

Adverse Drug Reaction Reporting

Lee B. Murdaugh, RPh, PhD



LEARNING OBJECTIVES

- Define an adverse drug reaction.
- Discuss the detection of adverse drug reactions.
- Discuss the assessment of adverse drug reactions.

The Conditions of Participation standards of the Centers for Medicare & Medicaid Services (CMS) and the standards of accrediting organizations such as The Joint Commission, the Healthcare Facilities Accreditation Program (HFAP), and the National Integrated Accreditation for Healthcare Organizations (NIAHOSM) require hospitals to identify and report adverse drug reactions (ADRs). These ADRs must be reported to patients' attending physicians and the hospital's quality assessment and performance improvement program. Additionally, hospitals are expected to report serious ADRs (as defined by the Food and Drug Administration [FDA]) to the FDA's MedWatch program and ADRs to vaccines to the FDA's Vaccine Adverse Events Reporting System (VAERS).

Defining Adverse Drug Reactions

To recognize and assess ADRs, there must be a definition of what constitutes an ADR. Examples of commonly used definitions are discussed in the following text.

The FDA defines a serious adverse reaction as one in which "the patient outcome is death, life threatening (real risk of dying), hospitalization (initial or prolonged), disability (significant, persistent, or permanent), congenital anomaly, or required intervention to prevent permanent impairment or damage."¹

The American Society of Health-System Pharmacists (ASHP) defines a 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 healthcare facility
- necessitates supportive treatment
- significantly complicates diagnosis
- negatively affects prognosis or
- results in temporary or permanent harm, disability, or death.”²

The ASHP definition includes allergic reactions (an immunologic hypersensitivity response to a drug) and idiosyncratic reactions (an abnormal response to a drug that is specific to an individual).

ASHP excludes the following from this definition:

- Drug withdrawal
- Drug-abuse syndromes
- Accidental poisonings
- Drug overdose complications
- Side effects

A *side effect* is defined as an “expected, well-known reaction resulting in little or no change in patient management” that occurs with a “predictable frequency and whose intensity and occurrence are related to the size of the dose.”²

The World Health Organization (WHO) defines an ADR as “any response to a drug, which is noxious and unintended, and which occurs at doses used in man for prophylaxis, diagnosis, or therapy or for modification of physiologic function.”³ The definition excludes cases attributed to drug abuse or overdose (intended or unintended).

Karch and Lasagna define an ADR as “any response to a drug that is noxious and unintended and that occurs at doses used in humans for prophylaxis, diagnosis, or therapy, excluding failure to accomplish the intended purpose.”⁴ In addition to the exclusions of the WHO definition, this definition also excludes therapeutic failures.

Review appropriate policies and procedures to identify the definition used by your organization.

Detection of Adverse Drug Events

Signs and Symptoms

Signs and symptoms of ADRs are many and varied and may be similar to signs and symptoms of disease states or medical conditions. Table 40-1 contains some of the common signs and symptoms of ADRs (grouped by body systems) that may be seen in patients during

routine observation and assessment. Inclusion of an individual sign or symptom will depend on the definition of an ADR at the specific institution.

Surveillance Systems

There are three types of surveillance systems that may be used to detect ADRs:

1. Prospective
2. Concurrent
3. Retrospective

Identifying which methods to use will depend on the unique characteristics of a facility. However, ADRs are more likely to be detected when a combination of surveillance systems are used. It should be noted that the success of any surveillance system depends on the willing participation of healthcare professionals in reporting ADRs.

PROSPECTIVE SURVEILLANCE SYSTEM

Prospective surveillance occurs prior to initiation of medication therapy and can be accomplished in two ways:

1. *Monitoring of patients who are at a high risk for experiencing ADRs*—Risk factors for ADRs include the following:
 - Polypharmacy
 - Extremes of age (e.g., neonatal, pediatric, and geriatric patients)
 - Presence of concurrent disease states (e.g., impaired renal or hepatic function)
 - Severity of illness
 - History of allergy/previous ADR
 - Pharmacodynamic/pharmacokinetic changes
2. *Monitoring of patients who are receiving medications known to have a high potential for causing ADRs*—The drug classes most frequently implicated in ADRs include the following:
 - Anticoagulants (e.g., heparin and warfarin)
 - Antimicrobials (e.g., penicillins, cephalosporins, sulfa antibiotics, and aminoglycosides)
 - Antineoplastics
 - Cardiac agents (e.g., antiarrhythmics, digoxin, diuretics, and antihypertensives)
 - Central nervous system (CNS) agents (e.g., analgesics, anticonvulsants, and sedatives/hypnotics)
 - Diagnostic agents (e.g., contrast media)

TABLE 40-1. Signs and Symptoms of ADRs by Body System

BODY SYSTEM	EXAMPLES	BODY SYSTEM	EXAMPLES
Cardiovascular	<ul style="list-style-type: none"> • Arrhythmias • Angina • Hypertension • Hypotension • Bradycardia • Tachycardia 	Hematological	<ul style="list-style-type: none"> • Bleeding • Increased eosinophils • Increased PT and PTT • Decreased WBC, RBC, HCT, and platelets
Dermatological	<ul style="list-style-type: none"> • Rash • Itching • Erythema • Hives • Phlebitis • Bruising • Petechiae • Ecchymosis 	Hepatic	<ul style="list-style-type: none"> • Hepatitis • Jaundice • Increased AST, ALT, and LDH
Endocrine/metabolic	<ul style="list-style-type: none"> • Hyperglycemia • Hypoglycemia • Sexual dysfunction • Hypothyroidism 	Musculoskeletal	<ul style="list-style-type: none"> • Arthritis • Joint pain • Myalgia
ENT/oral	<ul style="list-style-type: none"> • Altered taste • Stomatitis • Thrush • Tinnitus • Hearing loss 	Neurological	<ul style="list-style-type: none"> • Headache • Tremor • Seizures • Drowsiness/somnolence • Vertigo • Altered vision • Movement disorders (e.g., dyskinesia, akathisia, tardive dyskinesia) • Depression • Confusion • Agitation • Psychosis • Hallucinations
Reproductive	<ul style="list-style-type: none"> • Fetal hemorrhage • Fetal respiratory depression • Teratogenesis 	Renal	<ul style="list-style-type: none"> • Bladder spasms • Oliguria • Increased BUN or creatinine • Renal failure
Electrolyte homeostasis	<ul style="list-style-type: none"> • Hyperkalemia • Hypokalemia • Hyponatremia • Hypocalcemia 	Respiratory	<ul style="list-style-type: none"> • Wheezing • Increased or decreased respirations
Gastrointestinal	<ul style="list-style-type: none"> • Diarrhea • Constipation • Nausea/vomiting • Hemorrhage 		
Generalized	<ul style="list-style-type: none"> • Anaphylaxis • Fever • Skin reaction • Angioedema 		

ALT = alanine transaminase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ENT = ear, nose, throat; HCT = hematocrit; LDH = lactate dehydrogenase; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; WBC = white blood cell.

- Antidiabetic agents (including insulin)
- Corticosteroids

The major advantage of prospective surveillance is that it is the most sensitive and specific method for detecting ADRs.⁵ However, it has a significant disadvantage in that it is very labor intensive and involves continuous monitoring. Prospective surveillance systems are best accomplished through the use of decentralized pharmacists and/or utilization review personnel.

CONCURRENT SURVEILLANCE SYSTEM

Concurrent surveillance involves the identification of ADRs close to the time they occur. There are several methods that can be used to detect ADRs concurrently:

- Spontaneous reporting of ADRs by primary care practitioners (such as physicians and nurses) during the course of their work using telephone hotlines, ADR alert cards, report forms, etc.
- Analysis of medication usage evaluation (MUE) studies
- Reporting of suspected ADRs by hospital utilization review/quality assurance personnel from their concurrent review of patient charts
- Monitoring of orders and patient charts by pharmacy personnel for clues (often called *triggers*) that an ADR has occurred

Triggers include the following:

- Abnormal test results such as serum drug concentrations above therapeutic levels and laboratory test results outside a particular range or threshold (e.g., platelet count less than 50,000)
- Alerting order, which is an order or sequence of orders that suggests an adverse effect may have taken place

Monitoring for triggers by pharmacists is a very effective way to detect ADRs. Alerting orders include the sudden discontinuation of one or more medications, an unexpected reduction in dosage, and a stat order for an antidote or other medication used to manage ADRs, such as the following:

- Atropine
- Benztropine
- Dextrose 50%
- Glucagon
- Naloxone
- Diphenhydramine
- Epinephrine
- Furosemide
- Phytonadione (vitamin K)
- Potassium chloride

- Flumazenil
- Protamine
- Nitroglycerin
- Physostigmine
- Sodium polystyrene sulfonate (SPS)
- Antidiarrheals (e.g., loperamide, colestipol)
- Antiemetics (e.g., hydroxyzine, prochlorperazine)
- Glucocorticosteroids (e.g., methylprednisolone)

Alerting orders also include nonroutine orders for laboratory tests, such as the following:

- BUN
- AST, ALT
- PT, PTT, platelet count
- Drug serum concentration
- *Clostridium difficile*
- Guaiac test
- Serum creatinine
- Urine protein, cells, casts

Usually, a combination of orders gives the pharmacist the best clue that an ADR may have occurred. Table 40-2 includes examples of combination alerting orders and the corresponding possible ADR.

Concurrent surveillance has the advantage of allowing a more thorough investigation because the patient, nurse, and physician are available for interviews and are likely to recollect events more accurately. Also, this method allows interventions and management of the ADR to take place in a timely manner.

RETROSPECTIVE SURVEILLANCE SYSTEM

Retrospective surveillance involves the review of medical records for adverse drug reactions. It is not a desirable approach to monitoring for ADRs because of the disadvantages inherent in utilizing retrospective data. These disadvantages include inadequate documentation of events on medical records and the inability to intervene in a timely manner. Also, ADR programs based solely on retrospective surveillance do not comply with The Joint Commission expectations for active monitoring.

Assessment of Adverse Drug Reactions

Once an ADR is suspected through an alerting order or other means of surveillance, an investigation is conducted to evaluate causality and assess the probability of a reaction using standardized criteria and an algorithm developed for objectively rating potential ADRs.

TABLE 40-2. Alerting Orders

ALERTING ORDER	POSSIBLE ADR
Discontinue Coumadin Vitamin K 10 mg subcut now	<ul style="list-style-type: none"> • Coumadin may cause bleeding
Haldol 1–2 mg IM or po q 1–2 hr prn for confusion	<ul style="list-style-type: none"> • Possibility of other medications causing confusion, especially if patient is elderly and taking many medications
SoluCortef 100 mg IV now, Benadryl 50 mg IV now, Proventil inhaler now	<ul style="list-style-type: none"> • Patient may be experiencing an allergic reaction, but this could also be due to disease state
Discontinue: diltiazem, atenolol, Lanoxin Digoxin level	<ul style="list-style-type: none"> • Discontinuance of several cardiac medications along with digoxin level being ordered may indicate adverse effects, such as severe hypotension
Discontinue cefuroxime Benadryl 25–50 mg IM or po q 6 hr prn itching	<ul style="list-style-type: none"> • Allergic reaction
Serum iron, TIBC, stool for occult blood × 3	<ul style="list-style-type: none"> • Patient may be experiencing bleeding from medications that cause bleeding, ulcers, etc., or this may be due to disease state
Call platelet count to house officer if <100,000	<ul style="list-style-type: none"> • Patient may be experiencing platelet dysfunction due to medications such as NSAIDs, antibiotics, heparin, etc.
Questran 4 g tid × 48 hr Metronidazole 500 mg po q 8 hr	<ul style="list-style-type: none"> • Patient may be experiencing diarrhea from colitis, which may be caused by antibiotics or chemotherapy
KCl 40 mEq now and repeat in 4 hr SMA-6 (or K + level) now (or in 6 hr)	<ul style="list-style-type: none"> • Patient is experiencing hypokalemia, which may be caused by medications that decrease potassium levels (such as diuretics, corticosteroids, and overuse of laxatives)

IM = intramuscular; NSAIDs = nonsteroidal anti-inflammatory drugs; TIBC = total iron binding capacity.

Evaluation of causality determines the medication(s) suspected of causing the ADR. Assessment of the probability of a medication causing an ADR depends on evaluation of six criteria:

1. Event is a documented, known response to the suspected agent
2. Event is not explained by the disease state
3. Timing of events
4. Serum drug concentration
5. Dechallenge (discontinuing suspected agent)
6. Rechallenge (resuming suspected agent)

Usually, these criteria are incorporated in an algorithm developed to objectively rate ADRs. Several algorithms have been developed over the years.

One method, the Kramer algorithm, consists of 56 questions with weighted values for responses, which are totaled to obtain a score. The score corresponds with one of four categories of probability. Although this algorithm is detailed and thorough, it is very complicated and time consuming to complete. The Jones algorithm was developed to simplify assessment of probability. It consists of a flow chart of questions with diverging pathways depending on response. The FDA uses this method, but a study reported in the literature did not show a high correlation of the Jones algorithm with the Kramer algorithm.⁶

To simplify the process of assessing probability while maintaining validity and reproducibility, the Naranjo algorithm was developed (Figure 40-1). It

consists of 10 questions that are scored according to response and totaled. A high correlation has been found between the scores produced by the Kramer and Naranjo algorithms, indicating that the Naranjo algorithm is a valid substitute for the Kramer algorithm.²

A systematic approach to the assessment of ADRs (and any drug information requests related to the assessment of ADRs) provides the necessary data needed for researching the literature. The following questions formulate such a systematic approach:

- What medications are being taken by the patient?
- What are the doses and duration?
- When was each medication started?
- Which medication(s) is/are suspected to be causing the problem?
- Has/have the suspected medication(s) been discontinued?
- What are the symptoms of the reaction?
- When did the symptoms appear?
- What is the severity of the symptoms?
- What are the results of any relevant laboratory tests?
- What treatment has the patient received?
- Did symptoms decrease or subside following discontinuation of the medication and/or institution of treatment?

DRUG	YES	NO	NOT KNOWN	SCORE
1. Are there previous <i>conclusive</i> 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 <i>specific</i> antagonist was administered?	+1	0	0	
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could on their own 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				
≥9 = Definite 5–8 = Probable 1–4 = Possible ≤0 = Doubtful				

Source: Adapted with permission from Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of drug reactions. *Clin Pharmacol Ther.* 1981;30(2):239-245.

FIGURE 40-1. Naranjo Algorithm

- Does the patient have any allergies?
- For which conditions is the patient being treated?
- What are the liver and renal functions of the patient?

ADR REFERENCE SOURCES

Once the appropriate data have been gathered, reference sources should be consulted to confirm previous documentation of the ADR and to establish whether any alternative causes (such as other medications, disease states, etc.) could have caused the ADR. Information concerning the signs and symptoms, pathology (if appropriate), relevant laboratory findings, treatment, prognosis, and outcome of the ADR is gathered from the literature sources to not only help in assessing the ADR, but also to provide important information the pharmacist needs for appropriate intervention.

The three types of literature sources that may be useful in evaluating suspected ADRs include the following:

1. Tertiary literature
 - *Facts and Comparisons*
 - *AHFS Drug Information*
 - *Goodman & Gilman's The Pharmacological Basis of Therapeutics*
 - *Martindale: The Extra Pharmacopoeia*
 - *Handbook of Clinical Drug Data*
 - *Handbook of Nonprescription Drugs*
 - *Physician's Desk Reference*
 - *Applied Therapeutics: The Clinical Use of Drugs*
 - *Meyler's Side Effects of Drugs*
 - *Pharmacotherapy: A Pathophysiologic Approach*
 - Micromedex Drugdex database
2. Secondary literature
 - *Index Medicus*
 - *Clin-Alert*
3. Primary literature

- *American Journal of Health-System Pharmacy*
- *Annals of Pharmacotherapy*
- *Pharmacotherapy*
- *American Journal of Medicine*
- *Annals of Internal Medicine*
- *Journal of American Medical Association*
- *Lancet*
- *New England Journal of Medicine*

As one becomes familiar with these literature sources, it becomes easier to investigate and assess suspected ADRs. Also, frequent perusal of the primary literature provides knowledge that can be instrumental in early detection and treatment of ADRs.

References

1. Kessler DA. Introducing MEDWatch. A new approach to reporting medication and device adverse effects and product problems. *JAMA*. 1993;269(21):2765-2768.
2. American Society of Health-System Pharmacists. ASHP guidelines on adverse drug reaction monitoring and reporting. *Am J Health-Syst Pharm*. 1995;52(4):417-419.
3. World Health Organization (WHO). Requirements for adverse drug reaction reporting. Geneva, Switzerland: WHO; 1975.
4. Karch FE, Lasagna L. Adverse drug reactions. A critical review. *JAMA*. 1975;234(12):1236-1241.
5. Bennett BS, Lipman AF. Comparative study of prospective surveillance and voluntary reporting in determining the incidence of adverse drug reactions. *Am J Hosp Pharm*. 1977;34:931-936.
6. Michel DJ, Knodel LC. Comparison of three algorithms used to evaluate adverse drug reactions. *Am J Hosp Pharm*. 1986;43(7):1709-1714.

Resources

- American Society of Health-System Pharmacists. ASHP guidelines on adverse drug reaction monitoring and reporting. *Am J Health-Syst Pharm*. 1995;52(4):417-419.
- Calis KA, Young LR. Clinical analysis of adverse drug reactions: a primer for clinicians. *Hosp Pharm*. 2004;39:697-712.
- Griffin FA, Resar RK. *IHI Global Trigger Tool for Measuring Adverse Events*. 2nd ed. IHI Innovation Series white paper. Cambridge, MA: Institute for Healthcare Improvement; 2009. www.IHI.org.

Competence Checklist

Name: _____ Date: _____

KNOWLEDGE AND SKILLS	YES	NO
Able to define a significant ADR, according to the organization's policies		
Recognizes the procedure for reporting ADRs within the organization		
Identifies signs and symptoms that may be indicative of an ADR		
Recognizes the risk factors that increase a patient's potential for experiencing ADRs		
Demonstrates knowledge of the classes of medications that have an increased potential for causing ADRs		
Demonstrates knowledge of the types of surveillance methods used for detecting ADRs and the advantages and disadvantages of each		
Identifies triggers that may indicate potential ADRs		
Identifies and reports ADRs according to organizational policies and procedures		
Utilizes the Naranjo algorithm (or other appropriate criteria) to assess potential ADRs		
NOTES		

Competence certified by

Date

Competency Assessment Exam

Name: _____ Date: _____

1. What is your facility's current definition of a significant ADR?

- ___ 2. The ASHP definition of ADR includes _____.
 - a. Allergic reactions
 - b. Accidental poisonings
 - c. Idiosyncratic reactions
 - d. a and c

- ___ 3. A risk factor that increases a patient's potential for experiencing ADRs is _____.
 - a. No history of allergies
 - b. Normal renal function
 - c. Polypharmacy
 - d. b and c

- ___ 4. Which of the following classes of medications is frequently implicated in causing ADRs?
 - a. Vaccines
 - b. Anticoagulants
 - c. Antiemetics
 - d. a and b

- ___ 5. Which of the following symptoms may indicate the occurrence of an ADR?
 - a. Skin rash
 - b. Nausea and vomiting
 - c. Renal failure
 - d. All of the above

- ___ 6. Prospective surveillance for ADRs can be conducted by _____.
 - a. Monitoring patients who are taking medications frequently implicated in ADRs
 - b. Monitoring medication orders for triggers
 - c. Conducting random audits of medical records
 - d. a and b

- ___ 7. An advantage of concurrent surveillance of ADRs is it _____.
 - a. Is the most sensitive and specific method for detecting ADRs
 - b. Allows for timely intervention and management of ADRs
 - c. Is performed before the initiation of the medication
 - d. a and c

- ___ 8. Retrospective surveillance of ADRS _____.
- Is best conducted using decentralized pharmacists to monitor high-risk patients
 - Allows for timely intervention and management of ADRs
 - Involves review of medical records
 - b and c
- ___ 9. Which of the following criteria should be evaluated, if possible, when assessing the probability of a medication causing an ADR?
- Timing of events
 - Existence of a previously documented, known response to the medication
 - Discontinuation of the suspected medication
 - All of the above
- ___ 10. Which of the following suggest that an ADR may have taken place?
- Stat orders for antidotes
 - Unexpected reduction in dosage of a medication
 - Routine orders for laboratory tests
 - a and b
- ___ 11. ADRs are more likely to be detected by _____.
- Prospective surveillance
 - Concurrent surveillance
 - Retrospective surveillance
 - A combination of surveillance systems
- ___ 12. The Naranjo algorithm _____.
- Assesses the probability that a medication caused an ADR
 - Consists of 56 questions that are scored and totaled
 - Is used by the FDA
 - a and b
- ___ 13. When assessing ADRs, reference sources should be consulted to _____.
- Establish alternative causes that could have caused the ADR
 - Confirm previous documentation of the ADR in the medical literature
 - Gather information on the prognosis and outcome for the ADR
 - All of the above
- ___ 14. A primary literature source that may provide useful information on ADRs is _____.
- Facts and Comparisons*
 - AHFS Drug Information*
 - New England Journal of Medicine*
 - Micromedex Drugdex database

- ___ 15. A systematic approach to assessing ADRs involves gathering data about the patient including _____.
- a. Medications that the patient is taking
 - b. Medical conditions the patient is being treated for
 - c. The patient's medical insurance coverage
 - d. a and b

Competence certified by

Date

Answer Key

1. Answer is organization specific.
2. d. The ASHP definition of an ADR includes allergic reactions and idiosyncratic reactions but excludes accidental poisonings.
3. c. Polypharmacy is a risk factor that increases the potential for ADRs to occur.
4. b. Anticoagulants are frequently implicated in causing ADRs.
5. d. Symptoms that may indicate the occurrence of an ADR include skin rash, nausea and vomiting, and renal failure.
6. a. Monitoring patients who are taking medications frequently implicated in ADRs is a method of prospective surveillance. Monitoring medication orders for triggers is a method of concurrent surveillance for ADRs. Retrospective surveillance involves conducting random audits of medical records.
7. b. Concurrent surveillance allows for timely intervention and management of ADRs.
8. c. Retrospective surveillance involves review of medical records.
9. d. Criteria that should be evaluated when assessing the probability of a medication causing an ADR include timing of events; existence of a previously documented, known response to the medication; and discontinuation of the suspected medication.
10. d. Stat orders for antidotes and the unexpected reduction in dosage of a medication suggest that an ADR may have taken place.
11. d. ADRs are more likely to be detected by a combination of surveillance systems.
12. a. The Naranjo algorithm consists of 10 questions to assess the probability that a medication caused an ADR.
13. d. Reference sources should be consulted to establish alternative causes that could have caused the ADR, confirm previous documentation of the ADR in the medical literature, and gather information on the prognosis and outcome for the ADR.
14. c. The *New England Journal of Medicine* is a primary literature source that may provide useful information on ADRs. *Facts and Comparisons*, *AHFS Drug Information*, and the Micromedex Drugdex database are tertiary literature sources that provide information on ADRs.
15. d. Data used to assess ADRs include medications the patient is taking and medical conditions the patient is being treated for.