ADR occurs while the patient is hospitalized, length of stay can be prolonged and overall hospitalization costs may be increased (Gautier 2003; Classen 1997). Additional indirect costs incurred by ADRs include anxiety or depression and missed days of work for the patient and/or caregiver.

Pharmacovigilance involves the study of drug-related injuries and making warning or withdrawal recommendations for pharmaceutical agents; it encompasses the detection, assessment, understanding, and prevention of ADRs. Pharmacists play a vital role in every step of the pharmacovigilance process, which can prevent patients from undergoing unnecessary procedures or taking unwarranted drugs. In addition to preserving the safety and quality of life for the patient, pharmacovigilance can represent a cost savings to the patient and the health care institution. By reporting known or suspected ADRs, pharmacists, other health care practitioners, and patients can assist in identifying patterns and trends, which may lead to increased regulatory scrutiny or even the withdrawal of drugs that do not have a favorable risk-benefit ratio.

This chapter discusses methods of ADR detection and classification and the associated treatment strategies. Populations most at risk are identified, together with various worldwide ADR reporting methods. Pharmacovigilance strategies are described to assist practitioners in preventing ADRs, associated hospital admissions, and readmissions in their patient populations.

DETECTION OF ADRs

Defining ADRs

The definition of an ADR is often confused with that of an adverse drug event (ADE). The World Health Organization (WHO) defines an ADE as “any untoward medical occurrence that may present during treatment

with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment” (WHO 2005). The WHO defines an ADR as “a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function.” An ADR is a type of ADE whose cause can be directly attributed to a drug and its physiologic properties. A main distinction between ADRs and ADEs is that ADRs occur despite appropriate prescribing and dosing, whereas ADEs may also be associated with inappropriate use of the drug or other confounders that occur during drug therapy but are not necessarily caused by the pharmacology of the drug itself. A causal relationship is suspected for an ADR but is not required for an ADE. Adverse drug events may also be caused by medication errors, which the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) defines as “any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.” Figure 1-1 shows the relationship between ADRs, ADEs, and medication errors.

Published studies of ADRs, ADEs, and medication errors often use these terms interchangeably, leading to inconsistency in the reported prevalence of each. Definitions are often subject to the individual researcher’s preference, making the interpretation of results and reproducibility difficult (Lisby 2010). Standardizing and using terminology such as that defined by the [Medical Dictionary for Regulatory Activities](#) can improve the quality and consistency of research in this realm. Other publication authors and governing bodies that have proposed alternative

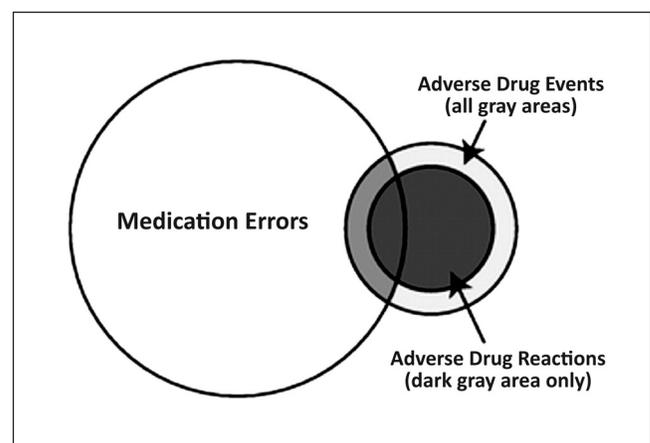


Figure 1-1. Relationship of key terms in medication administration.

Reprinted with permission from Nebeker JR, Barach P, Samore MH. Clarifying adverse drug events: a clinician’s guide to terminology, documentation, and reporting. *Ann Intern Med* 2004;140:795-801.

definitions for ADRs include the American Society of Health-System Pharmacists (ASHP), which defines a significant ADR as “any unexpected, unintended, undesired, or excessive response to a drug that requires discontinuing the drug (therapeutic or diagnostic), requires changing the drug therapy, requires modifying the dose (except for minor dosage adjustments), necessitates admission to a hospital, prolongs stay in a health care facility, necessitates supportive treatment, significantly complicates diagnosis, negatively affects prognosis, or results in temporary or permanent harm, disability, or death” (ASHP 1995). Some investigators define an ADR as “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 2000). The common theme in all definitions is that the reaction is undesired and unintended; thus, identifying, appropriately managing, and preventing ADRs is an understated, often overlooked goal of drug therapy. Box 1-1 lists several ADR terms and definitions that have been proposed by governing bodies and authors.

How an incident is defined can help determine its management. For example, a patient taking warfarin for a pulmonary embolism (goal INR 2–3) presents to the emergency department with a major bleeding episode. If the patient’s INR is within therapeutic goal range and no other contributing factors to bleeding are identified, the bleed is defined as an ADR, and the warfarin

Box 1-1. Adverse Drug Reaction Terms and Definitions

Adverse Drug Reaction (ADR)

- A response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease or for modification of physiological function (WHO)^a
- An appreciably harmful or unpleasant reaction, caused by 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)^b
- Any unexpected, unintended, undesired, or excessive response to a drug that requires discontinuing the drug (therapeutic or diagnostic), requires changing the drug therapy, requires modifying the dose (except for minor dosage adjustments), necessitates admission to a hospital, prolongs stay in a health care facility, necessitates supportive treatment, significantly complicates diagnosis, negatively affects prognosis, or results in temporary or permanent harm, disability, or death (ASHP)^c
- Harm directly caused by a drug at normal doses (Edwards)^b

Adverse Drug Event (ADE)

- Any untoward occurrence that may present during treatment with a pharmaceutical product but that does not necessarily have a causal relation to the treatment (WHO)^a
- Injuries caused by medical interventions related to a drug.

Adverse drug events may result from medication errors or from ADRs in which there was no error (Bates)^d

Unexpected Adverse Reaction

- An adverse reaction, the nature or severity of which is not consistent with domestic labeling or market authorization, or expected from characteristics of the drug (Cobert)^e

Serious Adverse Effect

- Any untoward medical occurrence that at any dose results in death, requires hospital admission or prolongation of existing hospital stay, results in persistent or significant disability/incapacity, or is life threatening (Edwards)^b

Signal

- Reported information on a possible causal relation between an adverse event and a drug, the relation being previously unknown or incompletely documented (Edwards)^b

Medication Error

- Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer (NCC MERP)^f
- Errors in the process of ordering or delivering a medication, regardless of whether an injury occurred or the potential for injury was present (Bates)^d
- Inappropriate use of a drug that may or may not result in harm (Nebeker)^g

^aWHO: International Drug Monitoring: The Role of the Hospital. Technical Report Series No. 425. Geneva: WHO, 1969.

^bEdwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet* 2000;356:1255-9.

^cAmerican Society of Health-System Pharmacists. ASHP guidelines on adverse drug reaction monitoring and reporting. *Am J Health Syst Pharm* 1995;52:417-9.

^dBates DW, Boyle DL, Vander Vliet MB, et al. Relationship between medication errors and adverse drug events. *J Gen Intern Med* 1995;10:199-205.

^eCobert B. The theory and definitions of drug safety (Pharmacovigilance). In: Cobert’s Manual of Drug Safety and Pharmacovigilance, 2nd ed. Sudbury, MA: Jones & Bartlett, 2012:4-5.

^fNCC MERP. About Medication Errors [homepage on the Internet]. Available at www.nccmerp.org/about-medication-errors. Accessed March 7, 2015.

^gNebeker JR, Barach P, Samore MH. Clarifying adverse drug events: a clinician’s guide to terminology, documentation, and reporting. *Ann Intern Med* 2004;140:795-801.

therapy is discontinued. Warfarin cannot be reinitiated and rechallenged in this patient. If, however, the patient has a supratherapeutic INR of 6 because of a drug-drug interaction with a newly prescribed antibiotic, the bleed is defined as an ADE, and warfarin therapy is temporarily interrupted until the INR decreases and the bleeding resolves. The physician may then choose to reinitiate the warfarin therapy at a lower dose to achieve a therapeutic INR.

After a drug-related incident is defined as an ADR, the next step is to classify the type of ADR that has occurred. This will further assist health care practitioners in developing a plan to treat or manage the ADR and its symptoms.

Classification of ADRs

Adverse drug reactions were originally classified into two subtypes. Type A ADRs are dose-dependent and predictable; they are augmentations of known pharmacologic effects of the drug, such as orthostatic hypotension with antihypertensive medications. Type B ADRs are uncommon and unpredictable, depending on the known pharmacology of the drug; they are independent of dose and affect a small population, suggesting that individual patient host factors are important (Pirmohamed 2003; Edwards 2000). Hypersensitivity (allergic) reactions to drugs are examples of type B ADRs. Type A reactions were later called *augmented*, and type B reactions, *bizarre*. Two further types of reactions were eventually added: *chronic* reactions, which relates to both dose and time (type C), and *delayed* reactions (type D). *Withdrawal* later became the fifth category (type E), and most recently, *unexpected failure of therapy* became the sixth (type F) (Rohilla 2013; Edwards 2000). Table 1-1 lists features and management options for each ADR classification.

About 80% of ADRs in the hospital setting or causing admission to a hospital are type A (Pirmohamed 1998). These ADRs are potentially avoidable and often predictable. The drug classes most commonly responsible for ADRs in adults are adrenal corticosteroids, antibiotics, anticoagulants, antineoplastic and immunosuppressive drugs, cardiovascular drugs, nonsteroidal anti-inflammatory drugs, and opiates. For children, the most prevalent drug classes for ADRs are anti-infective drugs, respiratory drugs, and vaccines (Kongkaew 2008; Bond 2006).

Identification of ADRs

In both the inpatient and outpatient setting, a patient's new or worsening symptom may be the first sign of an ADR. In a community pharmacy, patients often seek advice from the pharmacist to treat various symptoms at home. This can be an opportunity for the pharmacist to inquire about the patient's symptoms to determine whether they might have been caused by an ADR. For example, if a patient asks the pharmacist for a recommendation to treat diarrhea, the pharmacist could inquire about other medications the patient is taking to determine whether diarrhea is a known ADR associated with the drug therapy, such as with

antibiotics. An over-the-counter (OTC) medication may not be needed, and the diarrhea may resolve on completion of the antibiotic therapy. In the inpatient setting, patients may tell their nurse or physician about the new symptom they are having, which may result in a telephone call to the pharmacist. Asking detailed questions about the patient's symptoms, rather than immediately providing a treatment recommendation, could uncover an ADR and prevent unnecessary drug therapy or further ADR symptoms.

Noticing that an atypical laboratory or diagnostic procedure has been ordered may indicate that an ADR has occurred. Common laboratory tests can also assist in identifying an ADR. A new order for a serum drug level may alert the practitioner to investigate whether an ADR caused by drug toxicity or treatment failure is occurring. Laboratory monitoring can help determine improvement or decline after a change in therapy. Laboratory values can also establish baseline organ function and help confirm or rule out alternative diagnoses. When initiating a new drug therapy, it may be helpful to obtain baseline laboratory values in anticipation of an ADR. For example, baseline liver function tests are obtained before initiating therapy with a statin in anticipation that the therapy may cause an increase in these laboratory values, potentially warranting discontinuation. Abnormalities in laboratory results do not mean that an ADR has definitely occurred, but that the practitioner should take a close look at the patient to assess whether an ADR is the potential culprit.

Some less obvious methods of detection stem from medication order screening in both inpatient and outpatient practice. Often, an ADR can be detected by noticing an abrupt, unexpected discontinuation of a drug or a substantial dosage increase or reduction. Orders for new medications may occasionally alert the pharmacist that an ADR has occurred. Medication orders such as naloxone, flumazenil, diphenhydramine, antiemetics, vitamin K, sodium polystyrene sulfonate, corticosteroids, or antidiarrheals may be a sign that a practitioner is treating an ADR (Rozich 2003).

Another way to identify an ADR is by reading the daily multidisciplinary notes in a patient's chart. Notes pertaining to oversedation, lethargy, and falls may be the sign of an ADR caused by an analgesic, a sedative, or a muscle relaxant. Reports of a rash in a patient's progress notes may be indicative of an ADR and should be investigated for a drug-related cause, such as an allergic reaction or yeast infection caused by the overuse of antibiotics.

Some electronic medical record systems can compile reports for predetermined threshold changes in laboratory values. For example, if the health system determines that an increase or decrease in serum potassium values of 1 mEq/L in a 24-hour period is significant, a patient whose serum potassium falls from 4 mEq/L to 3 mEq/L will be included in the report. The pharmacist or other health care provider can then examine the medication profile to determine whether the drop in the potassium occurred because of an ADR (e.g., a diuretic in this case).

Often, when an ADR occurs, a patient may require transfer to a higher level of care, such as from a general surgery ward to an intensive care unit. If an unexpected change in a patient's clinical condition warrants transfer to a higher level of care, ADRs should always be included in the differential. Pharmacists should assess each medication that has been administered to the patient to identify whether an ADR could have occurred.

Although several triggers aid in identifying potential ADRs, determining whether a patient's symptoms or abnormal laboratory results are caused by a medication or by another underlying condition can be difficult. A causality assessment, performed for each potential ADR, can help determine future drug therapy options.

CAUSALITY ASSESSMENT OF SUSPECTED ADRs

Although several methods for assigning ADR causality probability have been developed, no system has been able to produce a definitive estimation of relationship likelihood. Regardless, causality assessment is a routine practice in pharmacovigilance. Although causality assessment cannot change possibility into certainty, it can provide a degree of likelihood to the relationship between a drug and an adverse reaction. One scheme used in the United States is the World Health Organization - Uppsala Monitoring Centre (WHO-UMC) Causality Categories scheme, described in Box 1-2. This scheme classifies the

Table 1-1. Classification of Adverse Drug Reactions

Type of Reaction (Mnemonic)	Features	Examples	Management
A: Dose related (Augmented)	Common Related to the pharmacologic action of the drug – exaggerated pharmacologic response Predictable Low mortality	Dry mouth with tricyclic antidepressants, respiratory depression with opioids, bleeding with warfarin, serotonin syndrome with SSRIs, digoxin toxicity	Reduce dose or withhold drug Consider effects of concomitant therapy
B: Non-dose related (Bizarre)	Uncommon Not related to the pharmacologic action of the drug Unpredictable High mortality	Immunologic reactions: anaphylaxis to penicillin Idiosyncratic reactions: malignant hyperthermia with general anesthetics	Withhold and avoid in future
C: Dose related and time related (Chronic)	Uncommon Related to the cumulative dose	Hypothalamic-pituitary-adrenal axis suppression by corticosteroids, osteonecrosis of the jaw with bisphosphonates	Reduce dose or withhold; withdrawal may have to be prolonged
D: Time related (Delayed)	Uncommon Usually dose related Occurs or becomes apparent sometime after use of the drug	Carcinogenesis Tardive dyskinesia Teratogenesis Leucopenia with lomustine	Often intractable
E: Withdrawal (End of use)	Uncommon Occurs soon after withdrawal of the drug	Withdrawal syndrome with opiates or benzodiazepines (e.g., insomnia, anxiety)	Reintroduce drug and withdraw slowly
F: Unexpected failure of therapy (Failure)	Common Dose related Often caused by drug interactions	Inadequate dosage of an oral contraceptive when used with an enzyme inducer Resistance to antimicrobial agents	Increase dosage Consider effects of concomitant therapy

SSRI = selective serotonin reuptake inhibitor.

Adapted with permission from Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet* 2000;356:1255-9.

Box 1-2. WHO-UMC Causality Categories

Certain

- Clinical event or laboratory test abnormality that occurs in a plausible time relation to drug administration
- Cannot be explained by underlying concurrent disease or other drugs or chemicals
- Response to withdrawal of the drug is clinically plausible
- The event is definitive pharmacologically or phenomenologically (an objective, specific medical disorder or a recognized pharmacologic phenomenon)
- If necessary, a rechallenge is satisfactory

Probable/Likely

- Clinical event or laboratory test abnormality that occurs in a reasonable time relation to drug administration
- Unlikely to be attributed to underlying concurrent disease or other drugs or chemicals
- Response to withdrawal of the drug is clinically reasonable
- Rechallenge is not required

Possible

- Clinical event or laboratory test abnormality that occurs with reasonable time in relation to drug administration
- Could also be explained by underlying concurrent disease or other drugs or chemicals
- Information on drug withdrawal may be lacking or unclear

Unlikely

- Clinical event or laboratory test abnormality with a time to drug administration that makes a relationship improbable, but not impossible
- Underlying concurrent disease or other drugs or chemicals provide plausible explanations

Conditional/Unclassified

- Clinical event or laboratory test abnormality
- Reported as an adverse reaction
- More data needed for proper assessment or additional data being examined

Unassessable/Unclassifiable

- Report suggesting an adverse reaction
- Cannot be judged because of insufficient or contradictory information
- Data cannot be supplemented or verified

Adapted with permission from: World Health Organization (WHO). The Use of the WHO-UMC System for Standardised Case Causality Assessment. Geneva: WHO, 2014.

ADR into one of six category terms: certain, probable/likely, possible, unlikely, conditional/unclassified, and unassessable/unclassifiable (WHO 2014). Few ADRs are certain or unassessable/unclassifiable because most fall into one of the categories in between (Nebeker 2004; Edwards 2000).

Determining the cause of a suspected ADR is a complex process. Because many patients take more than one drug, it can often be difficult to distinguish which agent

caused the ADR. Furthermore, the suspected ADR may in fact be a manifestation of the patient's underlying disease state. An important step in identifying an ADR and determining causality is to obtain an accurate patient drug list. Not only is this an opportunity to screen for ADRs that could have led to the hospitalization, but maintaining an updated, accurate medication history for each patient can also help prevent future ADRs. If the inpatient prescriber is unaware of the patient's home drug regimen on admission, duplicate therapy may be prescribed. If admission and discharge reconciliation are not done, discharged patients may resume taking their home medication in addition to the newly prescribed therapy; this could result in an ADR might result or lead to rehospitalization.

Assessing the timing between administration of the drug and development of the reaction is important. Does the reaction worsen with repeated or increased dosing? Does the reaction decrease in intensity when the dose of the drug is reduced or discontinued? Has the patient previously been exposed to the drug, in cases of allergic reaction? Is the reaction known to occur with long-term use of the medication? Did symptoms appear or worsen when a drug was discontinued? Answering such questions can help the pharmacist determine causality.

The next step is to identify patterns in ADR symptoms. Do the symptoms fit the normal pharmacology or allergy profile of the drug? Is this a known adverse reaction associated with this drug, or is it unique? Have case reports been published on this reaction? Particularly with new medications, much of the information about associated adverse reactions is unknown. By the time a drug has been approved for marketing in the United States, only about 1500 people have been exposed to the drug (Pirmohamed 2003). Postmarketing surveillance and case reports are important tools that should be used when assessing ADRs for newly marketed drugs. Reporting a suspected ADR to the drug manufacturer and/or the U.S. Food and Drug Administration (FDA) will help identify a causal relationship between the drug and the adverse reaction, if one exists. This, in turn, will provide valuable information or warnings to other health care practitioners and potentially prevent further ADRs in their patients.

Several algorithms and probability scales have been developed to assist with causality determination. Among those published are the Jones algorithm, the Yale algorithm, the Karch algorithm, the Begaud algorithm, and a quantitative approach algorithm (Srinivasan 2011). Two others are more commonly used because of their simplicity and time efficiency; one is the Naranjo ADR Probability Scale shown in Table 1-2 (Naranjo 1981). By answering 10 questions about the ADR and assigning a numeric score to each answer, the ADR probability classification can be determined. Another method commonly used to assist with causality determination is the Liverpool ADR causality assessment tool shown in Figure

1-2 (Gallagher 2011). This flowchart presents a series of questions with yes or no answers. These answers lead the user through the flowchart to eventually arrive at a causality classification of definite, probable, possible, or unlikely. Again, no scale has been proved to definitively determine the causality of an ADR, but tools such as the Naranjo scale and Liverpool ADR causality assessment flowchart can help guide thought processes regarding treatment or therapy options.

POPULATIONS AT GREATEST RISK

Pediatrics

Adverse drug reactions are common in the pediatric population. Developmental changes affect the pharmacodynamics and pharmacokinetics of many of the drugs used in neonates, infants, and children. For example, gastric emptying is delayed in neonates and infants, resulting in longer absorption time and potentially increasing the risk of an ADR. Volume of distribution also differs, compared with adults, as does protein-binding capacity, phase I and II metabolic pathways, and glomerular filtrate rate. Therefore, extrapolation of pediatric dosages from adult dosages should be avoided (Fabiano 2012).

Often, newborns, infants, and children are prescribed medications in an off-label fashion, which can increase the risk of ADRs (Neubert 2004; Turner 1999; Gill 1995). Drug evaluation studies are seldom done in this patient population because of practical difficulties and ethical concerns. In addition, the pediatric population often represents a small percentage of the pharmaceutical market, so clinical trials do not yield large profit expectations for drug companies (Fabiano 2012). Consequently, many medicinal products that have no pediatric marketing authorization are prescribed outside the licensed indications for age, dosage, route of administration, and therapeutic indication. This leads to a potentially dangerous scenario for an ADR to occur. The shortage of clinical trials in the pediatric population means that fewer pediatric patients are exposed to the drug before it is marketed in the United States, and notifications of pediatric ADRs are heavily dependent on voluntary reporting by health care providers to the FDA or by published case reports.

In the UK, the drug classes most often linked to ADR-related hospital admissions in neonates, infants, and children are cytotoxic drugs, corticosteroids, vaccines, immunosuppressants, and nonsteroidal anti-inflammatory drugs (Gallagher 2012). Although information is limited

Table 1-2. Naranjo ADR Probability Scale

Question	Yes	No	Do Not Know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4. Did the adverse event appear when the drug was readministered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that, on their own, could have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
Total Score	ADR Probability Classification			
9	Highly Probable			
5-8	Probable			
1-4	Possible			
0	Doubtful			

Adapted with permission from: Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30:239-45.

about pediatric ADR prevalence by drug class in the United States, drugs from these classes are commonly prescribed and would likely also result in ADR-related hospital admissions. The most common ADRs are dermatologic, followed by psychiatric, central nervous system (CNS), and gastrointestinal disorders. Adverse drug reactions can also be observed in neonates exposed to medications in utero.

Withdrawal syndromes are often reported in neonates whose mothers chronically used medications such as opioids or benzodiazepines.

One example of a pediatric ADR is anticonvulsant hypersensitivity syndrome (AHS), which is associated with use of the aromatic anticonvulsants phenytoin, carbamazepine, and phenobarbital. This delayed ADR presents

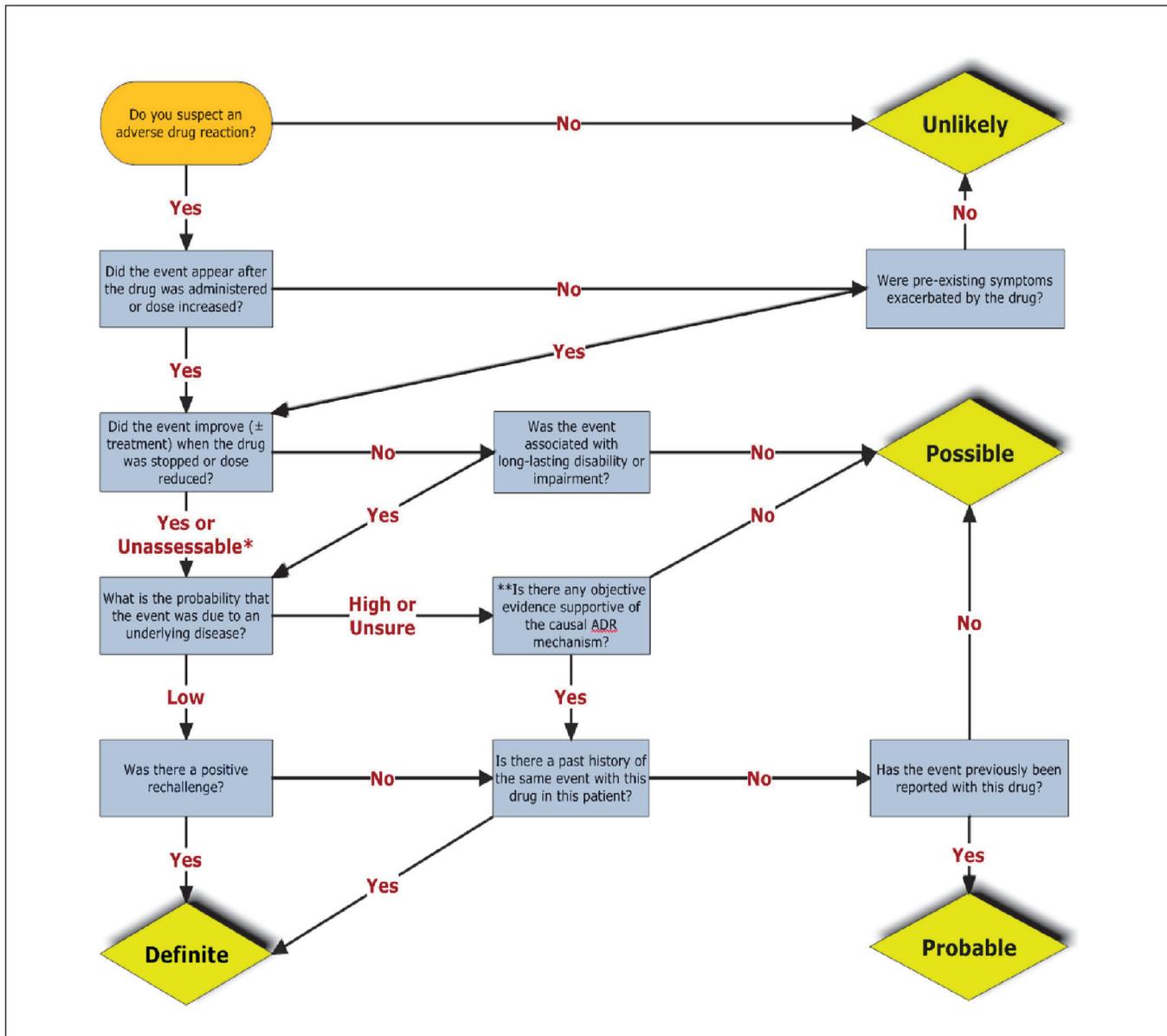


Figure 1-2. The Liverpool adverse drug reaction causality tool.

^aUnassessable refers to situations where the medicine is administered on one occasion (e.g., vaccine), the patient receives intermittent therapy (e.g., chemotherapy), or is on medication that cannot be stopped (e.g., immunosuppressants).

^bExamples of objective evidence: positive laboratory investigations of the causal adverse drug reaction mechanism (not those merely confirming the adverse reaction), supra-therapeutic drug levels, good evidence of dose-dependent relationship with toxicity in the patient.

Reprinted with permission from: Gallagher RM, Kirkham JJ, Mason JR, et al. Development and inter-rater reliability of the Liverpool adverse drug reaction causality assessment tool. PLoS One 2011;6:e28096.

as a triad of symptoms, including rash, fever, and evidence of systemic organ involvement, often affecting the liver, kidneys, CNS, or lungs (Knowles 1999). Management includes discontinuation of the drug and administration of systemic corticosteroids. Cross-sensitivity is high among the aromatic anticonvulsant drugs, and patients with a history of AHS should avoid using other aromatic anticonvulsant drugs. Computerized system warnings (e.g., updating the patient's allergy profile with a detailed description of the ADR) could alert prescribers to this severe reaction and avoid its reoccurrence. The patient's family should also be educated about the cause of the reaction and ways to prevent a similar ADR. Neonates, infants, and small children are unable to adequately communicate symptoms, making it difficult to diagnose an ADR. Underreporting of ADRs in pediatrics is of great concern because case reports may be the best aid in detection in this patient population. Pediatric ADRs are often undiagnosed or underdiagnosed because of the lack of published data. Educating health care providers to report known or suspected ADRs in this patient population is crucial to preventing future ADRs worldwide.

Geriatrics

The WHO defines *elderly* as individuals 60 years and older. The percentage of people in this age category continues to rise and the total is expected to reach 2 billion by 2050 (Brahma 2013). At 16.6%, the average rate of ADR-related hospital admissions is much greater in the older adult population (Petrovic 2012). Of these admissions, around 88% are considered preventable. Studies from around the world have shown a direct correlation between increasing age and the rate of ADRs (Petrovic 2012; Kongkaew 2008). The average patient older than 65 has two to six prescription drugs and also takes one to three OTC medications (Stewart 1994). Of all the factors associated with ADRs in geriatric patients, polypharmacy is arguably the most important for pharmacist intervention. Cognitive problems also contribute to the prevalence of ADRs by leading to nonadherence. As the number of drugs increases, the risk of medication nonadherence also increases, further increasing the risk of an ADR. By examining the patient's medication record and evaluating for duplicate therapies or medications being used to potentially treat ADRs caused by other medications, pharmacists can help reduce unnecessary prescribing and optimize the patient's drug therapy regimen.

With advanced age come changes in drug disposition and pharmacodynamic responses. This increased pharmacodynamic sensitivity in geriatric patients (e.g., with CNS agents) can lead to ADRs, even at low drug doses. Older adults are more likely to have type A reactions (e.g., drowsiness, impaired coordination) from drugs such as antihistamines or anti-anxiety drugs (Brahma 2013; Pirmohamed 1998). The use of antipsychotic medications in geriatric patients may cause ADR symptoms resembling

those in Parkinson disease, resulting in a misdiagnosis and unnecessary treatment (Masand 2000). Furthermore, this treatment can lead to additional ADRs from the associated drug therapy and polypharmacy. Prescribers should always consider the possibility of an ADR when a new symptom presents in geriatric patients; this can prevent a prescribing cascade, where ADRs are misinterpreted as a symptom of another disorder, leading to the ordering of unnecessary procedures or pharmacotherapy.

Elderly patients may also have decreased renal or hepatic clearance, leading to pharmacokinetic changes and the accumulation of various drugs, precipitating ADRs. Drugs that undergo significant hepatic first-pass metabolism may have a higher bioavailability and quicker onset in older adults (Petrovic 2012). Initiating these drugs at lower doses or at extended administration intervals can prevent an ADR. Cytochrome P450 (CYP) oxidation declines in this patient population, which increases the risk of ADRs when drugs are used that are substrates of these enzymes. During acute illness, serum albumin may decline in older patients, resulting in a larger unbound portion of drug available in the body. Cardiac output also declines with age, reducing blood flow to the kidneys and liver. The overall elimination of high extraction drugs, which depends on blood flow, is reduced, resulting in an increase in the half-life of the drug and its associated metabolites. Lean body mass and total body water decrease in geriatric patients, whereas the percentage of total body fat increases. This causes a decrease in volume of distribution for hydrophilic drugs and an increase in volume of distribution for lipid-soluble drugs. All of these factors contribute to the increased rate of ADRs in this patient population.

Detecting and preventing ADRs in the older adult population remains a challenging, yet important part of good clinical practice. Tools available to assist in evaluating potentially inappropriate prescribing in older adults include the Beers Criteria, IPET (Improved Prescribing in the Elderly Tool), MAI (Medication Appropriateness Index), and STOPP (Screening Tool of Older Persons' Potentially Inappropriate Prescriptions) (Petrovic 2012).

Renal and Hepatic Impairment

Most drugs are metabolized by the liver and excreted by the kidneys. Impairment or failure of either of these organs can affect drug absorption, distribution, bioavailability, CYP metabolism, and clearance. Monitoring the laboratory values and adjusting the doses of drugs using these metabolic and excretory pathways can prevent an ADR.

Physiologic changes in patients with hepatic impairment can influence drug dosing. The presence of ascites in a patient with cirrhosis can alter volume of distribution, affecting the bioavailability and elimination half-life of some drugs and potentially leading to an increased risk of ADRs (Lewis 2013). Decreased hepatic blood flow

and the presence of portosystemic shunts can lead to increased bioavailability and serum drug concentrations, often necessitating a dose reduction in drugs such as antipsychotics, anti-anxiety agents, sedatives, antiparkinson drugs, and antidepressants. Drugs that undergo extensive hepatic first-pass metabolism should be used cautiously in patients with hepatic impairment. For example, the bioavailability of propafenone triples in a patient with hepatic impairment, and the dose should be reduced by 2- to 3-fold (Lewis 2013). If the dose is not reduced and the patient is not closely monitored, a serious ADR (e.g., ventricular arrhythmia) can occur and result in hospitalization or even death. Special consideration should be given to identifying and, if possible, avoiding drugs that undergo extensive hepatic first-pass metabolism in patients with hepatic impairment. Pharmacovigilance can be used to assist prescribers with dosing or alternative drug selection in these patients.

Genetic Variations

Once considered non-preventable, some ADRs may now be preventable because of the emerging field of pharmacogenomics. Using pharmacogenomic testing to provide personalized medicine can maximize therapeutic benefit and avoid or reduce the incidence of ADRs. If a patient is identified as having a genetic predisposition for

an ADR to a particular medication, the detrimental effects associated with the potential toxicity can be avoided by prescribing a different medication. An example is *HLA-B*5701* screening for abacavir hypersensitivity. Abacavir use can result in an immunologically mediated hypersensitivity reaction during the first 6 weeks of treatment. Patients who have this hypersensitivity reaction are carriers of the *HLA-B*5701* allele (Mallal 2008). Although not all *HLA-B*5701*-positive patients will have a hypersensitivity reaction to abacavir, carriers of the allele are at higher risk of this potentially life-threatening ADR. In 2008, the FDA mandated a boxed warning about this increased risk for the abacavir prescribing information. Pharmacogenomic testing for this allele before initiating abacavir therapy can reduce the risk of this specific ADR (Mallal 2008).

Another instance of ADR prevention through pharmacogenomic testing is the highly polymorphic *CYP2D6* gene (Thorn 2009). The conversion of codeine to morphine depends on *CYP2D6* activity; *CYP2D6* variants can be categorized as poor, extensive, or ultrarapid metabolizers. Poor metabolizers will be unable to convert codeine to morphine efficiently and may not experience adequate pain relief. This could be considered a type F ADR (unexpected failure of therapy) if genetic testing was not performed in advance. Alternatively, in

Patient Care Scenario

A 73-year-old man was admitted from an outside facility for evaluation of a small bowel obstruction. Pertinent medical history includes Crohn disease, type 2 diabetes mellitus, multiple abdominal surgeries, tachycardia, hypotension, acute pancreatitis, and anemia (hemoglobin 7.5 mg/dL). The patient's nutritional status was evaluated, and he was initiated on total parenteral nutrition (TPN), together with a continuous infusion of regular insulin to run concurrently with the TPN infusion. On day 2 of therapy, the nurse held the TPN when the patient became febrile, but the insulin infusion was continued. The patient became unresponsive, with a blood glucose of 22 mg/dL (normal 70–110 mg/dL).

Answer

This case involves the mistaken administration of continuous-infusion regular insulin after the holding of parenteral nutrition, resulting in severe hypoglycemia. This error should be reported to the hospital's medication error/ADR database and reviewed by an interdisciplinary panel that includes physicians, nursing, pharmacy, and risk management professionals. The panel must first gather all the pertinent facts regarding the error, to include: interviews with the individual(s) involved in the error, a review of the initial orders for TPN and insulin, an outline of the sequence of events leading to the discontinuation of TPN

Dextrose 50% solution (25 g) was administered. Within 15 minutes, blood glucose rebounded to 141 mg/dL, and the patient became more alert and oriented. The pharmacist covering the floor notified the resident physician of the event and completed a hospital medication event report.

During patient care rounds the following morning, the attending physician learned of the event and called for an immediate review of the case. As the pharmacist covering the unit, you are asked by the attending physician to coordinate the activities of the meeting because the event involved a medication. What steps are necessary in effectively managing this medication error and the resulting ADR?

and the administration of insulin, and a determination of the potential root causes for the error. The panel should then develop system and process changes to prevent the error and ADR from occurring in the future, including programming an automatic discontinuation of the insulin orders when TPN is stopped or discontinued, programming the computer system to alert the prescriber when TPN is stopped and reminding the prescriber to adjust the insulin orders, and providing education on the role of insulin with TPN therapy.

1. Magaji V, Johnston JM. Inpatient management of hyperglycemia and diabetes. Clin Diabetes 2011;29:3-9.

an ultrarapid metabolizer, codeine will be converted to morphine too efficiently, leading to potential opioid intoxication. The FDA now requires a boxed warning on medications containing codeine regarding the risk of respiratory depression and death in patients who are ultrarapid metabolizers because of variants in *CYP2D6*.

Dosage guidelines are often based on the general population's ability to absorb, distribute, metabolize, and excrete the drug. Patients with genetic differences that affect drug dosages and efficacy fall outside the intended therapeutic index and are more likely to incur an ADR when general dosage guidelines are used. This is especially true of drugs with a narrow therapeutic index. The FDA has required that genetic information be added to the labeling of more than 100 drugs, and has posted an online [table of pharmacogenomic biomarkers in drug labels](#) (Wei 2012).

Although research supports the need to test for genetic variations, implementation of biomarker testing in clinical practice is underused for many reasons, including availability and cost. Key issues to consider with biomarker testing are patients to test, what to do with the test result, how the information obtained from the test will be relayed to clinicians and patients, and how the testing will be incorporated into clinical practice without significantly increasing health care costs (Loo 2010). As more pharmacogenomic research is done, more changes will be implemented to package inserts and drug labeling to assist prescribers with dosing and ADR prevention. This dosage optimization will allow for more personalized medication therapy.

REPORTING OF ADRs IN THE UNITED STATES

Premarketing Clinical Trials

Although valuable information about ADRs can be obtained from reviews of premarketing clinical trials, limitations exist. These trials are often of short duration, making ADRs that develop with long-term use impossible to detect (Goldman 1995). The trials may have a narrow patient population; exclusion criteria may exist for patient selection in the premarketing trial population, and ADR incidence in the trial may not be representative of the true incidence in the general population once the drug is marketed. For example, children and the elderly are often excluded from these studies, yet these populations are often at risk of ADRs. Premarketing studies may not reveal ADRs because of small sample sizes that lack the power to detect rare ADRs; these are often found many years after drug approval in postmarketing surveillance studies with much larger patient populations. Furthermore, as new drugs enter the market, the potential for interactions with other drugs increases; concomitant drug therapies must be continually evaluated in the presence of new drug therapies for possible ADRs or ADEs (Goldman 1995).

Postmarketing Surveillance

Much information is acquired about ADRs because of case reports submitted to the FDA or other national reporting agencies. When an ADR is suspected, reporting of the reaction is important so that trends can be monitored. If a pattern is identified, the FDA can take action to alert health care practitioners and the public to improve patient safety.

The goal of evaluating ADRs is to increase patient safety by preventing harm; each patient harmed by an ADR should be treated and evaluated as an individual case. Reporting ADRs by overall facility occurrence rate minimizes their significance to the bigger picture, which is preventing harm in individual patients. A low reported ADR occurrence rate at a facility may be because of underreporting rather than true incidence. A rare but serious ADR, reported at an overall rate of less than 1% of the entire patient population, may seem less significant than it truly is to the individual patient. The NCC MERP council does not recommend comparing incidence rates across health care organizations. The council sees no value in comparing rates because of differences in reporting culture (incentive-based and non-punitive vs. punishing the individuals involved); differences in definitions of ADR, ADE, and medication errors; differences in patient populations that can affect the number and severity of cases; and differences in the type of institutional reporting and detection system (NCC MERP 2015). Looking at outcomes classifications for patients and drugs thought to have caused the ADRs at the facility is a more effective way to provide individualized patient care. Reviewing these ADRs on a case-by-case basis and implementing focused monitoring and provider education regarding use of the drug will help prevent the ADR in other patients. Reporting these reactions to a national agency will strengthen the power of detecting a recurrent rare ADR, which could lead to changes in drug labeling, prescribing, or availability in the United States.

The FDA Adverse Event Reporting System

In the United States, the primary adverse event reporting system is MedWatch, the FDA Safety Information and Adverse Event Reporting Program. Health care professionals and consumers voluntarily report ADRs, ADEs, and medication errors for entry into [the FDA Adverse Event Reporting System](#) (FAERS) database. The events are evaluated by clinical reviewers in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER). This evaluation may lead to regulatory action by the FDA, including labeling changes, communicating new safety information to the public, restricting use of the drug, or removing the drug from the market.

The FDA may also require [Risk Evaluation and Mitigation Strategies \(REMS\)](#), which are plans that use risk minimization strategies beyond professional labeling to ensure that the benefits of the drug outweigh the risks. Drug sponsors develop REMS programs and submit them to the FDA, where they are reviewed and approved. This

requirement can be mandated either before or after a drug is approved for marketing, and can be required for a single drug or a class of drugs. Proposed REMS may include one or more of the following: a medication guide to be distributed to patients when filling a prescription for the drug; a communication plan to educate health care professionals on the safe and appropriate use of the drug; Elements to Assure Safe Use (ETASU) such as physician certification requirements to prescribe the drug or patient enrollment in a central registry; an implementation plan of how ETASUs will be implemented; and a timetable for submitting assessments on performance with respect to meeting the goals and objectives of the REMS. The timetable requires assessments by 18 months, 3 years, and in the seventh year after the REMS is approved. Assessment results may be used to modify the REMS or to eliminate it after 3 years if the REMS has met its goals.

The FDA can also require a boxed warning on product information inserts and other drug literature. A boxed warning is indicated when drug use presents potential serious risks that may outweigh the intended benefits. Boxed warnings are often based on serious adverse reactions reported by health care practitioners and patients. Boxed warnings inform the prescriber of appropriate use of the drug, such as patient selection, monitoring, concomitant therapies to avoid, adjunctive therapies to administer, or specific clinical situations in which to avoid the drug. The presence of a boxed warning in the drug literature should alert the health care provider to examine the risks and benefits of the therapy and to consider the consequences that potential ADRs can inflict. It is still important to report observation of a known ADR because the severity or prevalence may lead to further FDA action including, but not limited to, removal of the drug product from the market.

The [online MedWatch reporting form](#) is used to submit suspected ADRs, ADEs, or medication errors to the FDA. The form may also be printed and mailed to FAERS. Health care professionals and consumers may alternatively choose to report adverse events and/or medication errors to the product manufacturer, which is then required to send a report to the FDA. These reports are also entered into FAERS for review.

The data contained in FAERS are not without limitations. There is no certainty that the reported event was caused by the drug or product. The FDA does not require that a causal relationship be proved in order to submit a report. Many reports do not contain enough details about the event to properly evaluate the occurrence. Because reporting is voluntary, there is not an FDA report for every event that occurs in the United States; therefore, the FAERS data cannot be used to calculate the true incidence of any given adverse reaction or event.

Information contained in FAERS is available to the public through [FAERS statistics](#), [FAERS data files](#), and individual case safety reports from the FAERS database.

The FAERS statistics provide the number of reports the FDA has received for drug and biologic products during the past 10 years. The FAERS data files provide raw data from individual case safety reports within the FAERS database. Individual case safety reports can be obtained by sending a [Freedom of Information request](#) to the FDA. Quarterly reports on potential serious adverse effects identified by FAERS are published and can be found on the [FDA Web site](#).

The Institute for Safe Medication Practices

Other private, non-government-initiated systems and agencies in the United States assist in the detection and reporting of ADRs, ADEs, and medication errors. The Institute for Safe Medication Practices (ISMP) is a national patient safety organization with a confidential medication error-reporting program (MERP). Reporting to the ISMP MERP is most appropriate for known or suspected medication errors. Alerts and medication safety information are distributed to health care providers every other week by a series of newsletters. The ISMP accepts reports from health care professionals and patients regarding ADEs and hazards in medication delivery and management. Reports can be submitted [online](#) or by telephone, mail, or fax. Staff from ISMP often contact the reporter to elicit additional details about the submission. After analyzing the reports, ISMP works with drug manufacturers and the FDA to ensure that safe medication practices are maintained.

The Joint Commission

Sentinel events are those that result in an unanticipated death or major permanent loss of function, not related to the natural course of a disease state. Sentinel events should be reported to The Joint Commission (TJC), which implemented a sentinel event reporting system in 1996. The Joint Commission facilitates identification and learning among health care organizations of sentinel events and strategies for prevention. Any accredited health care organization may submit a report to TJC, which will then request a root-cause analysis and action plan from the facility. Reporting is voluntary, but if a report is submitted, the root-cause analysis is required. The organization's action plan is monitored by TJC, similar to the monitoring of corrective actions observed during an accreditation survey. National Patient Safety Goals are often a result of information obtained in the sentinel event reporting process. The Joint Commission periodically chooses a reported event type and develops a sentinel event alert that describes the events, causes, and prevention strategies.

MEDMARX

The [MEDMARX](#) is a subscription-based registry of medication errors, ADRs, and ADEs. Better understanding of ADRs and preventing medication errors are the goals of MEDMARX. Voluntary reports are

submitted from subscriber facilities to MEDMARX, where they are analyzed and compared. Classified data are then disseminated through reports to the facilities with benchmarking from the entire database. Targets for improvement are identified, and monitoring of progress is provided. Subscribers also have access to consultant services to address management of medication errors and ADRs at their institutions. More than 1.3 million medication error records and more than 40,000 ADR records are contained within the MEDMARX registry (Quantros, Milpitas, CA). Facilities can use the collective information obtained from subscriber reports to devise strategies and interventions aimed at preventing medication errors and ADRs. The information within the MEDMARX database is also provided to the FDA for its review. These data may be added to the FAERS system to further assist in identifying signals for potential ADRs. Reporting to MEDMARX is beneficial for all types of drug-related incidents. Subscribing institutions benefit from the robustness of information contained within the system, and by receiving personalized feedback and recommendations for improvement, which are not provided when reported solely to the FDA.

Published Case Reports

Another way of alerting health care practitioners about suspected ADRs is through case reports in the primary literature. Often, published case reports are the only available literature on a particular ADR. Practitioners should not only report a suspected ADR to MedWatch, together with any internal or additional external reporting programs for tracking purposes, but should also contribute to the medical literature and inform other practitioners by publishing a case report. This information may assist other practitioners in identifying and treating a potential ADR more quickly, often before the FDA has identified a trend. Case reports are especially valuable in identifying rare ADRs not previously seen or evaluated by the FDA. Case reports should always be used as an adjunct to MedWatch reporting, not as a substitute.

INTERNATIONAL ADR REPORTING

In addition to the formal systems present today in the United States, other countries have developed reporting systems to assist in identifying ADRs. The following presents a sample of the many countries with a developed ADR reporting system.

Canada

The Canada Vigilance Program is a postmarket surveillance program that collects and assesses reports of suspected ADRs for health products marketed in Canada, including prescription drugs, nonprescription drugs, biologics, natural health products, and radiopharmaceuticals. Health professionals and consumers can

voluntarily submit adverse reaction reports [online](#), by phone, or by submitting the Canada Vigilance reporting form by fax or mail. Seven Canada Vigilance Regional Offices exist to provide a regional point-of-contact for health professionals and consumers. The regional offices collect ADR reports and perform an initial review of the quality and completeness of the reports. They then forward them to the Canada Vigilance National Office in Ottawa, Ontario, for further analysis. Marketing authorization holders, which include drug manufacturers and distributors, are required to submit adverse reaction reports to Health Canada according to Canada's Food and Drugs Act. Regulatory actions and market interventions may be performed by Health Canada or the sponsor of the health product and may include postmarketing studies, comprehensive reassessment of the risk-benefit profile of the medication, product labeling changes, alterations to packaging to identify risks or instructions on use of the product, dissemination of information to health care professionals and consumers, addition of warnings in patient information leaflets, public alerts, and market withdrawals.

The *Canadian Adverse Reaction Newsletter (CARN)* is a quarterly publication that alerts health care professionals and consumers to potential signals detected through reviews of case reports submitted to Health Canada. This newsletter provides information on serious or unexpected adverse effects or adverse reactions suspected or associated with health products. It also publishes statistics on adverse reaction reporting annually. The *CARN* publishes information about adverse reactions before benefit-risk evaluations have been undertaken and regulatory decisions made. It also alerts health professionals and consumers to advisories and recalls. The newsletter is distributed by mail to physicians, pharmacists, and other health professionals and to the public on the Web or by e-mail to subscribers of the MedEffect e-Notice electronic mailing list. Individuals can subscribe to the mailing list by visiting the [MedEffect Canada Web site](#).

United Kingdom

Adverse drug reactions in the UK are reported by both health care professionals and the general public using the [Yellow Card Scheme](#) operated by the Medicines and Healthcare Products Regulatory Agency and the Commission on Human Medicines. Submitting a Yellow Card report for a suspected ADR can be done [online](#) or by mail. Adverse drug reaction reports are collected for both licensed and unlicensed medications, including prescription medications, vaccines, OTC medications, herbal remedies, and cosmetics. Information from Yellow Card reports is assessed by a team of physicians, pharmacists, and other scientists. When serious safety issues are identified, they are published in *Drug Safety Update*, a bulletin e-mailed to subscribers (chiefly UK health care professionals).

Medications under especially close monitoring for ADRs in the European Union are designated with an inverted black triangle in patient information leaflets and in information distributed to health care professionals. This symbol designates that the medicinal product is subject to additional monitoring. Products are assigned the black triangle symbol if they contain a new active substance (medications and vaccines authorized on or after January 2011), are a biologic (vaccine or medication derived from plasma), or have been given conditional approval or approved under exceptional circumstances or if the company that markets the product is required to conduct additional studies. Other medications can be placed under additional monitoring by request from the Medicines and Healthcare Products Regulatory Agency or other regulators if the request is approved by the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC). The list of black triangle medications is reviewed and updated monthly and is published on the Medicines and Healthcare Products Regulatory Agency Web site as well as on the European Medicines Agency Web site. Medications remain under additional monitoring with the black triangle designation for 5 years or until the PRAC is satisfied that they can be removed from the list. A medication that was previously removed from the black triangle list may be added back at any time if conditions related to the monitoring of risks and benefits are identified.

Global ADR Reporting

Adverse drug reactions are a global problem and pose a need for worldwide surveillance. Every country with an ADR reporting program has a common goal: to educate health care practitioners and the public and thereby reduce or eliminate ADRs. In most countries, including the United States, many different organizations collect ADR information. Sharing of information among all reporting facilities, both nationally and internationally, can expedite ADR identification.

The WHO, using the Uppsala Monitoring Centre in Sweden, aims to assist with global ADR detection through a database called VigiBase. Countries throughout the world submit ADR reports, which are then entered into VigiBase. Trends are tracked to identify signals. With the use of a large reporting base, rare ADRs may be discovered more quickly than had they been reported in each country alone. This expedited ADR identification method can save lives by allowing prescriber education to occur sooner, which can alter prescribing trends and ADR incidence or severity.

Ideally, countries throughout the world could submit ADR reports to a common repository, such as VigiBase. Using uniform definitions, such as those from the *Medical Dictionary for Regulatory Activities*, and standardizing reporting methods to maintain consistency in the collection of ADR information can expedite the identification and prevention of ADRs with a larger pool of data. Using a common reporting system can help promote international understanding and prevention of ADRs worldwide.

Barriers to Reporting

In the United States and many other countries, the reporting of ADRs is voluntary. The underreporting of ADRs remains the largest barrier to health care professionals in identifying an ADR when it presents. The most prevalent reasons for not reporting suspected ADRs are consistently stated to be inadequate staffing and the time-consuming nature of evaluating and submitting the reports (Fabiano 2012; Coley 2006). The time needed to collect the necessary information, document the findings, and submit the report can be considerable, and other staffing demands often take precedence. Many health care facilities lack dedicated staff for these tasks, so ADR reporting fails to occur.

Another barrier to ADR reporting involves information systems. Although several facilities have transitioned, or are in the process of transitioning, to electronic medical records, some still rely on paper charts. Data collection from paper charts can be even more time-consuming than that from electronic records. Although some computer systems can interface with many departments (e.g., the laboratory) and identify potential ADRs by cross-referencing drugs with laboratory values, other systems remain separate, making the identification, and thus the reporting, of an ADR more time-consuming and difficult. These disparate information systems present barriers to the detection and reporting of ADRs.

Many facilities have internal reporting methods for ADRs and medication errors, but often these reports are not submitted to the FDA or other reporting agencies. Some staff view this additional reporting step as duplication of effort (Coley 2006). Internal reporting systems may not require enough detail to enable a thorough evaluation of the ADR. Standardizing internal reporting forms to align with those of national reporting systems, such as the MedWatch form, or providing interfaces between internal and external reporting systems can assist staff in collecting appropriate data and reporting ADRs at the institution (Coley 2006). Taking the extra step of informing the FDA of the ADR can help improve patient safety on a national or global level by identifying signals that might otherwise go undetected at an individual facility.

Additional reasons cited for not reporting an ADR have included lack of information and available resources, unawareness of the importance of reporting, unavailability of training programs for health care professionals on ADR detection, and fear of the ramifications of reporting (Fabiano 2012; Coley 2006; Khong 2002). Still other reasons include difficulties in diagnosing the ADR, the assumption that the ADR is unimportant or minor, and uncertainty about how and to whom to report it. The absence of a formal pharmacovigilance system is an additional barrier to the reporting of ADRs in health care facilities, and developing such a system is strongly encouraged.

Although patients can also report the ADRs, many see this as not their concern or their responsibility (Lorimer

2012). Educating patients on the importance of reporting ADRs and encouraging them to report, as well as instructing them on where and how to complete the forms, can overcome this barrier; however, relying solely on patient reporting may be unrealistic.

By working to overcome perceived barriers to reporting, the number of reported ADRs may be increased, which can help patients throughout the world. Reporting leads to increased awareness and detection of ADRs and can prevent their occurrence in both inpatient and outpatient settings, which in turn can help prevent hospital admissions or readmissions.

REDUCING HOSPITAL READMISSIONS FROM ADRs

Hospital readmissions are a key contributor to rising health care costs in the United States. Almost one in five Medicare patients discharged from hospitals is readmitted within 30 days, and more than one-half of readmissions are potentially avoidable (Hubbard 2012). Total annual cost estimates of these readmissions range from \$15 billion to \$25 billion. The Medicare Payment Advisory Committee (MedPAC) estimates that readmissions cost \$7200 per patient. To address this problem, the Affordable Care Act created a Readmissions Reduction Program. Launched in October 2012, the program reduces payments to hospitals with excess readmissions for heart failure, heart attack, and pneumonia by up to 1%. In 2015, these payment reductions will increase to up to 3%, and the Centers for Medicare & Medicaid Services may expand the penalty to include other conditions. Other private insurance companies are also negotiating payment penalties for hospitals with high readmission rates.

Researchers have estimated that up to 20% of discharged patients have an adverse event after discharge, most (72%) of which are caused by drugs (Hansen 2013). About one-third of the ADEs resulting in hospital admission are related to medication nonadherence (Hubbard 2012). Hospitalized patients are likely seen by many physicians, both as inpatients and outpatients, and medications are likely managed by many prescribers. Communication and coordination between inpatient prescribers and outpatient community physicians are vital to preventing ADRs and ADEs. By reducing the number of ADRs or detecting an ADR early in the outpatient setting, readmissions may be reduced. Nationwide, several projects and initiatives, such as the Transitional Care and the Medical Home models, are being developed to address the problem of high readmission rates. Patient adherence and medication management are key elements of these initiatives.

One way to improve medication adherence is to prevent ADRs. More than 50% of medication histories taken on admission have some form of discrepancy requiring resolution (Gleason 2004). By doing medication reconciliation at admission and discharge, it is possible to identify errors

in medication therapy that could lead to ADRs. Often, patients may continue taking a medication that has been discontinued by their inpatient physician without their knowledge, or begin taking an OTC medication without notifying their outpatient physician. Furthermore, when several prescribers are involved in a patient's care, duplications in drug therapy or drug interactions may occur. The resulting ADRs may lead to medication nonadherence and precipitate a hospital admission or readmission. With the goal of eliminating these readmissions, some organizations include medication reconciliation at admission and discharge as a key element in their strategic plans to reduce ADRs and ADEs. An example of such an initiative is the [STAAR Initiative](#).

Project BOOST

Another initiative that aims to prevent hospital readmissions is Better Outcomes for Older Adults through Safe Transitions ([Project BOOST](#)). The Society of Hospital Medicine developed this program to identify patients at high risk of rehospitalization and target specific interventions to mitigate potential adverse events. Goals are reduced 30-day readmission rates, improved patient satisfaction scores and Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) scores, improved flow of information between hospital and outpatient physicians and providers, improved communication between providers and patients, and optimized discharge processes. The program's advisory board included leaders in care transitions, hospital medicine, payers, and regulatory agencies; participants included medical, pharmacy, and nursing professional societies, as well as patient advocates. There are now more than 180 Project BOOST mentor sites in 31 states, with an additional site in Canada.

One study found that the average 30-day hospital readmission rate among BOOST facilities was reduced from 14.7% pre-implementation to 12.7% post-implementation ($p=0.010$) (Hansen 2013). In the matched control group, rehospitalization rates were 14.0% in the pre-intervention period and 14.1% in the post-intervention period ($p=0.831$). The mean absolute reduction in readmission rates during the 1-year study was 2.0% higher in BOOST units than control units, corresponding to a relative risk reduction of 13.6% ($p=0.054$). Length of stay in BOOST units was reduced by an average of 0.5 days, compared with 0.3 days in the control units ($p=0.966$). Although length of stay was not significantly reduced, the overall readmission rate decreased significantly for facilities using Project BOOST methods.

DEVELOPING AN ADR SURVEILLANCE AND REPORTING PROGRAM

An ADR monitoring and surveillance program is a helpful step toward increasing ADR detection, evaluation, and reporting, as well as in developing mechanisms

to prevent ADRs and their associated morbidity, mortality, and costs. Because time and insufficient staffing have been identified as barriers to ADR reporting, the design of an ADR surveillance program should focus on ways to overcome these barriers.

The ADR reporting system at a facility should be easy to use; if the reporting process is simple, more personnel are likely to participate (Vitillo 2000). Assessment and reporting of ADRs is not the sole responsibility of the pharmacy department; a successful ADR surveillance and reporting system should be multidisciplinary. Members of other departments throughout the facility should be contacted for help with ADR detection and reporting in their respective areas. Nurses may be the first professionals to note an ADR because they interact with their patients several times a day and may notice a new symptom that could be related to an ADR. Patients often contact their nurse first if they are having an unpleasant reaction. The nurse can then contact the physician or pharmacist to report the suspected ADR. Respiratory therapists can report ADRs occurring with inhaled medication therapies in their patients, such as tachycardia with the use of albuterol. They can also report suspected ADRs when a medication may have led to respiratory depression and the need for intubation. Operating room staff may report ADRs associated with anesthetic agents, antibiotics used for surgical prophylaxis, sedatives, anxiolytics, and analgesics. By enlisting help from several departments, the number of ADR reports submitted is likely to increase because the responsibility does not fall on just the prescribers. The more reports submitted, the higher the likelihood that a trend will be detected and measures put in place to prevent the ADR in the future.

The availability of an ADR reporting system is of no use unless personnel are aware of its existence. Time should be dedicated during new employee orientation to inform new staff of the importance of ADR detection and reporting and to provide instruction on how to report ADRs at the facility.

Developing and continuing a successful ADR surveillance and reporting system is possible only with support from facility administration, including the chief executive officer, chief operating officer, director of nursing, and medical director. Reporting of ADRs must be a priority at the institution; funding and support of the program must occur from top-level management down. It is crucial that leaders understand and support that reporting of ADRs by staff will not be punitive or used for credentialing purposes. Stressing that ADR reporting can lead to changes in policies and procedures that affect patient safety may in turn lead to an overall decrease in hospital readmissions and overall health care dollars spent. Once top leadership recognizes the value of the ADR surveillance and reporting system for patients and the institution, support and funds may be granted for resources such as addition of staff dedicated to ADR management and reporting, or educational programs that enhance knowledge about ADRs.

Educational programs designed to provide information on prescribing, administering, and monitoring of drugs should be part of any quality ADR surveillance program. Regular continuing education can help remind staff of the importance of identifying and reporting ADRs. Pharmacists are a key information source for staff, particularly when a new drug is available on the market or on the facility's formulary. Providing information on pharmacology and known adverse reactions of the drug will help practitioners recognize an ADR as it arises.

Establishing an ADR surveillance and reporting system in a health care facility is an important step in identifying new ADRs and determining the incidence of known ADRs in patient populations. By passing on this information to reporting agencies, more thorough ADR evaluations can take place nationally and globally. It all begins with a single report in a single health care facility.

CONCLUSION

As medication experts, pharmacists are a vital part of the treatment team, especially when an ADR occurs. Treating an ADR consists mainly of supportive therapy with symptom management. Furthermore, additional steps should be taken to determine the cause of the patient's symptoms and whether they can be attributed to the use of a drug.

Begin by evaluating the nature of the event. Thoroughly review the medical history available in the patient's chart. Identify and document the clinical reaction, including the patient's subjective report of symptoms. Review the patient's medication list, and then use references such as product inserts, MedWatch reports, and published literature to evaluate whether the reaction is known to occur with any of the drugs the patient has taken. Classify the severity of the reaction. A severe reaction is fatal or life threatening; the drug should be discontinued and not rechallenged. A moderate reaction requires an antidote, a medical procedure, or hospitalization. In many cases, this may mean discontinuing the drug. Mild reactions have symptoms that often require therapy discontinuation. It is possible that the therapy can be reinitiated with an adjustment in dosage if management of the disease state warrants continuation. Incidental reactions have mild symptoms; patients can choose whether to discontinue treatment, depending on their tolerability of the ADR.

After the reaction is evaluated, the cause of the reaction should be established, if possible. Tools such as the Naranjo algorithm or the Liverpool ADR causality assessment tool can be used to assist in determining causality. Check to make sure the ADR is not caused by a medication error; this could influence whether a treatment is continued or discontinued. If the reaction can be attributed to a drug, a suggestion is to update the patient's allergy profile with the name of the drug and a brief description of the reaction.

Finally, take corrective action and follow up. Prescribers should be educated on the ADR. If necessary, a formulary review should be done to determine whether an alternative

agent with a better ADR profile could be added to the formulary instead of the offending agent. If the drug remains on formulary, monitoring values may need to be modified, or specific criteria for use may need to be formulated. Then, drug regulatory authorities and manufacturers should be notified of the ADR by a formal ADR report submission.

Because they possess the knowledge to identify, classify, assist with the management of, and report an ADR when it occurs, pharmacists are the ideal professionals to assist in developing an institutional pharmacovigilance program. When an ADR occurs, medical staff often seek the pharmacist's assistance; this is an ideal time to collect the information needed for reporting. By collecting data on patients and the ADRs they experience, pharmacists can monitor trends and suggest changes for drug monitoring and formulary management. Pharmacists can promote advocacy for ADR reporting in their facility and provide a user-friendly environment where reporting can occur.

Providing education to prescribers, other health care personnel, and patients about ADRs can increase awareness and help prevent ADRs or identify them earlier when they present. Pharmacists can also recommend and assist with systems changes to prevent ADRs, such as admission and discharge medication reconciliation, computer system alerts, and barcode-assisted medication administration, which can alert nurses of a drug allergy in their patients. Pharmacists can advocate for the facility's participation in national ADR and hospital readmission prevention programs. Finally, pharmacists can work as part of a multidisciplinary team to care for patients by reviewing medication profiles and identifying the potential for an ADR before it occurs. Pharmacists can affect each step of the pharmacovigilance process, from preventing an ADR to identifying and treating an ADR and preventing further ADRs. With support from other health care practitioners, the prevention, identification, management, and reporting of ADRs can be made an institutional priority to protect patients from many of the negative sequelae associated with the adverse reactions of drug therapy.

Adverse drug reactions will never completely be eliminated, even with the most sophisticated pharmacovigilance systems in place. The duty of the health care practitioner is to minimize the occurrence of ADRs by working to prevent them. Prevention is made possible through knowledge gained by the reporting of ADRs to national and global reporting agencies, to drug manufacturers, and in published primary literature. Sharing this information with colleagues and patients will create an awareness of ADR potential and can save lives. By including an ADR on the differential when a patient presents with new or worsening symptoms, the process of identifying, classifying, and determining the causality of a potential ADR can begin immediately, and future harm may be prevented. Pharmacists are on the front lines of ADR prevention, detection, and treatment. Through pharmacist-initiated education and advocacy for ADR reporting, other practitioners will join the crusade to protect patients from harmful ADRs, and lives will be saved.

Practice Points

In determining the optimal detection, management, and prevention of ADRs, practitioners should consider the following:

- Correctly defining and classifying an ADR can help determine management and future drug therapy options. Adverse drug reactions may not be treated the same as ADEs or medication errors. Type A ADRs may not be treated the same as type B.
- Tools such as the Naranjo ADR Probability Scale and the Liverpool ADR causality assessment flowchart can be used to assist with causality determination. Although they cannot give a definitive estimation of relationship likelihood, they can provide a degree of relationship between drug and adverse reaction.
- Pediatric and geriatric patients are at high risk of experiencing ADRs and are often excluded from premarketing drug evaluation studies, making case reports and national ADR reporting system data valuable tools for ADR-related information in these populations.
- Although internal health system ADR reporting may be valuable to the individual institution, further submission of these reports to the FDA by MedWatch can assist with ADR detection nationally and globally. This can lead to regulatory actions such as labeling changes, new public safety information, drug use restrictions, REMS, or removal of the drug from the market.
- Establishing a pharmacovigilance and ADR surveillance and reporting program is helpful for ADR detection, evaluation, reporting, and prevention. Pharmacists are ideal professionals to assist in development of such programs.

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SELF-ASSESSMENT QUESTIONS

Questions 1–3 pertain to the following case.

D.W. is a 9-year-old boy with osteosarcoma, which is being treated with ifosfamide and etoposide. He has no history of allergy. After two courses of chemotherapy, D.W. develops an upper arm deep venous thrombosis because of the chemotherapy. He is admitted to the hospital and initiated on heparin, omeprazole, and prophylactic antibiotics (piperacillin/tazobactam). On the third day of treatment, the swelling and pain in his upper arm have decreased significantly.

- Which one of the following best classifies D.W.'s chemotherapy adverse drug reaction (ADR)?
 - Type A.
 - Type B.
 - Type C.
 - Type D.
- Which one of the following would be best to use to document D.W.'s ADR?
 - Internal hospital quality reporting system.
 - FDA MedWatch.
 - Quantros MEDMARX international reporting system.
 - The Institute for Safe Medication Practices (ISMP) medication error reporting program.
- On the third hospital day, D.W.'s platelet count has dropped by 50% from baseline, and his alkaline phosphatase has increased to twice the normal value. He also begins to have some oozing of blood from his central catheter line site. The team agrees that these events are ADRs and asks you to narrow the suspected drugs to two agents. Which two-drug option is most likely causing these ADRs in D.W.?
 - Omeprazole and heparin.
 - Heparin and ifosfamide.
 - Ifosfamide and omeprazole.
 - Omeprazole and piperacillin/tazobactam.
- You have been asked by your department's director to compile a listing of your institution's reported ADRs for review by your health system's quality committee. Which one of the following metrics would be most helpful to ADR prevention?
 - Rate of ADRs per 100 admissions.
 - Rate of ADRs per 100 discharges.
 - Number of ADRs by therapeutic drug classification.
 - Number of ADRs resulting in harm.
- You have been asked to participate in an interdisciplinary panel at your hospital to reduce ADRs in patients aged 65 years or older. Which one of the following would be most effective?
 - Address and manage issues that cause frailty.
 - Continue the diuretic drugs prescribed in the hospital at the patient's home.
 - Use the STOPP (Screening Tool of Older Persons' Potentially Inappropriate Prescriptions) tool.
 - Improve medication adherence.
- A 92-year-old man reports to the emergency department from an extended-care facility with transient chest and jaw pain. He has a medical history of anemia with a hemoglobin concentration of 8.6 mg/dL, congestive heart failure, and atrial fibrillation. The patient is afebrile (98.9°F), and on admission, his SCr is 1.8 mg/dL (CrCl 26 mL/minute). Physical examination reveals a 2-cm × 2-cm × 0.5-cm ulceration in the left lower coccyx. The ulceration appears "clean," and the patient reports minimal pain in the area. Other significant findings are 2+ pitting edema in the lower extremities with diminished breath sounds in the left lung. The medical team is concerned about kidney-related adverse reactions if antibiotics are used. Which one of the following is best to recommend for this patient?
 - Begin conservative antibiotic therapy that may be nephrotoxic; measure serum concentrations at steady state and adjust, if necessary.
 - Assess the patient's fluid status, hydrate if necessary, obtain a culture specimen, and provide wound care to the decubitus ulcer.
 - Use an antibiotic that is not toxic to the kidneys.
 - Prescribe a broad-spectrum antibiotic as empiric therapy, obtain a culture specimen, and provide wound care.
- A 76-year-old patient is prescribed intravenous vancomycin 1500 mg every 12 hours on August 10. The patient's SCr on the morning of August 10 is 2.3 mg/dL, peaking at 5.4 mg/dL on August 15. Trough vancomycin level is 24.6 mcg/mL on August 16. Renal sonography is normal, and serum electrolytes are normal. According to the Naranjo algorithm, which one of the following ratings is most appropriate for the possible ADR of vancomycin and acute kidney injury in this patient?
 - Highly probable.
 - Probable.
 - Possible.
 - Doubtful.

8. Your director requests a summary document to justify hiring a pharmacist to develop a program to identify and prevent ADRs. According to your review of the literature, which one of the following would be best for the pharmacist to focus on to prevent ADRs?
- Work as an active member of a parenteral nutrition team.
 - Provide more staffing on the evening shifts of a hospital.
 - Provide discharge medication counseling and reconciliation.
 - Perform medication histories.

Questions 9 and 10 pertain to the following case.

F.G. is a 68-year-old man (weight 78 kg) who presents to the emergency department with signs of an ischemic stroke. Initial examination reveals a patient in atrial fibrillation with poor nutritional status. Further examination reveals a patient with normal renal function for age but severe carotid artery stenosis. F.G. is deemed a poor surgical candidate; he is stabilized in the neurologic intensive care unit and, 3 days later, is transferred to a regular floor. A feeding tube is placed before discharge. At discharge, the patient is prescribed enoxaparin 80 mg subcutaneously every 12 hours. Four days after discharge, F.G. is readmitted with a severe abdominal hematoma and significant drop in hemoglobin. Enoxaparin is discontinued with improvement in the hematoma and the hemoglobin concentration.

9. Which one of the following risk factors is most likely to be a contributing cause when assessing a possible enoxaparin ADR in F.G.?
- Atrial fibrillation and poor nutritional status.
 - Incorrect enoxaparin dosage.
 - Feeding tube placement.
 - Recent stroke event.
10. Using the Liverpool adverse drug reaction casualty assessment tool, which one of the following is the mostly likely probability of an enoxaparin ADR in F.G.?
- Unlikely.
 - Unassessable.
 - Possible.
 - Probable.

Questions 11 and 12 pertain to the following case.

N.P. is a 54-year-old man with superior vena cava stenosis, end-stage kidney disease, severe pruritus, and asthma. He is taken to the radiology suite for an angioplasty procedure. The patient is administered intravenous fentanyl 200 mcg, midazolam 4 mg, and morphine 10 mg. N.P. tolerates the procedure well, but in the recovery area, he has acute anxiety and tachypnea, with oxygen saturation levels

decreasing to 89%–92%. Two doses each of flumazenil 0.5 mg and naloxone 0.4 mg are administered, and his oxygen saturation increases to 93%–95%.

11. The nurse circulator on N.P.'s unit calls the pharmacotherapy specialist and asks whether an ADR report should be completed. Which one of the following is the best response to this question?
- The circulating nurse does not need to complete an ADR form because the reaction to fentanyl is expected.
 - The patient's end-stage kidney disease should have limited the dosages of sedation agents, so an ADR form should be completed.
 - Use of naloxone in 0.4-mg doses is dangerous, and an ADR report should be completed to enforce education on the use of reversal agents.
 - No significant clinical harm occurred, so an ADR form should not be completed.
12. The nurse circulator on N.P.'s unit decides to complete an ADR report. Which one of the following ADR reporting systems would be best to use in reporting N.P.'s ADR?
- Internal hospital quality reporting system.
 - FDA MedWatch.
 - Quantros MEDMARX international reporting system.
 - ISMP medication error reporting program.

Questions 13–15 pertain to the following case.

K.L., a 34-year-old woman with end-stage cancer, is being cared for by the palliative pain management service. She has received her home doses of hydromorphone 8 mg orally every 4 hours since her admission 3 days ago. On the morning of hospital day 4, K.L. has "pain and twitching all over." The resident physician asks you to evaluate K.L. for an ADR from opioid analgesics.

13. Which one of the following is the best first step to determine whether K.L. experienced an ADR to opioid analgesics?
- Replace hydromorphone with other opioids to see whether that changes her symptoms.
 - Add another opiate in equal doses, and see whether her symptoms change.
 - Review the medical record to determine any temporal relationships associated with a potential ADR.
 - Use both the Naranjo algorithm and the Liverpool adverse drug reaction causality assessment tool to score the potential ADR.

14. The nurse on K.L.'s unit decides to complete an ADR report. The nurse also notes that this is the third patient she has seen with opioid neurotoxicity in the past week. After completing a reporting form for review by the hospital's chief medical officer, this ADR should also be reported to which reporting system?
- Internal hospital quality reporting system.
 - FDA MedWatch.
 - Quantros MEDMARX international reporting system.
 - ISMP medication error reporting program.
15. Which one of the following best describes the ADR classification of the neurotoxicity K.L. experienced from hydromorphone?
- Augmented.
 - Bizarre.
 - Chronic.
 - Delayed.
16. You are a hospital's director of pharmacy. The chief executive officer calls you after reviewing a recent ADR report. He notes that the hospital has a low rate of ADRs. He also notes that he saw another hospital's report with a higher rate and asks, "Are we a safer hospital because we have a lower rate of ADRs?" Which one of the following is the best response to this question?
- The low rate of reported ADRs represents a high-quality organization because only serious reactions are reported in a voluntary reporting system.
 - The rate of ADRs is not related to the quality of an organization because collecting a sample size large enough for showing a difference between organizations' ADR rates is not feasible.
 - Individual patient impact is the most important factor in determining quality, and the rate of adverse events dilutes the importance of one patient case.
 - The rate of ADRs in a specific patient population defines quality, so a series of patient cases should be examined to determine the rate in a specific patient population.

Questions 17 and 18 pertain to the following case.

L.W. is a 28-year-old man with end-stage heart failure who has been placed on the waiting list for a heart transplant. A suitable donor is found for L.W., and the appropriate preoperative immunosuppression is given. During the preoperative anesthesia assessment, it is determined that the patient received a dose of dabigatran on admission to the hospital this morning. However, this drug had been discontinued by his cardiologist 1 month before this admission, and since then, L.W. had not taken any doses of dabigatran at home. This morning, the

admitting physician placed an order to reinstate the patient's home medications from the list on file in the hospital's computer system. The list had not been updated to indicate that the patient was no longer taking dabigatran. Further review showed that the nurse did not realize dabigatran was an anti-coagulant. The surgical case is canceled, and the donor heart is re-routed through the organ-sharing network to the next suitable donor. L.W. continues to do poorly, with progression of heart failure, and he is placed on life support while awaiting another donor heart.

17. You further review L.W.'s case. Which one of the following is the best response to give the chief quality officer when contacted about this case?
- This is not an ADR, but a medication error.
 - The continued cardiac decompensation by the patient classifies this as an ADR.
 - The surgery should not have been canceled because the relationship between dabigatran and surgical bleeding has not been established.
 - The only way to determine whether this is an ADR is to use a scale such as the Naranjo algorithm.
18. The multidisciplinary team discusses L.W.'s case to determine whether patient harm occurred. Which one of the following would be considered the most severe harm outcome?
- Prolonged hospital stay in remaining on the waiting list for another organ.
 - Psychological stress and fear in missing an opportunity to get a transplant.
 - Excessive bleeding from dabigatran.
 - Progression of heart failure caused by delayed heart transplant.

Questions 19 and 20 pertain to the following case.

K.K. is a 54-year-old man with stage III colon cancer receiving adjuvant chemotherapy. He is transported by wheelchair to have his subcutaneous catheter accessed for routine coagulation studies. On the way to the laboratory for blood testing, he develops acute shortness of breath and a scattered rash on his arms, back, and trunk. His blood pressure and heart rate remain stable; further examination reveals that although K.K. had a known allergy, the nurse used chlorhexidine scrub on him. His symptoms resolved after treatment and observation in the emergency department.

19. Using the Naranjo algorithm, which one of the following best describes the probability of K.K.'s ADR?
- Highly probable.
 - Probable.
 - Possible.
 - Doubtful.

20. K.K. files a formal complaint against the nursing unit where the chlorhexidine reaction occurred. He requests a root-cause analysis and asks that steps be taken to prevent the error in another patient. Which one of the following would best prevent drug-allergy contraindications and an ADR such as K.K. experienced?
- A. Barcode-assisted medication administration.
 - B. Computerized prescriber order entry with decision support.
 - C. Best practice alerts in computer systems.
 - D. Barcode scanning stocking of pharmacy shelves.