CHAPTER

27

Clinical Analysis of Adverse Drug Reactions

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INTRODUCTION

Adverse drug reactions (ADRs) are common, overlooked, expensive, serious, and under-reported. For the most part, our understanding of adverse reactions is based on anecdotal information that is reported on a voluntary basis, and these reports are commonly incomplete and even inaccurate [1–3]. However, Lazarou *et al.* [4] focused attention on the importance of ADRs in a careful meta-analysis of prospective ADR studies. These authors concluded that ADRs occurred in 10.9% of hospitalized patients, that serious ADRs accounted for 4.7% of hospital admissions, and that ADRs may rank somewhere between the fourth and sixth most common cause of death in the United States. Unfortunately, the frequency of ADRs remains unaffected by more than 10 years of process improvements such as use of order sets, care plans, computerized prescriber order entry, or other types of decision support systems [5].

There is general agreement that commonly used medications such as diuretics, anticoagulants, and antiplatelet and antidiabetic agents are implicated more often than high-risk agents [6–8]. Despite this, clinicians are left to make treatment decisions that usually are based on an imbalance of information about the benefit and harm of therapeutic options. Given the general lack of understanding of ADRs, clinicians may attribute a patient's symptoms to his or her underlying illness and not consider that these symptoms may be due to a potential ADR. By failing to consider an adverse drug reaction, even when faced with objective evidence to the contrary, clinicians may end up by adding a new agent to manage these symptoms instead of modifying the offending medication regimen [9]. This has the potential to initiate an entire cascade of adverse events [9, 10].

DEFINITIONS AND CLASSIFICATION

The terminology used to describe ADRs is confusing and frequently used incorrectly [9, 11, 12]. The US Food and Drug Administration (FDA) defines an ADR as any undesirable experience associated with the use of a medical product in a patient [13]. Edwards and Aronson [12] 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". When compared to an ADR, an *adverse event* (ADE) is a harmful outcome that presents during treatment with a medication and, as described in Chapter 28, includes some medication errors as well as ADRs. In an ADE there may not be enough information to even conclude that the event was caused by the medication [11, 12], Members of the Consolidated Standards of Reporting Trials (CONSORT) recommend use of the term "*Harms*" to refer to all possible adverse occurrences [11] (the sum of ADRs, ADEs, errors, plus other undesirable outcomes). Harms are the opposite of benefits [11].

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Classification by Severity

Classification of ADRs by severity allows comparisons to be made between medical teams or services, or, if standardized, to other medical centers, and a severity scale published by Hartwig *et al.* [14] is commonly used. A determination of severity is often necessary when setting priorities for actionable findings. The severity scale used by the authors of this chapter for clinical surveillance of adverse drug reactions is summarized in Table 27.1. This step-wise scale is graded by the expected consumption of resources in each level.

Classification by Type

ADRs can be considered as dose related (Type A) or not dose related (Type B) [15]. Type B reactions can be further subdivided into immunologic and idiosyncratic. Additional categories include time related, withdrawal, and failure of therapy [12]. The classification scheme used by the chapter authors is summarized in Table 27.2.

Pharmacologic ADRs

As pointed out over 40 years ago by Melmon [16], most pharmacologic ADRs are dose related and represent an exaggerated pharmacologic effect of the drug. This type of ADR can also be seen when reductions in renal clearance, due to renal insufficiency, or in non-renal clearance, due to hepatic disease or secondary to drug interactions, are not compensated for by reductions in the selected dose. Generally, these ADRs are predictable and reversible. They can be the result of a prescribing error, but are also seen during careful upward titration of doses to achieve a satisfactory therapeutic response.

TABLE 27.1 Definitions for the Determination of the Severity of an ADR

Minor:
Prolongation of hospital stay is not required. Therapy might include stopping the medication, reducing the dose, and/or administering palliative therapy. Additional testing or increased hospitalization is not required.
Moderate:
Requires further testing or procedures, to evaluate patient, or increases hospitalization by at least 1 day, or results in admission.
Serious:
Results in persistent or significant disability (e.g., hemorrhage requiring transfusion or hospitalization but without symptoms of hemodynamic instability) or results in transfer to critical care.
Serious life-threatening:
ex. Hemorrhage associated with hypotension, hypoglycemic encephalopathy, profound hyponatremia, and acute renal failure requiring hospitalization.
Serious lethal:
Contributes to the death of the patient.

TABLE 27.2 Surveillance Classification of ADRs by Type

1. *Pharmacologic*: These adverse effects are dose related and represent an exaggerated pharmacologic effect of the drug − for example a hypoglycemic event following an excessive dose of insulin, or symptomatic hypotension following an excessive dose of an antihypertensive medication
2. *Intolerance*: Refers to exaggerated pharmacologic effects seen at low doses of medication − for example, drowsiness following a very low dose of morphine, or dizziness from a low dose of diphenhydramine
3. *Idiosyncratic*: Reactions that are not predictable, and not related to dose or pharmacology − for example, muscle pain associated with statins
4. *Allergic*: Medication allergies are most commonly seen with antibiotics and are immune mediated reactions, such as hives, rashes of other types, bronchospasm

Idiosyncratic ADRs

Unlike pharmacologic ADRs, Type B ADRs, such as those described in Chapter 16, are not dose related and often are without an antidote. These ADRs include intolerance and allergic reactions as well as idiosyncratic drug reactions that cannot be explained by a known mechanism of drug action. Idiosyncratic ADRs are not seen at any dose in most patients, and thus are not classified as intolerance, but instead occur unpredictably and only in susceptible patients. It is important to be aware of idiosyncratic reactions because most severe and or life-threatening ADRs are idiosyncratic in nature and require discontinuation of treatment. As described in Chapter 16, these reactions result, in many cases, from patient differences in drug metabolism that result in accumulation of chemically reactive or otherwise toxic metabolites, or by variations in the human leukocyte antigen (HLA-B) complex. Severe dermatologic reactions to carbamazepine [17] and to allopurinol [18] are examples of HLA-B variation linked to ADRs. The Risk Evaluation and Mitigation Strategy (REMS), developed by the FDA and described later in this chapter, provides a systematic approach for improving medication safety, and tends to focus on these idiosyncratic reactions that are unpredictable yet severe.

Allergic ADRs

Medication allergies are considered as immune-mediated hypersensitivity and classified as one of the four types described by Gell and Coombs [19] and as expanded by Kay [20], or as an idiosyncratic drug hypersensitivity syndrome which generally involves fever, lymphadenopathy, rash, and internal organ involvement [21]. The Gell and Coombs Classification is summarized in Figure 27.1 [22].

ADR Detection

Hospitals generally have protocol-based strategies for preventing and detecting ADRs. Prevention is frequently achieved by a combination of pharmacist review or involvement at the time of prescription. [23–25]. Detection is often accomplished by a clinician observing conditions, laboratory values, or other data points indicating an ADR. For example, elevated plasma drug concentrations or prescription of reversal agents, such as digoxin-specific antibody fragments, have been used to trigger identification of potential adverse reactions [26–31]. This mode of surveillance can be enhanced by combining triggers such as use of vitamin K in a patient with an elevated INR value. Combining search terms is an effective method for reducing the number of false alerts [32]. Systematic use of a trigger tool has been reported to result in a significant increase in the number of recognized adverse events [33, 34].

Surveillance has successfully identified a number of avoidable high-risk situations, as well as medications whose proper use is misunderstood. Digoxin, phenytoin, theophylline, and warfarin toxicities can be avoided by (1) reacting to predictable changes in drug clearance secondary to renal or hepatic insufficiency or due to drug–drug interactions, and (2) proper interpretation of non-steady-state or spurious serum concentration (e.g., due to improperly timed blood sampling) or other laboratory values such as the INR [28–30]. Careful assessment and documentation of medication allergy histories is necessary to prevent future allergic reactions, or to avoid use of unnecessary alternative medications when true allergy symptoms did not occur [35, 36].

Although ADRs have traditionally been identified by voluntary, retrospective reporting, several concurrent studies have found that adding a pharmacist to the medical team at the decision-making stage

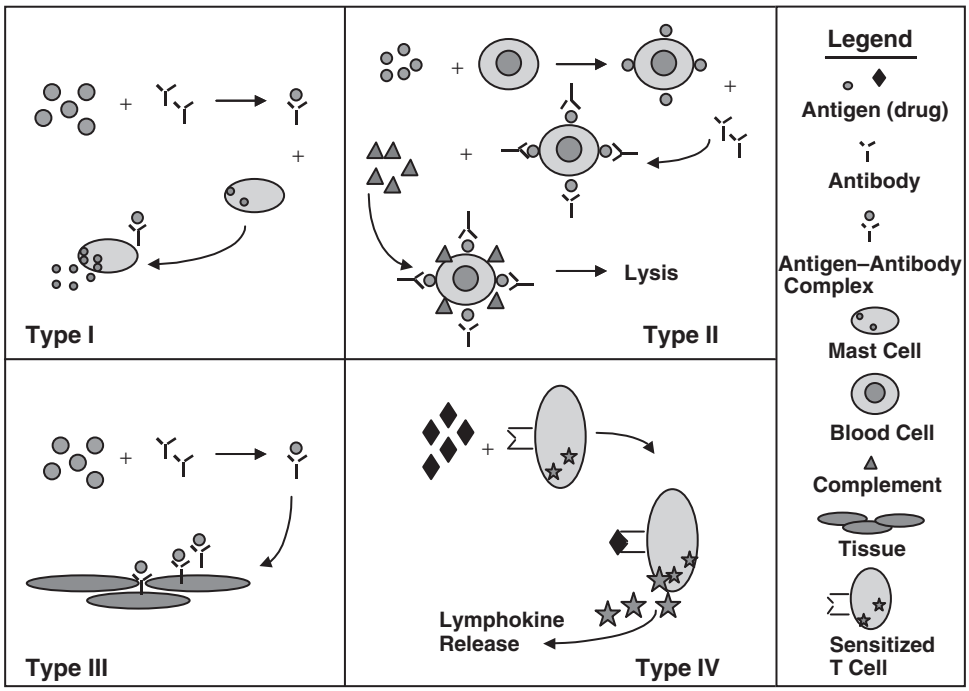

FIGURE 27.1 Mechanisms of hypersensitivity reactions. Type I: Antigens bind to antibodies on mast cells, causing degranulation and release of histamine and other mediators. Type II: Antibodies attach to cell-surface antigens, causing activation of complement or other effector cells (neutrophils, K lymphocytes, etc.) resulting in cell damage and cell death. Type III: Antigen–antibody complexes are deposited in tissue. Type IV: T cells are sensitized to a specific antigen, thereby causing lymphokine release. Reproduced with permission from Young LR, Wurtzbacher JD, Blankenship CS. Am J Manag Care 1997;3:1884–906 [22].

improves reporting and reduces the frequency of all adverse events [24, 27]. Decision support systems such as computerized physician order entry or pharmacy information systems are often used in a concurrent manner to identify at-risk scenarios [37]. Surveillance systems continue to add value to the medication-use process. Surveillance methods recently successfully identified bleeding risks associated with low molecular weight heparin dosing in patients with renal insufficiency [38], harms associated with epoetin alpha [39] and thiazolidinediones [40], and fatalities found with off-label use of dronedarone [41] and dabigatran [42]. An active retrospective approach, or even a prospective surveillance approach, is necessary, as many potential ADRs are unrecognized or are never reported, thus escaping detection and preventing flaws in the medication-use process from being corrected [26, 43].

Determining Causality

It is difficult to determine if patients are experiencing an ADR to a medication or if the noted symptoms are caused by their underlying disorder or worsening of their condition, because the symptoms caused by ADRs are sometimes similar to disease symptoms (e.g., headache caused by excessive consumption of NSAIDs such as aspirin, or increases in patient temperature following administration of empiric broad-spectrum antibiotics) [44]. To overcome this problem, several rating scales have been developed to relate symptoms to medications [12, 45]. An ADR usually occurs shortly after the initiation of a treatment, and symptoms frequently begin to improve once treatment is stopped. It is clear that the event is an adverse drug reaction if administration of a specific antidote provides a dramatic improvement in symptoms. This is seen when naloxone is used to reverse excessive effects of an opioid. An ADR is often related to the mechanism of action of the medication, or is one of a series of known examples of intolerance or idiosyncratic reactions. Sometimes there is laboratory confirmation of the ADR (for example, elevated blood concentrations of the medication), and at times the patient may describe a similar reaction to this medication in the past. This process of causality assessment is summarized in Table 27.3 and an example is provided in Table 27.4. Definitions are listed in Table 27.5, and the widely-used Naranjo scoring system is described in Table 27.6 [45]. Determining the proper diagnosis can prevent patient exposure to additional and unnecessary medications, and proper documentation of the diagnosis of an ADR can prevent future occurrences [9, 10].

TABLE 27.3 Causality Checklist

Is the reaction timely to medication initiation?
Is resolution timely to discontinuation?
Response to antidote or reversal agent?
Other plausible explanations and medications are ruled out?
Objective confirmation?
Reaction resumes if rechallenged?

ASSESSING ADR RISK

The search for ADR information appropriately begins with the review of the approved labeling for the specific drug or drugs. Supplemental safety information also is provided by both the FDA and international regulatory agencies. In addition, ADR risk can be assessed from the published literature on ADRs, which is largely comprised of case reports and sometimes reviews. Tertiary drug resources, including books and databases, also can provide ADR information. Finally, one may consider contacting a drug's manufacturer for information beyond what appears in the approved labeling.

Evaluating Drug Labels for ADR Risk

In addition to the Adverse Reactions section of the approved labeling, other sections of the label should

TABLE 27.4 Clinical Example: Determining the Causality of an ADR

Problem: Suspected corticosteroid induced hyperglycemia seen during rCHOP[a] regimen for non-Hodgkin's lymphoma.
Time frame: Hyperglycemia seen with scheduled lab work 1 week after first course. Resolved upon review of labs 2 weeks after first course. Repeats after rechallenge during second course of rCHOP. HA1C remains at baseline throughout six-course regimen.
Analysis: Reaction is timely to initiation, withdrawal and rechallenge with suspected agent. Confirmed by laboratory results. Patient does not have type 1 diabetes, and does not meet criteria for type 2 diabetes. Prednisone is the only component of rCHOP known to promote hyperglycemia.
Conclusion: Naranjo score of 8; probable hyperglycemic reaction to high-dose prednisone.

[a]rCHOP: rituximab, cyclophosphamide, hydroxydaunorubicin (doxorubicin), Oncovin®, (vincristine), prednisone.

TABLE 27.5 Criteria for the Classification of Causality of Potential ADRs

Unlikely	• Untimely relationship to treatment or • Reversible symptoms continue after stopping treatment
Possible	• Timely relationship to treatment and • Therapy is continued or • Reversible symptoms resolve upon discontinuation and negative response to rechallenge
Probable	• Timely relationship to treatment and • Reversible symptoms resolve upon discontinuation • No rechallenge
Definite	• Timely relationship to treatment and • Reversible symptoms resolve upon discontinuation • Positive response to rechallenge

TABLE 27.6 The Naranjo Adverse Drug Reaction Probability Scale

To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score	Yes	No	Do not know	Score
1. Are there previous *conclusive* reports on this reaction?	+1	0	0	
2. Did the adverse event occur 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 reaction reappear when the drug was re-administered?	+2	−1	0	
5. Are there alternative causes (other than the drug) that could have on their own caused the reaction?	−1	+2	0	
6. Did the reaction reappear when a placebo was given?	−1	+1	0	
7. Was the medication 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	
The ADR is assigned to a probability category from the total score as follows: *definite* if the overall score is 9 or greater, *probable* for a score of 5−8, *possible* for 1−4, and *doubtful* if the score is 0			Total	

Reproduced with permission from Naranjo CA, Busto U, Sellers EM *et al.* Clin Pharmacol Ther. 1981; 30:239–45 [45].

be examined as these may contain important information along with important guidance. For example, the significant known ADRs also will usually be included in one or more of the sections for Contraindications, Precautions, or Warnings. Black Box Warnings are usually placed at the very beginning of the product information to give prominence to the most serious known risks. Because one study identified inconsistencies between drug information resources and the manufacturer's prescribing information, with some key elements of the official boxed warning missing in the drug information resources, the current label may be the most reliable source for the complete boxed warning for a given drug [46]. For this reason, clinicians are well advised to reach beyond the drug resources they commonly use and to consult sources that provide the most up-to-date approved labeling, such as DailyMed or Drugs@FDA.

Drug labels use a number of methods to categorize ADRs, but the most common is to list ADRs by frequency of occurrence [47]. For example, the package insert for dronedarone (Multaq™) states that "Most common adverse reactions ($\geq 2\%$) are diarrhea, nausea, abdominal pain, vomiting and asthenia" (see Table 27.7) [48]. The frequency method provides an idea of what ADRs can be expected and of the frequency with which they can be anticipated. Unfortunately, since serious ADRs are rare for products that receive marketing approval, they are often missing from lists based on frequency. Also, this

TABLE 27.7 Comparison of Frequency-Based ADR Reporting to a REMS

Adverse effects: Dronedarone
Most common adverse reactions ($\geq$ 2%) are diarrhea, nausea, abdominal pain, vomiting and asthenia
(Official Prescribing Information Sanofi–Aventis, 2011, accessed May 17, 2011)
REMS: Dronedaron
There is a risk mitigation strategy in place for dronedarone
Goals:
• To **prevent** use in patients with NYHA Class IV heart failure or Class II–III heart failure with recent decompensation requiring hospitalization or referral to a specialized heart unit
• To inform healthcare professionals and patients about the serious risks including increased mortality in patients with severe unstable heart failure and signs and symptoms of liver injury
(FDA: Approved REMS accessed May 17, 2011)
Note the focus on prevention of serious adverse effects seen in the REMS

approach is a passive approach to understanding ADRs, and it would be more useful to include a risk-mitigation approach that specifies actions to prevent ADRs, such as shown in Table 27.7 for dronedarone.

The focus of drug labels does change to ADR prevention in the sections that specify contraindications, warnings, and precautions. Contraindications describe situations in which the drug should absolutely NOT be used. The warnings and precaution section provides a summary of clinically significant adverse reactions and how to avoid them [47]. All three of these sections should be considered when evaluating the potential for harm that is associated with each treatment option.

Safety Alerts from FDA and International Regulators

FDA Safety Alerts are a valuable source of ADR risk information, and they can be easily accessed online at MedWatch Safety Alerts for Human Medical Products [49]. The following example illustrates the evolution of a drug safety issue. A May 21, 2007 FDA alert first described the differing rate of ischemic cardiovascular events (some fatal) associated with Avandia® (rosiglitazone) relative to other drugs used for the treatment of type 2 diabetes mellitus [50]. As additional data were analyzed, this led to the August 2007 notice of changes to the prescribing information for rosiglitazone that included a new boxed warning about the potential increased risk of myocardial ischemia [51]. Finally, in September 2010, the FDA announced its intent to significantly restrict the use of rosiglitazone and require that the manufacturer develop a restricted access program under a REMS [52].

The point of the above sequence is that one can be alerted to a safety issue at the very early stages of its recognition and can proactively adopt a more restrained and vigilant approach to the use of drugs with emerging safety concerns, particularly when safer therapeutic alternatives exist. Clinicians can obtain such emerging safety information by directly subscribing to the FDA's free e-mail subscription service and setting one of the preferences for MedWatch Safety Alerts (https://public.govdelivery.com/accounts/USFDA/subscriber/new). This will assure prompt delivery of new safety information for all human medical products, including prescription drugs, over-the-counter drugs, biologicals, and vaccines. The FDA also posts quarterly reports listing potential signals of the serious safety risks identified in FDA's Adverse Event Reporting System (AERS) database. These can be accessed at: www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082196.htm.

In addition, clinicians might find notice of medication issues that have not yet been raised by the FDA from international health regulators, such as Health Canada and EMEA. Health Canada's Advisories, Warnings, and Recalls for Health Professionals page can be accessed at www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/index-eng.php. An example is the advisory about the possible association of mycophenolate mofetil with red cell aplasia that was issued by Health Canada on June 3, 2009 [53]. This was later communicated by the FDA on August 14, 2009 [54]. Health Canada's website also offers a free e-mail subscription service to receive such notices. The European Medicines Agency (EMA) is responsible for the evaluation of medicines developed by pharmaceutical companies intended for use in the European Union. The EMA also provides notices of important patient safety information on their website at www.ema.europa.eu/ema/index.jsp?curl=pages/home/Home_Page.jsp&mid=.

Evaluating Publications for ADR Risk

In theory, a published clinical trial provides the best opportunity for a clinician to obtain a systematic analysis of a particular medication's ADR risk. In practice, the reader should proceed cautiously and carefully to evaluate the provided safety information, as outlined in Table 27.8. The first step is to determine if ADRs are even reported in the publication, as a surprising percentage (20–30%) do not even report ADRs [55–59]. It should not be assumed that the absence of safety reporting is evidence of safety, and publications that exclusively report on favorable information should be discarded. Specialty publications and high-impact journals are equally implicated. When safety is reported, the methodology should be carefully assessed and the reader should note how adverse effects were identified by the investigators. Spontaneous reporting and other methods of passively collecting ADRs may overlook important information. The final step is to verify that the subjects in the study are similar to the patients you plan to treat. Age, severity of illness, other illnesses and medications are important exclusions to note.

A high-quality publication will follow a systematic approach to collect safety information and use an active adverse event surveillance system based upon a validated checklist. The publication should report results of prespecified objective safety endpoints, while accounting for all patient withdrawals because of ADRs. Unfortunately, only about 20% of publications report adverse effects using this systematic approach, and the usefulness of data from many clinical trials is compromised by the absence of ADR reporting and by weak methodology [11].

Although adverse reactions sections in a tertiary reference or drug database may be consulted (AHFS DI, Clinical Pharmacology, Micromedex, eFacts, etc.), it should be recognized that the ADR information found there is in great part taken from the clinical trials submitted to the FDA as part of a drug's approval process. As postmarket surveillance findings may emerge that supplement this initial information, these can result in important modifications of a drug's approved labeling by the FDA. However, retrieval of the primary literature is time consuming, so shortcuts to citations from tertiary resource references can help establish a starting point from which one can proceed to related articles. For example, when viewing such a citation in MEDLINE, one can examine the links to related citations or the Medical Subject Heading (MeSH) tags to further the search. Web of Science can similarly help map a given citation forward to subsequent articles that have referenced it.

TABLE 27.8 Evaluating a Publication for ADRs

Are adverse events actually reported?
Passive or active surveillance used to identify AE?
Is a validated checklist available?
Are pre-specified objective endpoints reported?
Are patient withdrawals because of adverse events reported?
Are AE reported in the abstract, methods, and results section?
Discussion includes a balanced discussion of harms and benefits?
Is there external validity?

Adapted from Ionnidis PA, Evans S, Gotzsche P *et al.* Ann Intern Med 2004;141:781–8 [11].

Risk Associated with Recently Approved Drugs

Clinicians should exercise caution before prescribing a recently approved medication, particularly when using it outside of the inclusion criteria used for the drug registration trial [10, 60, 61]. The design of the drug research studies that are conducted to obtain marketing approval limits their ability to detect rare yet serious ADRs. These studies are designed to see if the medication can show benefit under optimal circumstances, and a study with many fewer exclusion criteria would be needed in order to show benefit and safety under the usual conditions of clinical care [61]. Unfortunately, the cost and time necessary to conduct studies with this high level of external validity would be prohibitive, so most studies limit their enrollment to only the healthiest of eligible patients [62, 63]. These groups of included study patients often are not representative of the population that will receive the medication after marketing [62]. Jadad [64] reports that patients with multiple chronic diseases were excluded from 63% of published randomized controlled trials. Other limiting factors inherent in the design of these studies include the small numbers of patients receiving the study medication, and their short duration. Thus, the structure of drug development trials, including use of a controlled setting, documented patient compliance, short-term and intermediate outcomes, and low external validity, is very different from what is encountered in clinical practice, and ADR risk may be much higher in the clinical setting when compared to the research setting [10, 61]. For these reasons, prescribing decisions should be guided by giving first consideration to medications having an established track record of safety and efficacy, and clinicians should avoid succumbing to marketing-based claims, such as are often made for novel compounds with a unique mechanism of action [10].

Risk Associated with Off-Label Prescribing

The risk of an ADR is magnified when a drug is prescribed for an off-label indication or in a dose that exceeds that recommended in the package insert. Off-label prescribing is particularly likely to occur with new drugs. For example, an oral anticoagulant may be approved for thrombosis prevention, but not for treatment, and yet prescribers may try to use it for treatment. Both efficacy and safety evidence may be unavailable to support risk–benefit decisions for an unapproved use. Besides anticoagulants, many other drugs, due to their inherent high risk (antiarrhythmics, chemotherapeutics, hypoglycemics, opioids, skeletal muscle blockers, etc.), must be assumed to pose elevated risk with uncertain benefit when used off-label. Ultimate evidence may emerge that expected efficacy endpoints are not attained, yet patients are exposed to predictable adverse effects [65].

The enhanced risk of off-label prescribing can be evaluated by a *safety specification study* that compares the frequency of reported ADRs between patients receiving a medication for its labeled indications to the ADRs seen when the medication is used off-label. This information provides an early warning about types of patients or situations that are at a particularly high ADR risk [62]. Safety specification studies might also warn about drug–drug or drug–diet interactions and special risks for female patients, children, elderly, or other types of patients that are often excluded from registration trials. Both comparative effectiveness and safety specification studies offer new research opportunities for clinicians interested in identifying and preventing adverse drug reactions.

MINIMIZING AND MANAGING ADRS

Risk Evaluation and Mitigation Strategy (REMS)

In 2005, the FDA announced a plan to incorporate pharmacovigilance into its drug approval process. The plan was named *Risk Minimization Action Plans*, often referred to as RiskMAPs. A RiskMAP could be recommended for a particular medication because of the type or frequency of known risks when compared to expected benefits, such as for a drug that has a high risk of side effects but is the only option to treat a serious condition (e.g., an anticancer agent, particularly when failure to treat might be fatal). A RiskMAP might also be recommended for a high-risk medication used to treat elderly patients, children, or patients with renal failure for whom there is limited availability of alternative treatments. Finally, a RiskMAP could be recommended for a high-risk drug when there is a remedy that can prevent or reverse the ADR (e.g., vitamin K used to reverse the effects of warfarin) [63].

In 2007, the Food and Drug Administration Amendments Act (FDAA) was signed into law and Title IX was enacted the following year to provide the FDA with the authority to place medication safety requirements on drug sponsors. As a result, the FDA developed Risk Evaluation and Mitigation Strategies (REMS) that evolved from and are very similar to RiskMAPs [63]. The FDA now has authority under REMS to include fines as an enforcement mechanism. Most products do not require a REMS or a RiskMAP, and it is not required as part of an FDA submission for marketing approval (although many applications do include a REMS). However, the availability of these risk-mitigation strategies is thought to be necessary to ensure that a drug's benefits outweigh its risks of serious ADRs, and a requirement for either can be identified after a medication is placed on the market [66, 67]. A REMS is unique to a medication, is a result of a negotiation between the FDA and the sponsor, and is based on the occurrence of ADRs either in clinical trials or subsequent to marketing.

Traditionally, contraindications are added to a drug's label for conditions or circumstances in which its risks are expected to outweigh its benefits. A Black Box Warning may subsequently be added to the label if prescribers do not adhere to these contraindications. Currently, there are more than 500 medications that have a Black Box Warning, often meaning that earlier contraindication warnings did not change prescribing in the face of known risk factors for adverse events. In fact, between 1995 and 2007 there were 174 biological products approved by the FDA and European regulatory agencies, and 19 Black Box Warnings were issued for 47 (23.6%) of these products [68]. However, under a REMS approach many potential contraindications can be spelled out initially under a REMS so that a new medication can be approved for marketing even before clear evidence has emerged that its benefits outweigh its risks. This has permitted faster approval of drugs for a broader range of indications and with warnings that are less restrictive than contraindications. A medication eligible for a REMS may have a unique REMS requirement since different drugs have different adverse effects, different mechanisms of action, and therefore different risks. Thus, a REMS for a cardiovascular medication may need to be very different from a REMS for an analgesic [69]. The goal of the REMS approach is to help clinicians avoid many serious ADRs by becoming aware of these warnings before they either prescribe or advise a prescriber to order a medication for a patient.

Managing ADRs

Information on managing ADRs, other than discontinuation of suspected offending agents, can often be unsatisfactory, with little or no guidance to be found. Therefore, while information may well be acquired from an array of sources, answers remain lacking to many practical questions, such as if continued use will lead to progression or regression of an ADR, or how long after drug discontinuation will it take for ADRs to resolve. A practical approach to managing suspected ADRs is certainly needed. Whenever it is reasonably clear that a specific drug is causal, there should be a re-evaluation for its need and consideration of therapeutic alternatives with an unlikely association to the ADR. If the ADR is likely a dose-related one, a dose reduction may be all that is needed, rather than changing treatments. In a few cases, treatment with an antidote may be warranted (e.g., administration of vitamin K to a patient over-anticoagulated with warfarin). When a patient is taking multiple drugs that fall under ADR suspicion, eliminating those least essential to care one at a time is a reasonable approach to follow.

Actual clinical experience can provide useful insight into the types of ADRs that are commonly encountered. For example, a recent publication was based on a retrospective evaluation of queries related to ADRs received by the Drug Information Center (DIC) of a tertiary care teaching hospital over a period of three and a half years [70]. In that report, 600 (25.9%) of the 2312 DIC queries were related to ADRs. The organ system most commonly involved was the nervous system (14.7%), antibacterials were the most commonly drug class involved (18.6%), and phenytoin was the single drug that most frequently caused ADRs (35%).

The authors of this chapter have conducted a similar retrospective evaluation of 289 ADR-related inquiries that they received. The purpose of the ADR questions is summarized in Table 27.9, and was to obtain evidence for a particular suspected drug–ADR association or to request a review of a complete medication regimen in order to determine the likely drug or drugs that might be causing a specific ADR. Suspected neurologic ADRs were cited most frequently, in 14% of the questions, and the majority of those fell within the following types in descending order: hearing changes, neuromuscular issues, paresthesias, seizure-related, cognitive impairment, hallucinations, sedation, movement disorders, coma, and confusion. Allergy or hypersensitivity reactions were the next largest group of patient-specific ADR questions, and included questions about alternative therapy for patients who had experienced ADRs in the past.

Inquirers asked about specific drugs in 247 of the 289 patient-specific ADR questions. Psychiatric drugs were asked about most often (16%), followed by anti-infective drug questions (11%). The anti-infective drug

TABLE 27.9 Reasons for 289 Inquiries Concerning ADRs in Specific Patients

Reason for inquiry	Patient currently suspected of having ADR occurrence	Patient had past ADR occurrence prompting screening to avoid recurrence with same or related drug	Screening for ADR issue in advance of planned initial drug exposure	Total
Locate evidence that a specific drug or drugs are associated with a specific ADR	108 (37.4%)		7 (2.4%)	115 (39.8%)
Help determine likely cause of a specific ADR (requiring review of regimen with >1 medication)	53 (18.3%)			53 (18.3%)
Provide guidance on managing a specific ADR	13 (4.5%)			13 (4.5%)
Help determine suitable alternative to a medication that is causing or caused a specific ADR	2 (0.7%)	5 (1.7%)	5 (1.7%)	12 (4.2%)
Provide information to prevent or minimize a specific ADR of concern	2 (0.7%)	24 (8.3%)	59 (20.4%)	85 (29.4%)
Provide general information on a specific ADR or a range of ADRs			11 (3.8%)	11 (3.8%)
Total	178 (61.6%)	29 (10%)	82 (28.4%)	289 (100%)

questions were primarily about renal effects or allergy/hypersensitivity reactions, but also included requests to locate evidence that a specific drug was associated with a particular ADR, or were requests for information to prevent or minimize a specific ADR of concern, such as prevention of an allergic or hypersensitivity reaction. The majority of the ADR inquiries came from physicians about specific patients who were suspected of having an ADR. These inquiries sought evidence about the strength of association of an ADR with a drug. Less frequently, the physician was attempting to screen for ADR issues in advance of starting therapy, in some cases prompted by a prior ADR occurrence.

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