67 Principles of Clinical Pharmacology

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Drugs are the cornerstone of modern therapeutics. Nevertheless, it is well recognized among health care providers and the lay community that the outcome of drug therapy varies widely among individuals. While this variability has been perceived as an unpredictable, and therefore inevitable, accompaniment of drug therapy, this is not the case.

Drugs interact with specific target molecules to produce their beneficial and adverse effects. The chain of events between administration of a drug and production of these effects in the body can be divided into two components, both of which contribute to variability in drug actions. The first component comprises the processes that determine drug delivery to, and removal from, molecular targets. The resulting description of the relationship between drug concentration and time is termed *pharmacokinetics*. The second component of variability in drug action comprises the processes that determine variability in drug actions independent of variability in drug delivery to effector drug sites. This description of the relationship between drug concentration and effect is termed *pharmacodynamics*. As discussed further below, pharmacodynamic variability can arise as a result of variability in function of the target molecule itself or of variability in the broad biologic context in which the drug-target interaction occurs to achieve drug effects. The principles described below were developed by studying small drug molecules but are equally useful in describing the effects of very large molecules, such as the therapeutic antibodies increasingly applied to autoimmune diseases and cancer.

Two important goals of clinical pharmacology are (1) to provide a description of conditions under which drug actions vary among human subjects; and (2) to determine mechanisms underlying this variability, with the goal of improving therapy with available drugs as well as pointing to mechanisms whose targeting by new drugs may be effective in the treatment of human disease. The drug development process is briefly described at the end of this chapter.

The first steps in the discipline of clinical pharmacology were empirical descriptions of the influence of disease on drug actions and of individuals or families with unusual sensitivities to adverse drug reactions (ADRs). These important descriptive findings are now being replaced by an understanding of the molecular mechanisms underlying variability in drug actions. Importantly, it is often the personal interaction of the patient with the physician or other health care provider that first identifies unusual variability in drug actions; maintained alertness to unusual drug responses continues to be a key component of improving drug safety.

One useful unifying framework is to consider that the effects of disease, drug coadministration, or familial factors in modulating drug action reflect variability in expression or function of specific genes whose products determine pharmacokinetics and pharmacodynamics. This idea forms the basis for pharmacogenomic science; a few examples are cited in this chapter, and further details are addressed in Chap. 68.

GLOBAL CONSIDERATIONS

It is true across all cultures and diseases that factors such as compliance, genetic variants affecting pharmacokinetics or pharmacodynamics (which themselves vary by ancestry), and drug interactions contribute to drug responses. Cost issues or cultural factors may determine the likelihood that specific drugs, drug combinations, or over-the-counter (OTC) remedies are prescribed. The broad principles of clinical pharmacology enunciated here can be used to analyze the mechanisms underlying successful or unsuccessful therapy with any drug.

INDICATIONS FOR DRUG THERAPY: RISK VERSUS BENEFIT

It is self-evident that the benefits of drug therapy should outweigh the risks. Benefits fall into broad categories: alleviation of symptoms, prevention of disease progression or complications, and prolonged life. However, establishing the balance between risk and benefit for an individual patient is not always simple. In addition to variability seen even within highly controlled drug trials, patients treated in clinical settings may display responses that were not observed in trials, sometimes due to comorbidities that were trial exclusion criteria. In addition, therapies that provide symptomatic benefits but shorten life may be entertained in patients with serious and highly symptomatic diseases such as heart failure or cancer. These considerations illustrate the continuing, highly personal nature of the relationship between the prescriber and the patient.

Adverse Effects Some adverse effects are so common and so readily associated with drug therapy that they are identified very early during clinical use of a drug. By contrast, serious ADRs may be sufficiently uncommon that they escape detection for many years after a drug begins to be widely used. The issue of how to identify rare but serious ADRs (that can profoundly affect the benefit-risk perception in an individual patient) has not been satisfactorily resolved. Potential approaches range from an increased understanding of the molecular and genetic basis of variability in drug actions to expanded postmarketing surveillance mechanisms. None of these have been completely effective, so practitioners must be continuously vigilant to the possibility that unusual symptoms may be related to specific drugs, or combinations of drugs, that their patients receive.

Therapeutic Index Beneficial and adverse reactions to drug therapy can be described by a series of dose-response relations (Fig. 67-1). Well-tolerated drugs demonstrate a wide margin, termed the *therapeutic ratio*, *therapeutic index*, or *therapeutic window*, between the doses required to produce a therapeutic effect and those producing toxicity. In cases where there is a similar relationship between plasma drug concentration and effects, monitoring plasma concentrations can be a highly effective aid in managing drug therapy by enabling concentrations to be maintained above the minimum required to produce an effect and below the concentration range likely to produce toxicity. Such monitoring has been widely used to guide therapy with specific agents, such as certain antiarrhythmics, anticonvulsants, and antibiotics. Many of the principles in clinical pharmacology and

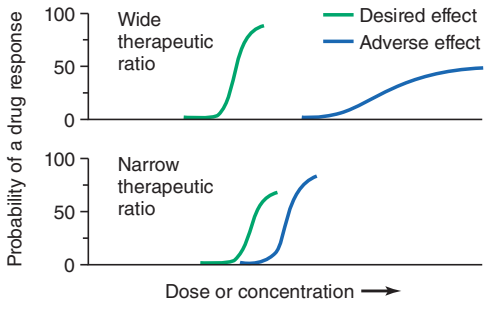

FIGURE 67-1 The concept of a therapeutic ratio. Each panel illustrates the relationship between increasing dose and cumulative probability of a desired or adverse drug effect. ***Top.*** A drug with a wide therapeutic ratio, that is, a wide separation of the two curves. ***Bottom.*** A drug with a narrow therapeutic ratio; here, the likelihood of adverse effects at therapeutic doses is increased because the curves are not well separated. Further, a steep dose-response curve for adverse effects is especially undesirable, as it implies that even small dosage increments may sharply increase the likelihood of toxicity. When there is a definable relationship between drug concentration (usually measured in plasma) and desirable and adverse effect curves, concentration may be substituted on the abscissa. Note that not all patients necessarily demonstrate a therapeutic response (or adverse effect) at any dose and that some effects (notably some adverse effects) may occur in a dose-independent fashion.

examples outlined below, which can be applied broadly to therapeutics, have been developed in these arenas.

PRINCIPLES OF PHARMACOKINETICS

The processes of absorption, distribution, metabolism, and excretion—collectively termed *drug disposition*—determine the concentration of drug delivered to target effector molecules.

ABSORPTION AND BIOAVAILABILITY

When a drug is administered orally, subcutaneously, intramuscularly, rectally, sublingually, or directly into desired sites of action, the amount of drug eventually entering the systemic circulation may be less than with the intravenous route (Fig. 67-2*A*). The fraction of drug available to the systemic circulation by other routes is termed *bioavailability*. Bioavailability may be <100% for two main reasons: (1) incomplete absorption, or (2) metabolism or elimination prior to entering the systemic circulation.

Compared to the same dose given intravenously, a nonintravenous dose will have a later and lower peak plasma concentration (Fig. 67-2). Drug absorption may be reduced because a drug is incompletely released from its dosage form, undergoes destruction at the site of administration, or has physicochemical properties such as insolubility that prevent complete absorption from its site of administration. Slow absorption rates are deliberately designed into "slow-release" or "sustained-release" drug formulations in order to minimize variation in plasma concentrations during the interval between doses. Therapeutic antibodies administered subcutaneously may take days to reach the systemic circulation.

"First-Pass" Effect When a drug is administered orally, it must traverse the intestinal epithelium, the portal venous system, and the liver prior to entering the systemic circulation (Fig. 67-3). Once a drug enters the enterocyte, it may undergo metabolism, be transported into the portal vein, or be excreted back into the intestinal lumen. Both excretion into the intestinal lumen and metabolism decrease bioavailability. Once a drug passes this enterocyte barrier, it may also be taken up into the hepatocyte, where bioavailability can be further limited by metabolism or excretion into the bile. This elimination in intestine and liver, which reduces the amount of drug delivered to the systemic circulation, is termed *presystemic elimination*, *presystemic extraction*, or *first-pass elimination*.

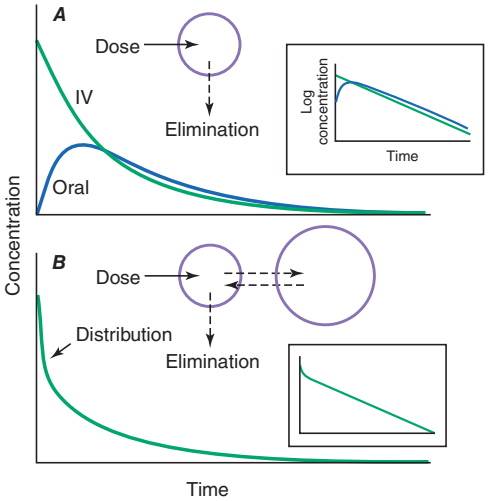

FIGURE 67-2 Idealized time-plasma concentration curves after a single dose of drug. ***A.*** The time course of drug concentration after an instantaneous intravenous (IV) bolus or an oral dose in the one-compartment model shown. The area under the time-concentration curve is clearly less with the oral drug than the IV drug, indicating incomplete bioavailability. Note that despite this incomplete bioavailability, concentration after the oral dose can be higher than after the IV dose at some time points. The inset shows that the decline of concentrations over time is linear on a log-linear plot, characteristic of first-order elimination, and that oral and IV drugs have the same elimination (parallel) time course. ***B.*** The decline of central compartment concentration when drug is distributed both to and from a peripheral compartment and eliminated from the central compartment. The rapid initial decline of concentration reflects not drug elimination but distribution.

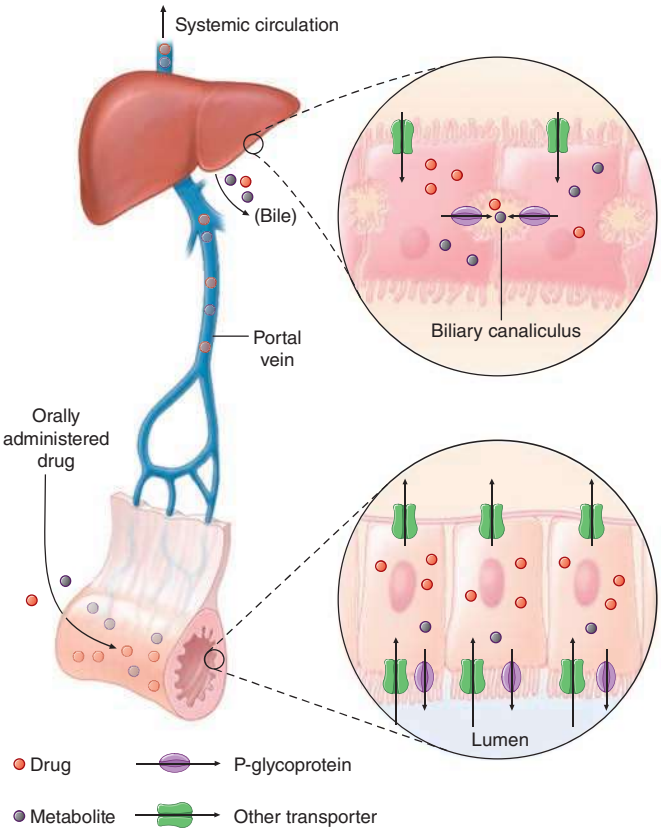

FIGURE 67-3 Mechanism of presystemic elimination. After drug enters the enterocyte, it can undergo metabolism, excretion into the intestinal lumen, or transport into the portal vein. Similarly, the hepatocyte may accomplish metabolism and biliary excretion prior to the entry of drug and metabolites to the systemic circulation. *(Adapted by permission from DM Roden, in DP Zipes, J Jalife [eds]: Cardiac Electrophysiology: From Cell to Bedside, 4th ed. Philadelphia, Saunders, 2003. Copyright 2003 with permission from Elsevier.)*

DRUG TRANSPORT

Drug movement across the membrane of any cell, including enterocytes and hepatocytes, is a combination of passive diffusion and active transport, mediated by specific drug uptake and efflux molecules. One widely studied drug transport molecule is the drug efflux pump P-glycoprotein, the product of the *ABCB1* (or *MDR1*) gene. P-glycoprotein is expressed on the apical aspect of the enterocyte and on the canalicular aspect of the hepatocyte (Fig. 67-3). In both locations, it serves as an efflux pump, limiting availability of drug to the systemic circulation. P-glycoprotein–mediated drug efflux from cerebral capillaries limits drug brain penetration and is an important component of the blood-brain barrier. Other transporters mediate uptake into cells of drugs and endogenous substrates such as vitamins or nutrients.

DRUG METABOLISM

Drug metabolism generates compounds that are usually more polar and, hence, more readily excreted than parent drug. Metabolism takes place predominantly in the liver but can occur at other sites such as kidney, intestinal epithelium, lung, and plasma. Phase I metabolism involves chemical modification, most often oxidation accomplished by members of the cytochrome P450 (CYP) monooxygenase superfamily. CYPs and other molecules that are especially important for drug metabolism are presented in Table 67-1, and each drug may be a substrate for one or more of these enzymes. Phase II metabolism involves conjugation of specific endogenous compounds to drugs or their metabolites. The enzymes that accomplish phase II reactions include glucuronyl-, acetyl-, sulfo-, and methyltransferases. Drug metabolites

TABLE 67-1 Molecular Pathways Mediating Drug Disposition

ENZYME	SUBSTRATES[a]	INHIBITORS[a]
CYP3A	Calcium channel blockers	Amiodarone
	Antiarrhythmics (lidocaine, quinidine, mexiletine)	Ketoconazole, itraconazole
	HMG-CoA reductase inhibitors ("statins"; see text)	Erythromycin, clarithromycin
	Cyclosporine, tacrolimus	Ritonavir
	Indinavir, saquinavir, ritonavir	Gemfibrozil and other fibrates
CYP2D6[b]	Timolol, metoprolol, carvedilol	Quinidine (even at ultra-low doses)
	Propafenone, flecainide	Tricyclic antidepressants
	Tricyclic antidepressants	Fluoxetine, paroxetine
	Fluoxetine, paroxetine	
CYP2C9[b]	Warfarin	Amiodarone
	Phenytoin	Fluconazole
	Glipizide	Phenytoin
	Losartan	
CYP2C19[b]	Omeprazole	Omeprazole
	Mephenytoin	
	Clopidogrel	
CYP2B6[b]	Efavirenz	
Thiopurine S-methyltransferase[b]	6-Mercaptopurine, azathioprine	
N-acetyltransferase[b]	Isoniazid	
	Procainamide	
	Hydralazine	
	Some sulfonamides	
UGT1A1[b]	Irinotecan	
Pseudocholinesterase[b]	Succinylcholine	
TRANSPORTER	**SUBSTRATES[a]**	**INHIBITORS[a]**
P-glycoprotein	Digoxin	Quinidine
	HIV protease inhibitors	Amiodarone
	Many CYP3A substrates	Verapamil
		Cyclosporine
		Itraconazole
		Erythromycin
SLCO1B1[b]	Simvastatin and some other statins	

[a]Inhibitors affect the molecular pathway and thus may decrease substrate metabolism. [b]Clinically important genetic variants described; **see Chap. 68**.

Note: A listing of CYP substrates, inhibitors, and inducers is maintained at *https://drug-interactions.medicine.iu.edu/MainTable.aspx*.

may exert important pharmacologic activity, as discussed further below. Therapeutic antibodies are very slowly eliminated (allowing infrequent dosing, e.g., monthly injections), probably by lysosomal uptake and degradation.

Clinical Implications of Altered Bioavailability Some drugs undergo near-complete presystemic metabolism and thus cannot be administered orally. Nitroglycerin cannot be used orally because it is completely extracted prior to reaching the systemic circulation. The drug is, therefore, used by the sublingual, transdermal, or intravascular routes, which bypass presystemic metabolism.

Some drugs with very extensive presystemic metabolism can still be administered by the oral route, using much higher doses than those required intravenously. Thus, a typical intravenous dose of verapamil is 1–5 mg, compared to a usual single oral dose of 40–120 mg. Administration of low-dose aspirin can result in exposure of cyclooxygenase in platelets in the portal vein to the drug, but systemic sparing because of first-pass aspirin deacylation in the liver. This is an example of presystemic metabolism being exploited to therapeutic advantage.

PLASMA HALF-LIFE

Most pharmacokinetic processes, such as elimination, are first-order; that is, the rate of the process depends on the amount of drug present. Elimination can occasionally be zero-order (fixed amount eliminated per unit time), and this can be clinically important (see "Principles of Dose Selection," later in this chapter). In the simplest pharmacokinetic model (Fig. 67-2*A*), a drug bolus (D) is administered instantaneously to a central compartment, from which drug elimination occurs as a first-order process. Occasionally, central and other compartments correspond to physiologic spaces (e.g., plasma volume), whereas in other cases, they are simply mathematical functions used to describe drug disposition. The first-order nature of drug elimination leads directly to the relationship describing drug concentration (C) at any time (t) following the bolus:

$$C = \frac{D}{V_c} \bullet e^{(-0.69t/t_{1/2})}$$

where V_c is the volume of the compartment into which drug is delivered and $t_{1/2}$ is elimination half-life. As a consequence of this relationship, a plot of the logarithm of concentration versus time is a straight line (Fig. 67-2*A*, inset). *Half-life* is the time required for 50% of a first-order process to be completed. Thus, 50% of drug elimination is achieved after one drug-elimination half-life, 75% after two, 87.5% after three, etc. In practice, first-order processes such as elimination are near-complete after four to five half-lives.

In some cases, drug is removed from the central compartment not only by elimination but also by distribution into peripheral compartments. In this case, the plot of plasma concentration versus time after a bolus may demonstrate two (or more) exponential components **(Fig. 67-2*B*)**. In general, the initial rapid drop in drug concentration represents not elimination but drug distribution into and out of peripheral tissues (also first-order processes), while the slower component represents drug elimination; the initial precipitous decline is usually evident with administration by intravenous but not by other routes. Drug concentrations at peripheral sites are determined by a balance between drug distribution to and redistribution from those sites, as well as by elimination. Once distribution is near-complete (four to five distribution half-lives), plasma and tissue concentrations decline in parallel.

Clinical Implications of Half-Life Measurements The elimination half-life not only determines the time required for drug concentrations to fall to near-immeasurable levels after a single bolus, it is also the sole determinant of the time required for steady-state plasma concentrations to be achieved after any change in drug dosing **(Fig. 67-4)**. This applies to the initiation of chronic drug therapy (whether by multiple oral doses or by continuous intravenous infusion), a change in chronic drug dose or dosing interval, or discontinuation of drug.

Steady state describes the situation during chronic drug administration when the amount of drug administered per unit time equals drug eliminated per unit time. With a continuous intravenous infusion, plasma concentrations at steady state are stable, while with chronic oral drug administration, plasma concentrations vary during the dosing interval, but the time-concentration profile between dosing intervals is stable (Fig. 67-4).

DRUG DISTRIBUTION

In a typical 70-kg human, plasma volume is ~3 L, blood volume is ~5.5 L, and extracellular water outside the vasculature is ~20 L. The volume of distribution of drugs extensively bound to plasma proteins but not to tissue components approaches plasma volume; warfarin is an example. By contrast, for drugs highly bound to tissues, the volume of distribution can be far greater than any physiologic space. For example, the volume of distribution of digoxin and tricyclic antidepressants is hundreds

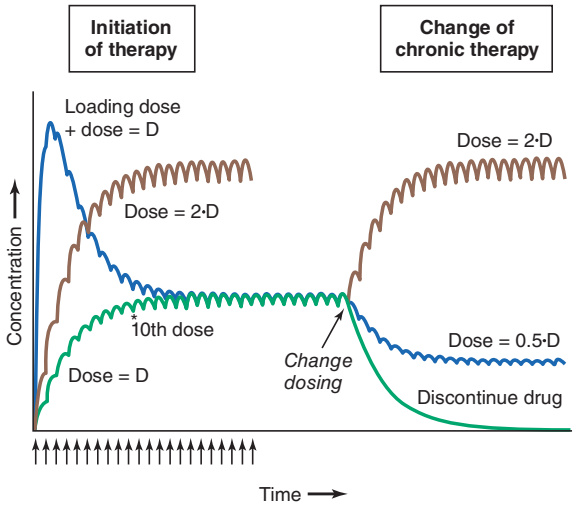

FIGURE 67-4 Drug accumulation to steady state. In this simulation, drug was administered (arrows) at intervals = 50% of the elimination half-life. Steady state is achieved during initiation of therapy after ~5 elimination half-lives, or 10 doses. A loading dose did not alter the eventual steady state achieved. A doubling of the dose resulted in a doubling of the steady state but the same time course of accumulation. Once steady state is achieved, a change in dose (increase, decrease, or drug discontinuation) results in a new steady state in ~5 elimination half-lives. *(Adapted by permission from DM Roden, in DP Zipes, J Jalife [eds]: Cardiac Electrophysiology: From Cell to Bedside, 4th ed. Philadelphia, Saunders, 2003. Copyright 2003 with permission from Elsevier.)*

of liters, obviously exceeding total-body volume. Such drugs are not readily removed by dialysis, an important consideration in overdose.

Clinical Implications of Drug Distribution In some cases, pharmacologic effects require drug distribution to peripheral sites. In this instance, the time course of drug delivery to and removal from these sites determines the time course of drug effects; anesthetic uptake into the central nervous system (CNS) is an example.

LOADING DOSES For some drugs, the indication may be so urgent that administration of "loading" dosages is required to achieve rapid elevations of drug concentration and therapeutic effects earlier than with chronic maintenance therapy (Fig. 67-4). Nevertheless, the time required for a true steady state to be achieved is still determined only by the elimination half-life.

RATE OF INTRAVENOUS DRUG ADMINISTRATION Although the simulations in Fig. 67-2 use a single intravenous bolus, this is usually inappropriate in practice because side effects related to transiently very high concentrations can result. Rather, drugs are more usually administered orally or as a slower intravenous infusion. Some drugs are so predictably lethal when infused too rapidly that special precautions should be taken to prevent accidental boluses. For example, solutions of potassium for intravenous administration >20 mEq/L should be avoided in all but the most exceptional and carefully monitored circumstances. This minimizes the possibility of cardiac arrest due to accidental increases in infusion rates of more concentrated solutions.

Transiently high drug concentrations after rapid intravenous administration can occasionally be used to advantage. The use of midazolam for intravenous sedation, for example, depends upon its rapid uptake by the brain during the distribution phase to produce sedation quickly, with subsequent egress from the brain during the redistribution of the drug as equilibrium is achieved.

Similarly, adenosine must be administered as a rapid bolus in the treatment of reentrant supraventricular tachycardias **(Chap. 246)** to prevent elimination by very rapid ($t_{1/2}$ of seconds) uptake into erythrocytes and endothelial cells before the drug can reach its clinical site of action, the atrioventricular node.

Clinical Implications of Altered Protein Binding Many drugs circulate in the plasma partly bound to plasma proteins. Since only unbound (free) drug can distribute to sites of pharmacologic action, drug response is related to the free rather than the total circulating plasma drug concentration. In chronic kidney or liver disease, protein binding may be decreased and thus drug actions increased. In some situations (myocardial infarction, infection, surgery), acute phase reactants transiently increase binding of some drugs and thus decrease efficacy. These changes assume the greatest clinical importance for drugs that are highly protein-bound since even a small change in protein binding can result in large changes in free drug; for example, a decrease in binding from 99 to 98% doubles the free drug concentration from 1 to 2%. For some drugs (e.g., phenytoin), monitoring free rather than total drug concentrations can be useful.

DRUG ELIMINATION

Drug elimination reduces the amount of drug in the body over time. An important approach to quantifying this reduction is to consider that drug concentrations at the beginning and end of a time period are unchanged, and that a specific volume of the body has been "cleared" of the drug during that time period. This defines clearance as volume/time. Clearance includes both drug metabolism and excretion.

Clinical Implications of Altered Clearance While elimination half-life determines the time required to achieve steady-state plasma concentration (C_{ss}), the *magnitude* of that steady state is determined by clearance (Cl) and dose alone. For a drug administered as an intravenous infusion, this relationship is:

$$C_{ss} = \text{dosing rate}/Cl \quad \text{or} \quad \text{dosing rate} = Cl \bullet C_{ss}$$

When a drug is administered orally, the average plasma concentration within a dosing interval ($C_{avg,ss}$) replaces C_{ss}, and the dosage (dose per unit time) must be increased if bioavailability (F) is <100%:

$$\text{Dose/time} = Cl \bullet C_{avg,ss}/F$$

Genetic variants, drug interactions, or diseases that reduce the activity of drug-metabolizing enzymes or excretory mechanisms lead to decreased clearance and, hence, a requirement for a downward dose adjustment to avoid toxicity. Conversely, some drug interactions and genetic variants increase the function of drug elimination pathways, and hence, increased drug dosage is necessary to maintain a therapeutic effect.

ACTIVE DRUG METABOLITES

Metabolites may produce effects similar to, overlapping with, or distinct from those of the parent drug. Accumulation of the major metabolite of procainamide, *N*-acetylprocainamide (NAPA), likely accounts for marked QT prolongation and torsades de pointes ventricular tachycardia **(Chap. 252)** during therapy with procainamide. Neurotoxicity during therapy with the opioid analgesic meperidine is likely due to accumulation of normeperidine, especially in renal disease.

Prodrugs are inactive compounds that require metabolism to generate active metabolites that mediate the drug effects. Examples include many angiotensin-converting enzyme (ACE) inhibitors, the angiotensin receptor blocker losartan, the antineoplastic irinotecan, the antiestrogen tamoxifen, the analgesic codeine (whose active metabolite morphine probably underlies the opioid effect during codeine administration), and the antiplatelet drug clopidogrel. Drug metabolism has also been implicated in bioactivation of procarcinogens and in the generation of reactive metabolites that mediate certain ADRs (e.g., acetaminophen hepatotoxicity, discussed below).

THE CONCEPT OF HIGH-RISK PHARMACOKINETICS

When plasma concentrations of active drug depend exclusively on a single metabolic pathway, any condition that inhibits that pathway (be it disease related, genetic, or due to a drug interaction) can lead to dramatic changes in drug concentrations and marked variability in drug action. Two mechanisms can generate highly variable drug concentrations and effects through such "high-risk pharmacokinetics." *First*, variability in bioactivation of a prodrug can lead to striking variability in drug action; examples include decreased CYP2D6 activity, which prevents analgesia

by codeine, and decreased CYP2C19 activity, which reduces the antiplatelet effects of clopidogrel. The s*econd* setting is drug elimination that relies on a single pathway. In this case, inhibition of the elimination pathway by genetic variants or by administration of inhibiting drugs leads to marked elevation of drug concentration and, for drugs with a narrow therapeutic window, an increased likelihood of dose-related toxicity. The active S-enantiomer of the anticoagulant warfarin is eliminated by CYP2C9, and co-administration of amiodarone or phenytoin, CYP2C9 inhibitors, may therefore increase the risk of bleeding unless the dose is decreased. When drugs undergo elimination by multiple-drug metabolizing or excretory pathways, absence of one pathway (due to a genetic variant or drug interaction) is much less likely to have a large impact on drug concentrations or drug actions.

PRINCIPLES OF PHARMACODYNAMICS

Time Course of Drug Action Pharmacokinetic parameters, such as half-life and clearance, explain drug concentrations over time, but understanding the action of a drug over time (pharmacodynamics) often requires an understanding of its precise mechanism of action. Drugs act through interactions with drug targets, often in specific tissues, and with a cascade of downstream consequences. For drugs used in the urgent treatment of acute symptoms, little or no delay is anticipated (or desired) between the administration of the drug, the drug-target interaction, and the development of a clinical effect. Examples of such acute situations include vascular thrombosis, shock, or status epilepticus.

For many conditions, however, the indication for therapy is less urgent, and a delay in the onset of action clinically acceptable. Delay can be due to pharmacokinetic mechanisms such as slow elimination (resulting in slow accumulation to steady state), slow uptake into the target tissue, or slow accumulation of active metabolites. A common pharmacodynamic explanation for such a delay is the biological mechanism of action. For example, the glucocorticoid prednisolone has a plasma half-life of about 60 min. The mechanism of action, however, involves binding of the glucocorticoid receptor, translocation to the cell nucleus, and alterations in gene transcription. These downstream effects alter immune function for a much longer time frame, as evidenced by the biological half-life of 24–36 h. Other examples include proton pump inhibitors, which irreversibly bind the hydrogen/potassium adenosine triphosphatase enzyme and thus affect acid secretion for the lifetime of that enzyme, and the irreversible antiplatelet drugs, which exert effects for the duration of the life of the platelet.

Drug Effects May Be Disease Specific A drug may produce no action or a different spectrum of actions in unaffected individuals compared to patients with underlying disease. Further, concomitant disease can complicate interpretation of response to drug therapy, especially ADRs. For example, high doses of anticonvulsants such as phenytoin may cause neurologic symptoms, which may be confused with the underlying neurologic disease. Similarly, increasing dyspnea in a patient with chronic lung disease receiving amiodarone therapy could be due to the drug, underlying disease, or an intercurrent cardiopulmonary problem. As a result, alternate antiarrhythmic therapies may be preferable in patients with chronic lung disease.

While drugs interact with specific molecular receptors, drug effects may vary over time, even if stable drug and metabolite concentrations are maintained. The drug-receptor interaction occurs in a complex biologic milieu that can vary to modulate the drug effect. For example, ion channel blockade by drugs, an important anticonvulsant and antiarrhythmic effect, is often modulated by membrane potential, itself a function of factors such as extracellular potassium or local ischemia. Receptors may be up- or downregulated by disease or by the drug itself. For example, β-adrenergic blockers upregulate β-receptor density during chronic therapy. While this effect does not usually result in resistance to the therapeutic effect of the drugs, it may produce severe agonist-mediated effects (such as hypertension or tachycardia) if the blocking drug is abruptly withdrawn.

As molecular mechanisms of disease become better defined, drugs targeting those mechanisms are being introduced into practice. Antineoplastic agents targeting mutant kinases overexpressed in cancers (e.g., *BRAF* V600E in melanoma, hairy cell leukemia, and other malignancies) are revolutionizing cancer care. Ivacaftor was originally developed and marketed for patients with cystic fibrosis (CF) carrying the G551D mutation in the disease gene *CFTR* **(Chap. 291)**. While the most common *CFTR* mutations causing CF generate normal chloride channels that are not correctly trafficked to the cell surface, G551D channels are trafficked normally but do not conduct chloride correctly, and ivacaftor corrects this "gating" defect. Following initial marketing for only G551D patients (5% of all CF patients), the U.S. Food and Drug Administration (FDA) approved ivacaftor for use in patients carrying other *CFTR* mutations that confer gating defects corrected by ivacaftor in vitro.

PRINCIPLES OF DOSE SELECTION

The desired goal of therapy with any drug is to maximize the likelihood of a beneficial effect while minimizing the risk of ADRs. Previous experience with the drug, in controlled clinical trials or in postmarketing use, defines the relationships between dose or plasma concentration and these dual effects (Fig. 67-1) and has important implications for initiation of drug therapy:

1. *The target drug effect should be defined when drug treatment is started*. With some drugs, the desired effect may be difficult to measure objectively, or the onset of efficacy can be delayed for weeks or months; drugs used in the treatment of cancer and psychiatric disease are examples. Sometimes a drug is used to treat a symptom, such as pain or palpitations, and here it is the patient who will report whether the selected dose is effective. In yet other settings, such as anticoagulation or hypertension, the desired response can be repeatedly and objectively assessed by simple clinical or laboratory tests.
2. *The nature of anticipated toxicity often dictates the starting dose*. If side effects are minor, it may be acceptable to start chronic therapy at a dose highly likely to achieve efficacy and down-titrate if side effects occur. However, this approach is rarely, if ever, justified if the anticipated toxicity is serious or life-threatening; in this circumstance, it is more appropriate to initiate therapy with the lowest dose that may produce a desired effect. In cancer chemotherapy, it is common practice to use maximally tolerated doses.
3. *The above considerations do not apply if these relationships between dose and effects cannot be defined*. This is especially relevant to some ADRs (discussed further below) whose development is not readily related to drug dose.
4. *If a drug dose does not achieve its desired effect, a dosage increase is justified only if toxicity is absent and the likelihood of serious toxicity is small.*

Failure of Efficacy Even assuming the diagnosis is correct and the correct drug and dose are prescribed, drugs may fail to be effective because 100% efficacy is not expected. A complete therapeutic response is often absent with antihypertensive or antidepressant drugs, and a major challenge in contemporary therapeutics is to identify patient-specific predictors of response to individual drugs. Other explanations for failure of efficacy include drug interactions, noncompliance, or unexpectedly low drug concentration due to administration of expired or degraded drug. These are situations in which measurement of plasma drug concentrations, if available, can be especially useful. Noncompliance is an especially frequent problem in the long-term treatment of diseases such as hypertension and epilepsy, occurring in ≥25% of patients in therapeutic environments in which no special effort is made to involve patients in the responsibility for their own health. Multidrug regimens with multiple doses per day are especially prone to noncompliance.

Monitoring response to therapy, by physiologic measures or by plasma concentration measurements, requires an understanding of the relationships between plasma concentration and anticipated effects. For example, measurement of QT interval is used during treatment with sotalol or dofetilide to avoid marked QT prolongation that can herald serious arrhythmias. In this setting, evaluating the

electrocardiogram at the time of anticipated peak plasma concentration and effect (e.g., 1–2 h postdose at steady state) is most appropriate. Maintained high vancomycin levels carry a risk of nephrotoxicity, so dosages should be adjusted on the basis of plasma concentrations measured at trough (predose). Similarly, for dose adjustment of other drugs (e.g., anticonvulsants), concentration should be measured at its lowest during the dosing interval, just prior to a dose at steady state (Fig. 67-4), to ensure a maintained therapeutic effect.

Concentration of Drugs in Plasma as a Guide to Therapy

Factors such as interactions with other drugs, disease-induced alterations in elimination and distribution, and genetic variation in drug disposition combine to yield a wide range of plasma levels in patients given the same dose. Hence, if a predictable relationship can be established between plasma drug concentration and beneficial or adverse drug effect, measurement of plasma levels can provide a valuable tool to guide selection of an optimal dose, especially when there is a narrow range between the plasma levels yielding therapeutic and adverse effects. Such therapeutic drug monitoring is commonly used with certain types of drugs including many anticonvulsants, antirejection agents, antiarrhythmics, and antibiotics. By contrast, if no such relationship can be established (e.g., if drug access to important sites of action outside plasma is highly variable), monitoring plasma concentration may not provide an accurate guide to therapy **(Fig. 67-5)**.

The common situation of first-order elimination implies that average, maximum, and minimum steady-state concentrations are related linearly to the dosing rate. Accordingly, the maintenance dose may be adjusted on the basis of the ratio between the desired and measured concentrations *at steady state*; for example, if a doubling of the steady-state plasma concentration is desired, the dose should be doubled. This does not apply to drugs eliminated by zero-order kinetics (fixed amount per unit time), where small dosage increases will produce disproportionate increases in plasma concentration; examples include phenytoin and theophylline.

If an increase in dosage is needed, this is usually best achieved by increasing the drug dose and leaving the dosing interval constant (e.g., by giving 200 mg every 8 h instead of 100 mg every 8 h). However, this approach is acceptable only if the resulting maximum concentration is not toxic and the trough value does not fall below the minimum effective concentration for an undesirable period of time. Alternatively, the steady state may be changed by altering the frequency of intermittent dosing but not the size of each dose. In this case, the magnitude of the fluctuations around the average steady-state level will change—the shorter the dosing interval, the smaller the difference between peak and trough levels.

EFFECTS OF DISEASE ON DRUG CONCENTRATION AND RESPONSE

RENAL DISEASE

Renal excretion of parent drug and metabolites is generally accomplished by glomerular filtration and by specific drug transporters. If a drug or its metabolites are primarily excreted through the kidneys and increased drug levels are associated with ADRs (an example of "high-risk pharmacokinetics" described above), drug dosages must be reduced in patients with renal dysfunction to avoid toxicity. The antiarrhythmics dofetilide and sotalol undergo predominant renal excretion and carry a risk of QT prolongation and arrhythmias if doses are not reduced in renal disease. In end-stage renal disease, sotalol has been given as 40 mg after dialysis (every second day), compared to the usual daily dose, 80–120 mg every 12 h. At approved doses, the anticoagulant edoxaban appears to be somewhat more effective in subjects with mild renal dysfunction, possibly reflecting higher drug levels. The narcotic analgesic meperidine undergoes extensive hepatic metabolism, so that renal failure has little effect on its plasma concentration. However, its metabolite, normeperidine, does undergo renal excretion, accumulates in renal failure, and probably accounts for the signs of CNS excitation, such as irritability, twitching, and seizures, that appear when multiple doses of meperidine are administered to patients with renal disease. Protein binding of some drugs (e.g., phenytoin) may be altered in uremia, so measuring free drug concentration may be desirable.

In non-end-stage renal disease, changes in renal drug clearance are generally proportional to those in creatinine clearance, which may be measured directly or estimated from the serum creatinine. This estimate, coupled with the knowledge of how much drug is normally excreted renally versus nonrenally, allows an estimate of the dose adjustment required. In practice, most decisions involving dosing adjustment in patients with renal failure use published recommended adjustments in dosage or dosing interval based on the severity of renal dysfunction indicated by creatinine clearance. Any such modification of dose is a first approximation and should be followed by plasma concentration data (if available) and clinical observation to further optimize therapy for the individual patient.

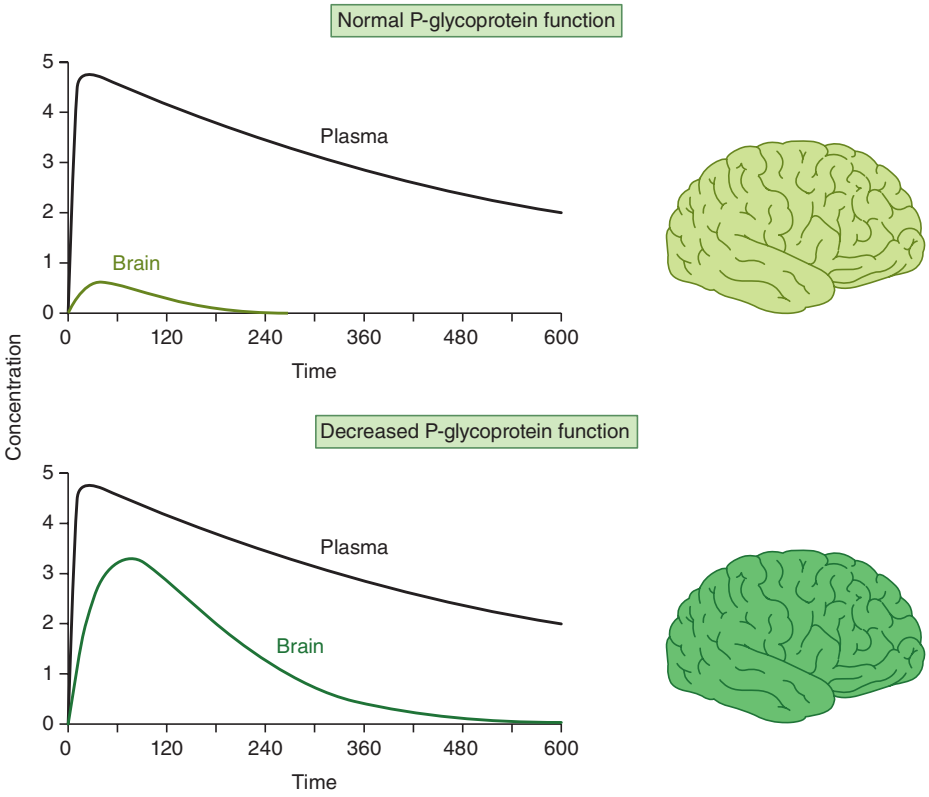

FIGURE 67-5 Drug concentrations in specific tissues may not always parallel those in plasma. For example, the efflux pump P-glycoprotein excludes drugs from the endothelium of capillaries in the brain and so constitutes a key element of the blood-brain barrier. Reduced P-glycoprotein function (e.g., due to drug interactions) can thus increase penetration of substrate drugs into the brain, even when plasma concentrations are unchanged.

LIVER DISEASE

Standard tests of liver function are not useful in adjusting doses in diseases like hepatitis or cirrhosis. First-pass metabolism may decrease, leading to increased oral bioavailability as a consequence of disrupted hepatocyte function, altered liver architecture, and portacaval shunts. The oral bioavailability for high first-pass drugs such as morphine, meperidine, midazolam, and nifedipine is almost doubled in patients with cirrhosis, compared to those with normal liver function. Therefore, the size of the oral dose of such drugs should be reduced in this setting.

HEART FAILURE AND SHOCK

Under conditions of decreased tissue perfusion, the cardiac output is redistributed to preserve blood flow to the heart and brain at the expense of other tissues (Chap. 257). As a result, drugs may be distributed into a smaller volume of distribution, higher drug concentrations will be present in the plasma, and the tissues that are best perfused (the brain and heart) will be exposed to these higher concentrations, resulting in increased CNS or cardiac effects. In addition, decreased perfusion of the kidney and liver may impair drug clearance. Another consequence of severe heart failure is decreased gut perfusion, which may reduce drug absorption and thus lead to reduced or absent effects of orally administered therapies.

DRUG USE IN THE ELDERLY

In the elderly, multiple pathologies and medications used to treat them result in more drug interactions and ADRs. Aging also results in changes in organ function, especially of the organs involved in drug disposition. Initial doses should be less than the usual adult dosage and should be increased slowly. The number of medications, and doses per day, should be kept as low as possible.

Even in the absence of kidney disease, renal clearance may be reduced by 35–50% in elderly patients. Dosages should be adjusted on the basis of creatinine clearance. Aging also results in a decrease in the size of, and blood flow to, the liver and possibly in the activity of hepatic drug-metabolizing enzymes; accordingly, the hepatic clearance of some drugs is impaired in the elderly. As with liver disease (above), these changes are not readily predicted.

Elderly patients may display altered drug sensitivity. Examples include increased analgesic effects of opioids, increased sedation from benzodiazepines and other CNS depressants, and increased risk of bleeding while receiving anticoagulant therapy, even when clotting parameters are well controlled. Exaggerated responses to cardiovascular drugs are also common because of the impaired responsiveness of normal homeostatic mechanisms. Conversely, the elderly display decreased sensitivity to β-adrenergic receptor blockers.

ADRs are especially common in the elderly because of altered pharmacokinetics and pharmacodynamics, the frequent use of multidrug regimens, and concomitant disease. For example, use of long half-life benzodiazepines is linked to the occurrence of hip fractures in elderly patients, perhaps reflecting both a risk of falls from these drugs (due to increased sedation) and the increased incidence of osteoporosis in elderly patients. In population surveys of the noninstitutionalized elderly, as many as 10% had at least one ADR in the previous year.

DRUG USE IN CHILDREN

Although there are very few pediatric-specific drugs, there are many pediatric-specific drug indications (e.g., intravenous immunoglobulin and aspirin for Kawasaki disease) and ADRs (e.g., pyloric stenosis after erythromycin exposure in infants). Drug metabolism and drug response pathways mature at different rates after birth, and the relative size of various body compartments and function of various organs change during development. There is increased motivation to avoid organ toxicity, given the anticipated long post-drug-exposure life expectancy. There are few studies providing empiric evidence to guide pediatric dosing. In practice, doses are adjusted for size (weight or body surface area) as a first approximation unless age-specific data are available. As in adults, the lowest doses anticipated to achieve clinical benefit are generally prescribed, potentially followed by titration.

INTERACTIONS BETWEEN DRUGS

Drug interactions can complicate therapy by increasing or decreasing the action of a drug; interactions may be based on changes in drug disposition or in drug response in the absence of changes in drug levels (Table 67-2). *Interactions must be considered in the differential diagnosis of any unusual response occurring during drug therapy.* Prescribers should recognize that patients often come to them with a legacy of drugs acquired during previous medical experiences, often with multiple physicians who may not be aware of all the patient's medications. A meticulous drug history should list all medications, including agents

TABLE 67-2 Drug Interactions

MECHANISM	EXAMPLE
Pharmacokinetic Interactions Causing Decreased Drug Effect	
Decreased absorption due to drug binding in the gut	Antacids or bile acid sequestrants decrease the absorption of many drugs: Antacids/tetracyclines Cholestyramine/digoxin
Decreased solubility due to altered gastric pH	H_2 receptor blockers or proton pump inhibitors decrease solubility and absorption of weak bases: Omeprazole/ketoconazole
Induction of drug metabolism and/or drug transport: Rifampin Carbamazepine Phenytoin St. John's wort Glutethimide (also smoking, exposure to chlorinated insecticides, and chronic alcohol ingestion)	Decreased concentrations and effects of: Warfarin Quinidine Cyclosporine Losartan Oral contraceptives Methadone Dabigatran
Decreased prodrug bioactivation	Proton pump inhibitors may prevent clopidogrel bioactivation CYP2D6 inhibitors (fluoxetine, paroxetine, quinidine, and others) may prevent codeine bioactivation
Reduced delivery of drug to active sites of action	Tricyclics prevent clonidine uptake into adrenergic neurons, preventing antihypertensive effects
Pharmacokinetic Interactions Causing Increased Drug Effect	
Inhibited drug metabolism	Cimetidine (inhibits many CYPs): Warfarin Theophylline Phenytoin CYP2D6 inhibitors[a]/β blockers CYP3A inhibitors[a]: HMG-CoA reductase inhibitors Colchicine (toxicity risk) Decreased cyclosporine dose requirement
Inhibited drug transport	Amiodarone (inhibits many CYPs and P-glycoprotein): Warfarin Digoxin Dabigatran
Inhibition of drug metabolism causing accumulation of toxic metabolites	Allopurinol (xanthine oxidase inhibitor) inhibits an alternate pathway for azathioprine and 6-mercaptopurine elimination, increasing risk for toxicity
Decreased elimination due to altered renal function	Inhibitors of renal tubular transport (phenylbutazone, probenecid, salicylates) increase methotrexate toxicity
Pharmacodynamic Drug Interactions	
Combined effects on the same biologic process	Excess bleeding with combinations of antiplatelet drugs, anticoagulants, and NSAIDs Long QT–related arrhythmias with QT-prolonging antiarrhythmics plus diuretics Hyperkalemia with ACE inhibitors plus potassium Hypotension with nitrates plus sildenafil
Antagonistic effects on the same biologic process	Loss of antihypertensive drug effects with NSAIDs

[a]See Table 67-1.

Abbreviations: ACE, angiotensin-converting enzyme; CYP, cytochrome P; NSAID, nonsteroidal anti-inflammatory drug.

not often volunteered during questioning, such as OTC drugs, health food supplements, and topical agents such as eye drops. Lists of interactions are available from a number of electronic sources. While it is unrealistic to expect the practicing physician to memorize these, certain drugs consistently run the risk of generating interactions, often by inhibiting or inducing specific drug elimination pathways; these include CYP2D6, CYP3A, and P-glycoprotein inhibitors (Table 67-1) and CYP3A/P-glycoprotein inducers (Table 67-2). Accordingly, when these drugs are started or stopped, prescribers must be especially alert to the possibility of interactions.

ADVERSE DRUG REACTIONS

The beneficial effects of drugs are coupled with the inescapable risk of untoward effects. The morbidity and mortality from these ADRs often present diagnostic problems because they can involve every organ and system of the body and may be mistaken for signs of underlying disease. In addition, some surveys have suggested that drug therapy for a range of chronic conditions such as psychiatric disease or hypertension does not achieve its desired goal in up to half of treated patients; thus, the most common "adverse" drug effect may be failure of efficacy.

ADRs can be classified in two broad groups. Type A reactions result from exaggeration of an intended pharmacologic action of the drug, such as increased bleeding with anticoagulants or bone marrow suppression with some antineoplastics, and tend to be dose-dependent. Type B reactions result from toxic effects unrelated to the intended pharmacologic actions. The latter effects are often unanticipated (especially with new drugs) and frequently severe and may result from recognized (often immunologic) as well as previously undescribed mechanisms. Type B reactions may occur at low dosages and are often termed dose-independent.

Drugs may increase the frequency of an event that is common in a general population, and this may be especially difficult to recognize; an example is the increase in myocardial infarctions that was seen with the COX-2 inhibitor rofecoxib. Drugs can also cause rare and serious ADRs, such as hematologic abnormalities, arrhythmias, severe skin reactions, or hepatic or renal dysfunction. Prior to regulatory approval and marketing, new drugs are tested in relatively few patients who tend to be less sick and to have fewer concomitant diseases than those patients who subsequently receive the drug therapeutically. Because of the relatively small number of patients studied in clinical trials and the selected nature of these patients, rare ADRs are generally not detected prior to a drug's approval; indeed, if they are detected, the new drugs are generally not approved. Therefore, physicians need to be cautious in the prescription of new drugs and alert for the appearance of previously unrecognized ADRs.

Elucidating mechanisms underlying ADRs can assist development of safer compounds or allow a patient subset at especially high risk to be excluded from drug exposure. National adverse reaction reporting systems, such as those operated by the FDA (suspected ADRs can be reported online at *http://www.fda.gov/safety/medwatch/default.htm*) and the Committee on Safety of Medicines in Great Britain, can prove useful. The publication or reporting of a newly recognized ADR can in a short time stimulate many similar such reports of reactions that previously had gone unrecognized.

Occasionally, "adverse" effects may be exploited to develop an entirely new indication for a drug. Unwanted hair growth during minoxidil treatment of severely hypertensive patients led to development of the drug for hair growth. Sildenafil was initially developed as an antianginal, but its effects to alleviate erectile dysfunction not only led to a new drug indication but also to increased understanding of the role of type 5 phosphodiesterase in erectile tissue. These examples further reinforce the concept that prescribers must remain vigilant to the possibility that unusual symptoms may reflect unappreciated drug effects.

Some 25–50% of patients make errors in self-administration of prescribed medicines, and these errors can be responsible for ADRs. Similarly, patients commit errors in taking OTC drugs by not reading or following prescribing directions on the containers. Health care providers must recognize that providing directions with prescriptions does not always guarantee compliance.

In hospitals, drugs are administered in a controlled setting, and patient compliance is, in general, ensured. Errors may occur nevertheless—the wrong drug or dose may be given or the drug may be given to the wrong patient—and improved drug distribution and administration systems should help with this problem.

SCOPE OF THE PROBLEM

One estimate in the United Kingdom was that 6.5% of all hospital admissions are due to ADRs and that 2.3% of these patients (0.15%) died as a result. The most common culprit drugs were aspirin, nonsteroidal anti-inflammatory drugs, diuretics, warfarin, ACE inhibitors, antidepressants, opiates, digoxin, steroids, and clopidogrel. One study in the late 1990s suggested that ADRs were responsible for >100,000 in-hospital deaths in the United States, making them the fourth to sixth most common cause of in-hospital death. Another study 10 years later showed no change in this trend.

In hospital, patients receive, on average, 10 different drugs during each hospitalization. The sicker the patient, the more drugs are given, and there is a corresponding increase in the likelihood of ADRs. When <6 different drugs are given to hospitalized patients, the probability of an ADR is ~5%, but if >15 drugs are given, the probability is >40%. Serious ADRs are also well recognized with "herbal" remedies and OTC compounds; examples include kava-associated hepatotoxicity, L-tryptophan-associated eosinophilia-myalgia, and phenylpropanolamine-associated stroke, each of which has caused fatalities.

TOXICITY UNRELATED TO A DRUG'S PRIMARY PHARMACOLOGIC ACTIVITY

Drugs or, more commonly, reactive metabolites generated by CYPs can covalently bind to tissue macromolecules (such as proteins or DNA) to cause tissue toxicity. Because of the reactive nature of these metabolites, covalent binding often occurs close to the site of production, typically the liver.

Acetaminophen The most common cause of drug-induced hepatotoxicity is acetaminophen overdosage **(Chap. 340)**. Normally, reactive metabolites are detoxified by combining with hepatic glutathione. When glutathione becomes depleted, the metabolites bind instead to hepatic protein, with resultant hepatocyte damage. The hepatic necrosis produced by the ingestion of acetaminophen can be prevented or attenuated by the administration of substances such as *N*-acetylcysteine that reduce the binding of electrophilic metabolites to hepatic proteins. The risk of acetaminophen-related hepatic necrosis is increased in patients receiving drugs such as phenobarbital or phenytoin, which increase the rate of drug metabolism, or ethanol, which exhausts glutathione stores. Such toxicity has even occurred with therapeutic dosages, so patients at risk through these mechanisms should be warned.

Immunologic Reactions Most pharmacologic agents are haptens, small molecules with low molecular weights (<2000) that are therefore poor immunogens. Generation of an immune response to a drug therefore often requires in vivo activation and covalent linkage to protein, carbohydrate, or nucleic acid.

Drug stimulation of antibody production may mediate tissue injury by several mechanisms. The antibody may attack the drug when the drug is covalently attached to a cell and thereby destroy the cell. This occurs in penicillin-induced hemolytic anemia. Antibody-drug-antigen complexes may be passively adsorbed by a bystander cell, which is then destroyed by activation of complement; this occurs in quinine- and quinidine-induced thrombocytopenia. Heparin-induced thrombocytopenia arises when antibodies against complexes of platelet factor 4 peptide and heparin generate immune complexes that activate platelets; thus, the thrombocytopenia is accompanied by "paradoxical" thrombosis and is treated with thrombin inhibitors. Drugs or their reactive metabolites may alter a host tissue, rendering it antigenic and eliciting autoantibodies. For example, hydralazine and procainamide (or their reactive metabolites) can chemically alter nuclear material, stimulating the formation of antinuclear antibodies and occasionally causing lupus erythematosus. Drug-induced pure red cell aplasia **(Chap. 102)** is due to an immune-based drug reaction.

Serum sickness **(Chap. 352)** results from the deposition of circulating drug-antibody complexes on endothelial surfaces. Complement activation occurs, chemotactic factors are generated locally, and an inflammatory response develops at the site of complex entrapment. Arthralgias, urticaria, lymphadenopathy, glomerulonephritis, or cerebritis may result. Foreign proteins (vaccines, streptokinase, therapeutic antibodies) and antibiotics are common causes. Many drugs, particularly antimicrobial agents, ACE inhibitors, and aspirin, can elicit anaphylaxis with production of IgE, which binds to mast cell membranes. Contact with a drug antigen initiates a series of biochemical events in the mast cell and results in the release of mediators that can produce the characteristic urticaria, wheezing, flushing, rhinorrhea, and (occasionally) hypotension.

Drugs may also elicit cell-mediated immune responses. One serious reaction is Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), which can result in death due to T-cell-mediated massive skin sloughing. Another probable immune-mediated drug reaction is the DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome, a rare ADR with a chronic relapsing course, often triggered by antiseizure medications and possibly arising from herpes virus reactivation. As described in **Chap. 68**, specific genetic variants appear necessary but not sufficient to elicit SJS/TEN or DRESS.

While the use of antibodies targeting immune checkpoints is dramatically improving prognosis in many cancers, these agents have also been associated with the unpredictable development of many apparently immune-related ADRs. Some, like colitis or thyroiditis, may be self-limited or medically manageable, while others, notably myocarditis, are rarer but can be rapidly fatal.

DIAGNOSIS AND TREATMENT OF ADVERSE DRUG REACTIONS

The manifestations of drug-induced diseases frequently resemble those of other diseases, and a given set of manifestations may be produced by different and dissimilar drugs. Recognition of the role of a drug or drugs in an illness depends on appreciation of the possible ADRs to drugs in any disease, on identification of the temporal relationship between drug administration and development of the illness, and on familiarity with the common manifestations of the drugs.

A suspected ADR developing after introduction of a new drug naturally implicates that drug; however, it is also important to remember that a drug interaction may be responsible. Thus, for example, a patient on a chronic stable warfarin dose may develop a bleeding complication after introduction of amiodarone; this does not reflect a direct reaction to amiodarone but rather its effect to inhibit warfarin metabolism. Many associations between particular drugs and specific reactions have been described, but there is always a "first time" for a novel association, and any drug should be suspected of causing an ADR if the clinical setting is appropriate.

Illness related to a drug's intended pharmacologic action is often more easily recognized than illness attributable to immune or other mechanisms.

For example, side effects such as cardiac arrhythmias in patients receiving digitalis, hypoglycemia in patients given insulin, or bleeding in patients receiving anticoagulants are more readily related to a specific drug than are symptoms such rash, which may be caused by many drugs or by other factors. Drug fever often escapes initial diagnosis because fever is such a common manifestation of disease.

Electronic listings of ADRs can be useful. However, exhaustive compilations often provide little sense of perspective in terms of frequency and seriousness, which can vary considerably among patients.

Eliciting a drug history from each patient is important for diagnosis. Attention must be directed to OTC drugs and herbal preparations as well as to prescription drugs. Each type can be responsible for ADRs, and adverse interactions may occur between OTC drugs and prescribed drugs. Loss of efficacy of oral contraceptives or cyclosporine with concurrent use of St. John's wort (a P-glycoprotein inducer) is an example (Table 67-2). In addition, it is common for patients to be cared for by several physicians, and duplicative, additive, antagonistic, or synergistic drug combinations may therefore be administered if the physicians are not aware of the patients' drug histories. Electronic health records (EHRs) may help mitigate this problem, but only if all treating physicians use the same EHR system. Medications stopped for inefficacy or adverse effects should be documented to avoid pointless and potentially dangerous reexposure. A frequently overlooked source of additional drug exposure is topical therapy; for example, a patient complaining of bronchospasm may not mention that an ophthalmic beta blocker is being used unless specifically asked. A history of previous ADRs in patients is common. Since these patients have shown a predisposition to drug-induced illnesses, such a history should dictate added caution in prescribing new drugs.

Laboratory studies may include demonstration of serum antibody in some persons with drug allergies involving cellular blood elements, as in agranulocytosis, hemolytic anemia, and thrombocytopenia. For example, both quinine and quinidine can produce platelet agglutination in vitro in the presence of complement and the serum from a patient who has developed thrombocytopenia following use of this drug. Biochemical abnormalities such as G6PD deficiency, serum pseudocholinesterase level, or genotyping may also be useful in diagnosis, especially after an ADR has occurred in the patient or a family member **(Chap. 68)**.

Once an ADR is suspected, discontinuation of the suspected drug followed by disappearance of the reaction is presumptive evidence of a drug-induced illness. Confirming evidence may be sought by cautiously reintroducing the drug and seeing if the reaction reappears. However, that should be done only if confirmation would be useful in the future management of the patient. Because rechallenge does carry risks, it is generally avoided unless the suspected culprit drug is critical to the patient's care. When the reaction is thought to be immunologic, challenge is generally avoided. With concentration-dependent ADRs, lowering the dosage may cause the reaction to disappear, and raising it may cause the reaction to reappear. Serious immunologically mediated ADRs have been treated with high-dose steroids; other immunosuppressive agents such as rituximab, infliximab, or mycophenolate mofetil; or plasmapheresis.

If the patient is receiving many drugs when an ADR is suspected, the drugs likeliest to be responsible can usually be identified; this should include both potential culprit agents as well as drugs that alter their elimination. All drugs may be discontinued at once or, if this is not practical, discontinued one at a time, starting with the ones most suspect, and the patient observed for signs of improvement. The time needed for a concentration-dependent ADR to disappear depends on the time required for the concentration to fall below the range associated with the ADR; that, in turn, depends on the initial blood level and on the rate of elimination or metabolism of the drug. Adverse effects of drugs with long half-lives or those not directly related to serum concentration may take a considerable time to disappear.

THE DRUG DEVELOPMENT PROCESS

Drug therapy is an ancient feature of human culture. The first treatments were plant extracts discovered empirically to be effective for indications like fever, pain, or breathlessness. This symptom-based empiric approach to drug development was supplanted in the twentieth century by identification of compounds targeting more fundamental biologic processes, such as bacterial growth or elevated blood pressure. The term "magic bullet," coined by Paul Ehrlich to describe the search for effective compounds for syphilis, captures the essence of the hope that understanding basic biologic processes will lead to highly effective new therapies.

A common starting point for the development of many widely used modern therapies has been basic biologic discovery that implicates potential target molecules: examples of such target molecules include HMG-CoA reductase, a key step in cholesterol biosynthesis, or the *BRAF* V600E mutation that appears to drive the development of some malignant melanomas and other tumors. The development of compounds targeting these molecules has not only revolutionized treatment for diseases such as hypercholesterolemia or malignant melanoma, but has also revealed new biologic features of disease. Thus, for example, initial spectacular successes with vemurafenib (which targets

BRAF V600E) were followed by near-universal tumor relapse, strongly suggesting that inhibition of this pathway alone would be insufficient for tumor control. This reasoning, in turn, supports a view that many complex diseases will not lend themselves to cure by targeting a single magic bullet, but rather single drugs or combinations that attack multiple pathways whose perturbation results in disease. The use of combination therapy in settings such as hypertension, tuberculosis, HIV infection, and many cancers highlights the potential for such a "systems biology" view of drug therapy.

A common approach in contemporary drug development is to start with a high-throughput screening procedure to identify "lead" chemical(s) modulating the activity of a potential drug target. The next step is application of increasingly sophisticated medicinal chemistry-based modification of the "lead" to develop compounds with specificity for the chosen target, lack of "off-target" effects, and pharmacokinetic properties suitable for human use (e.g., consistent bioavailability, long elimination half-life, and no high-risk pharmacokinetic features). Drug evaluation in human subjects then proceeds from initial safety and tolerance (phase 1) to dose finding (phase 2) and then to large efficacy trials (phase 3). This is a very expensive process, and the vast majority of lead compounds fail at some point. Thus, new approaches to identify likely successes and failures early are needed. One idea, described further in **Chap. 68**, is to use genomic and other high-throughput profiling approaches not only to identify new drug targets but also to identify disease subsets for which drugs approved for other indications might be "repurposed," thereby avoiding the costly development process.

SUMMARY

Modern clinical pharmacology aims to replace empiricism in the use of drugs with therapy based on in-depth understanding of factors that determine an individual's response to drug treatment. Molecular pharmacology, pharmacokinetics, genetics, clinical trials, and the educated prescriber all contribute to this process. No drug response should ever be termed *idiosyncratic*; all responses have a mechanism whose understanding will help guide further therapy with that drug or successors. This rapidly expanding understanding of variability in drug actions makes the process of prescribing drugs increasingly daunting for the practitioner. However, fundamental principles should guide this process:

- The benefits of drug therapy, however defined, should always outweigh the risk.
- The smallest dosage necessary to produce the desired effect should be used.
- The number of medications and doses per day should be minimized.
- Although the literature is rapidly expanding, accessing it is becoming easier; electronic tools to search databases of literature and unbiased opinion will become increasingly commonplace.
- Genetics play a role in determining variability in drug response and may become a part of clinical practice.
- EHR and pharmacy systems will increasingly incorporate prescribing advice, such as indicated medications not used; unindicated medications being prescribed; and potential dosing errors, drug interactions, or genetically determined drug responses.
- Prescribers should be particularly wary when adding or stopping specific drugs that are especially liable to provoke interactions and adverse drug reactions.
- Prescribers should use only a limited number of drugs, with which they are thoroughly familiar.

FURTHER READING

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68 Pharmacogenomics

Dan M. Roden

The previous chapter discussed mechanisms underlying variability in drug action, highlighting pharmacokinetic and pharmacodynamic pathways to beneficial and adverse drug events. Work in the past several decades has defined how genetic variation can play a prominent role in modulating these pathways. Initial studies described unusual drug responses due to single genetic variants in individual subjects, defining the field of pharmacogenetics. A more recent view extends this idea to multiple genetic variants across populations, and the term "pharmacogenomics" is often used. Understanding the role of genetic variation in drug response could improve the use of current drugs, avoid drug use in those at increased risk for adverse drug reactions (ADRs), guide development of new drugs, and even be used as a lens through which to understand mechanisms of diseases themselves. This chapter will outline the principles of pharmacogenomics, the evidence as currently available that genetic factors play a role in variable drug actions, and areas of controversy and ongoing work.

PRINCIPLES OF GENETIC VARIATION AND DRUG RESPONSE (SEE ALSO CHAPS. 466 AND 467)

A goal of traditional Mendelian genetics is to identify DNA variants associated with a distinct phenotype in multiple related family members (**Chap. 467**). However, it is unusual for a drug response phenotype to be accurately measured in more than one family member, let alone across a kindred. Some clinical studies have examined drug disposition traits (such as urinary drug excretion after a fixed test dose) in twins and have, in some instances, shown greater concordance in monozygotic compared to dizygotic pairs, supporting a genetic contribution to the trait under study. However, in general, non-family-based approaches are usually used to identify and validate DNA variants contributing to variable drug actions. Both candidate gene and genome-wide studies have been used, and as with any genomic study, results require replication before they should be accepted as valid.

Types of Genetic Variants Influencing Drug Response (Table 68-1) The most common type of genetic variant is a single nucleotide polymorphism (SNP), and nonsynonymous SNPs (i.e., those that alter primary amino acid sequence encoded by a gene) are a common cause of variant function in genes regulating drug responses, often termed *pharmacogenes*. Small insertions and deletions can similarly alter protein function or lead to functionally important splice variation. Examples of synonymous coding region variants altering pharmacogene function have also been described; the postulated mechanism is an alteration in the rate of RNA translation, and hence in folding of the nascent protein. Variation in pharmacogene promoters has been described, and copy number variation (gene deletion or multiple copies of the same gene) is also well described.

Table 68-1 lists examples of individual types of genomic variation and the impact they can have on function of pharmacogenes. Multiple genotyping approaches may be needed to detect important variants; for example, SNP assays may fail to detect large gene duplications, and highly polymorphic regions (such as the major histocompatibility locus on chromosome 6 that includes multiple genes of the human leukocyte antigen [HLA] family) are currently best evaluated by sequencing.

TABLE 68-1 Examples of Genetic Variation and Ancestry

STRUCTURAL VARIANT	EXAMPLE		FUNCTIONAL EFFECT	MINOR ALLELE FREQUENCY (%)[a]		
	COMMON NAME	dbSNP		EUROPEAN	AFRICAN	EAST ASIAN
Single nucleotide polymorphism (SNP) (or single nucleotide variant, SNV)	CYP2C9*2	rs1799853	R144C: Reduction of function	12.7	2.4	[b]
	CYP2C9*3	rs1057910	I359L: Loss of function	6.9	1.3	3.4
	CYP2C9*8	rs7900194	R150H: Reduction of function	[b]	5.6	[b]
	CYP2C19*2	rs4244285	Splicing defect: Loss of function	14.8	18.1	31.0
	CYP2C19*3	rs4986893	Premature stop: Loss of function	[b]	[b]	6.7
	CYP2C19*17	rs12248560	Gain of function	45	45	<5
	CYP2D6*4[c]	rs3892097	Splicing defect: Loss of function	23.1	11.9	0.4
	CYP2D6*10[c]	Multiple SNPs define CYP2D6*10 (reduction of function allele):				
		rs1065852	P34S	24.9	15.1	59.1
		rs1135840	S486T			
	CYP3A5*3	rs776746	Splicing defect: Loss of function	90	33	85
	VKORC1*2	rs9923231	Promoter variant associated with decreased warfarin dose	39	11	91
	VKORC1	rs61742245	D36Y: Reduction of function, associated with increased warfarin dose	5% in East Africa, Middle East, Oceania; rare elsewhere		
	ABCB1	rs1045642	Synonymous variant; may affect mRNA stability and protein folding	47.2	79.8	62.5
Insertion/deletion	UGT1A1*28		Reduction of function promoter variant (7 TA repeats versus 6 repeats in reference allele); homozygotes have Gilbert's syndrome	31.6	39.1	14.8
Multiple variants constituting specific haplotypes	HLA-B*15:01		Predispose to immunologically mediated adverse drug reactions	[b]	[b]	5
	HLA-B*57:01			6.8	1.0	1.6
Gene deletion	CYP2D6*5		Loss of function	2.7	6	5.6
Gene duplication	CYP2D6*1xN	Duplication of normal allele	Ultra-rapid metabolizer phenotype	0.8	1.5	0.3
				Up to 3% in North Africa and the Middle East		
	CYP2D6*4xN	Duplication of loss of function allele	Extensive or poor metabolizer phenotype, depending on the opposite allele	0.3	1.4	[b]

Note: Allele frequencies from *https://gnomad.broadinstitute.org/* and *https://cpicpgx.org/*.

[a]Includes heterozygotes and homozygotes. [b]Allele frequency <0.05%. [c]*CYP2D6* is highly polymorphic, and multiple SNPs may be required to define a specific variant. For example, rs1065852 is present in both *4 and *10 variants. See *https://www.pharmvar.org/*.

Table 68-1 also highlights the fact that the frequency of important variation across pharmacogenes can vary strikingly by ancestry, with the result that certain ethnic groups may be at unusually high risk of displaying variant response to specific drugs.

Candidate Gene Approaches Most studies to date have used an understanding of the molecular mechanisms modulating drug action to identify candidate genes in which variants could explain variable drug responses. One very common scenario is that variable drug actions can be attributed to variability in plasma drug concentrations. When plasma drug concentrations vary widely (e.g., more than an order of magnitude), especially if their distribution is non-unimodal as in **Fig. 68-1**, variants in single genes controlling drug concentrations often contribute. In this case, the most obvious candidate genes are those responsible for drug metabolism and elimination. Other candidate genes are those encoding the target molecules with which drugs interact to produce their effects or molecules modulating that response, including those involved in disease pathogenesis.

Genome-Wide Association Studies The field has also had some success with "unbiased" approaches such as genome-wide association (GWA) **(Chap. 466)**, particularly in identifying single variants associated with high risk for certain forms of drug toxicity, and in validating the results of candidate gene studies. GWA studies have identified variants in the HLA locus that are associated with high risk for severe skin rashes during treatment with the anticonvulsant carbamazepine and hepatotoxicity with flucloxacillin, an antibiotic never marketed in the United States. A GWA study of simvastatin-associated myopathy identified a single noncoding SNP in *SLCO1B1*, encoding OATP1B1, a drug transporter known to modulate simvastatin uptake into the liver, which accounts for 60% of myopathy risk. African-American subjects are known to have higher dose requirements to achieve stable anticoagulation with warfarin, due in part to variations in *CYP2C9* and *VKORC1*, discussed below. In addition, a GWA study identified novel SNPs near *CYP2C9* that contribute to this effect in African Americans.

GENETIC VARIANTS AFFECTING PHARMACOKINETICS

Clinically important genetic variants have been described in multiple molecular pathways of drug disposition **(Table 68-2)**. A distinct multimodal distribution of drug disposition (as shown in Fig. 68-1) argues for a predominant effect of variants in a single gene in the metabolism of that substrate. Individuals with two alleles (variants) encoding for nonfunctional protein make up one group, often termed *poor metabolizers* (PM phenotype). For most genes, many variants can produce such a loss of function, and assessing whether they are on the same or different alleles (i.e., the *diplotype*) can complicate the use of genotyping in clinical practice. Furthermore, some variants produce only partial loss of function, and the presence of more than one variant may be required to define a specific allele. Individuals with one functional allele, or multiple reduction of function alleles, make up a second group (*intermediate metabolizers*) and may or may not be distinguishable from those with two functional alleles (normal metabolizers, sometimes termed *extensive metabolizers*, EMs). *Ultra-rapid metabolizers* (UMs) with especially high enzymatic activity (occasionally due

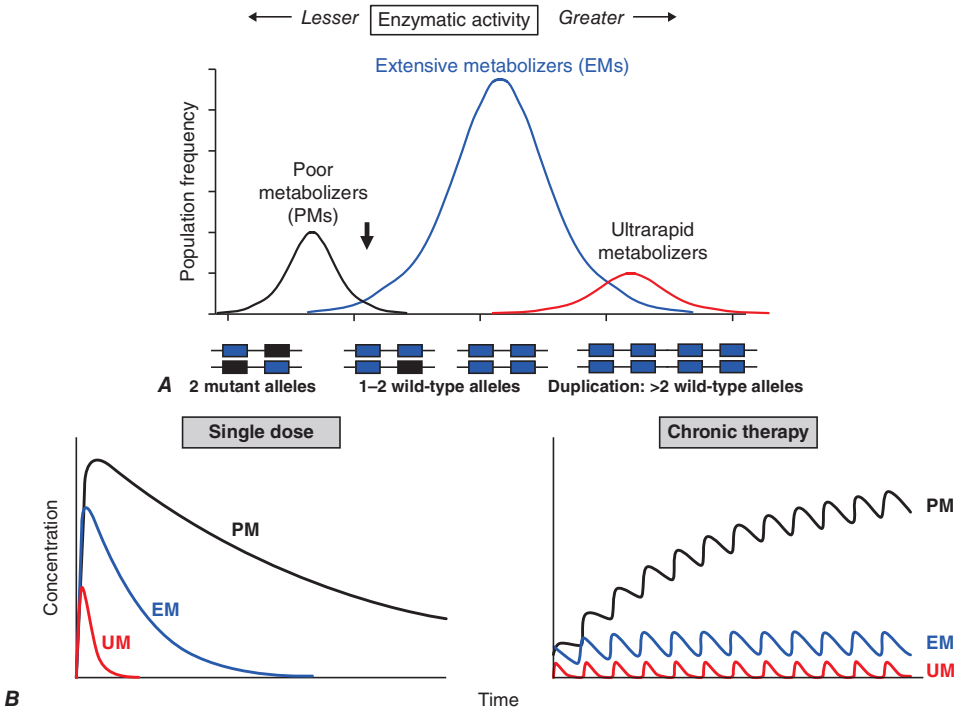

FIGURE 68-1 ***A.*** Distribution of CYP2D6 metabolic activity across a population. The heavy arrow indicates an antimode, separating poor metabolizer subjects (PMs, black), with two loss-of-function CYP2D6 alleles (black), indicated by the intron-exon structures below the chart. Individuals with one or two functional alleles are grouped together as extensive metabolizers (EMs, blue). Also shown are ultra-rapid metabolizers (UMs, red), with 2–12 functional copies of the gene, displaying the greatest enzyme activity. *(Adapted from M-L Dahl et al: J Pharmacol Exp Ther 274:516, 1995.)* ***B.*** These simulations show the predicted effects of CYP2D6 genotype on disposition of a substrate drug. With a single dose (left), there is an inverse "gene-dose" relationship between the number of active alleles and the areas under the time-concentration curves (smallest in UM subjects; highest in PM subjects); this indicates that clearance is greatest in UM subjects. In addition, elimination half-life is longest in PM subjects. The right panel shows that these single-dose differences are exaggerated during chronic therapy: steady-state concentration is much higher in PM subjects (decreased clearance), as is the time required to achieve steady state (longer elimination half-life).

TABLE 68-2 Genetic Variants and Drug Responses

GENE	DRUGS	EFFECT OF GENETIC VARIANTS[a]
Variants in Drug Metabolism Pathways		
CYP2C9	Losartan	Decreased bioactivation and effects (PMs)
	Warfarin	Decreased dose requirements; possible increased bleeding risk (PMs)
	Phenytoin	Decreased dose requirement (PMs)
CYP2C19	Omeprazole, voriconazole	Decreased effect in EMs
	Celecoxib	Exaggerated effect in PMs
	Clopidogrel	Decreased effect in PMs and IMs Consider alternate drug in PMs and alternate drug or dose increase in IMs Possible increased bleeding risk in carriers of gain-of-function variants
	Citalopram, escitalopram	Choose alternate drug in UMs; reduce dose in PMs
CYP2D6	Codeine, tamoxifen	Decreased bioactivation and drug effects in PMs
	Codeine	Respiratory depression in UMs
	Tricyclic antidepressants[b]	Increased adverse effects in PMs: Consider dose decrease Decreased therapeutic effects in UMs: Consider alternate drug
	Metoprolol, carvedilol, timolol, propafenone	Increased beta blockade in PMs
	Fluvoxamine	Reduce dose or chose alternate drug in PMs
CYP3A5	Tacrolimus, vincristine	Decreased drug concentrations and effect (CYP3A5*3 carriers)
Dihydropyrimidine dehydrogenase (*DPYD*)	Capecitabine, 5-fluorouracil, tegafur	Possible severe toxicity (PMs)
NAT2	Rifampin, isoniazid, pyrazinamide, hydralazine, procainamide	Increased risk of toxicity in PMs
Thiopurine *S*-methyltransferase (*TPMT*)	Azathioprine, 6-mercaptopurine, thioguanine	PMs: Increased risk of bone marrow aplasia EMs: Possible decreased drug action at usual dosages
Uridine diphosphate glucuronosyltransferase (*UGT1A1*)	Irinotecan	PM homozygotes: Increased risk of severe adverse effects (diarrhea, bone marrow aplasia)
	Atazanavir	High risk of hyperbilirubinemia during treatment; can result in drug discontinuation
Pseudocholinesterase (*BCHE*)	Succinylcholine and other muscle relaxants	Prolonged paralysis (autosomal recessive); diagnosis established by genotyping or by measuring serum cholinesterase activity

(*Continued*)

TABLE 68-2 Genetic Variants and Drug Responses (Continued)

GENE	DRUGS	EFFECT OF GENETIC VARIANTS[a]
Variants in Other Genes		
Glucose 6-phosphate dehydrogenase (*G6PD*)	Rasburicase, primaquine, chloroquine	Increased risk of hemolytic anemia in G6PD-deficient subjects
HLA-B*15:02	Carbamazepine	Carriers (1 or 2 alleles) at increased risk of SJS/TEN (mainly Asian subjects)
HLA-B*31:01	Carbamazepine	Carriers (1 or 2 alleles) at increased risk of SJS/TEN and milder skin toxicities (Caucasian and Asian subjects)
HLA-B*15:02	Phenytoin	Carriers (1 or 2 alleles) at increased risk of SJS/TEN
HLA-B*57:01	Abacavir	Carriers (1 or 2 alleles) at increased risk of SJS/TEN
HLA-B*58:01	Allopurinol	Carriers (1 or 2 alleles) at increased risk of SJS/TEN
IFNL3 (IL28B)	Interferon	Variable response in hepatitis C therapy
SLCO1B1	Simvastatin	Encodes a drug uptake transporter; variant nonsynonymous single nucleotide polymorphism increases myopathy risk especially at higher dosages
VKORC1	Warfarin	Decreased dose requirements with variant promoter haplotype Increased dose requirement in individuals with nonsynonymous loss-of-function variants
ITPA	Ribavirin	Variants modulate risk for hemolytic anemia
RYR1	General anesthetics	Variants predispose to malignant hyperthermia
CFTR	Ivacaftor, lumacaftor	Targeted therapies for cystic fibrosis indicated only in certain genotypes
Variants in Other Genomes (Infectious Agents, Tumors)		
Chemokine C-C motif receptor (CCR5)	Maraviroc	Drug effective only in HIV strains with CCR5 detectible
C-KIT	Imatinib	In gastrointestinal stromal tumors, drug indicated only with c-kit–positive cases
ALK (anaplastic lymphoma kinase)	Crizotinib	Indicated in patients with non-small cell lung cancer and ALK mutations
Her2/neu overexpression	Trastuzumab, lapatinib	Drugs indicated only with tumor overexpression
K-ras mutation	Panitumumab, cetuximab	Lack of efficacy with *KRAS* mutation
Philadelphia chromosome	Dasatinib, nilotinib, imatinib	Decreased efficacy in Philadelphia chromosome–negative chronic myelogenous leukemia

[a]Drug effect in homozygotes unless otherwise specified. [b]Many tricyclic antidepressants and selective serotonin uptake inhibitors are metabolized by CYP2D6, CYP2C19, or both, and some metabolites have pharmacologic activity. See *https://www.pharmgkb.org/view/dosing-guidelines.do*.

Abbreviations: EM, extensive metabolizer (normal enzymatic activity); IM, intermediate metabolizer (heterozygote for loss-of-function allele); PM, poor metabolizer (homozygote for reduced or loss-of-function allele); SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis; UM, ultra-rapid metabolizer (enzymatic activity much greater than normal, e.g., with gene duplication, Fig. 68-1).

Further data at:

U.S. Food and Drug Administration: *http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm*

Pharmacogenetics Research Network/Knowledge Base: *http://www.pharmgkb.org*

The Clinical Pharmacogenomics Implementation Consortium: *https://www.pharmgkb.org/page/cpic*

Dutch Pharmacogenetics Working Group: *https://www.knmp.nl/patientenzorg/medicatiebewaking/farmacogenetica/pharmacogenetics-1/pharmacogenetics*

to gene duplication; Table 68-1 and Fig. 68-1) have also been described for some traits. Many drugs in widespread use can inhibit specific drug disposition pathways **(see Chap. 67, Table 67-1)**, and so EM individuals receiving such inhibitors can respond like PM patients (*phenocopying*). Polymorphisms in genes encoding drug uptake or drug efflux transporters may be other contributors to variability in drug delivery to target sites and, hence, in drug effects.

CYP3A Members of the CYP3A family (*CYP3A4*, *CYP3A5*) metabolize the greatest number of drugs in therapeutic use. CYP3A4 activity is highly variable (up to an order of magnitude) among individuals, but nonsynonymous coding region polymorphisms (those that change the encoded amino acid) are rare. Thus, the underlying mechanism likely reflects genetic variation in regulatory regions.

Most subjects of European or Asian origin carry a polymorphism that disrupts splicing in the closely related *CYP3A5* gene. As a result, these individuals display reduced CYP3A5 activity, whereas CYP3A5 activity tends to be greater in subjects of African origin. Decreased efficacy of the antirejection agent tacrolimus in subjects of African origin has been attributed to more rapid CYP3A5-mediated elimination, and a lower risk of vincristine-associated neuropathy has been reported in CYP3A5 "expressers."

CYP2D6 CYP2D6 is second to CYP3A4 in the number of commonly used drugs that it metabolizes. CYP2D6 activity is polymorphically distributed, and 5–10% of European- and African-derived populations (but few Asians) display the PM phenotype (Fig. 68-1). Dozens of loss-of-function variants in *CYP2D6* have been described; the PM phenotype arises in individuals with two such alleles. In addition, UMs with multiple functional copies of *CYP2D6* have been identified especially in East Africa, the Middle East, and Oceania. PMs have slower elimination rates and lower clearance of substrate drugs; as a consequence (Fig. 68-1*B*), steady-state concentrations are higher and the time taken to achieve steady state is longer than in EMs **(Chap. 67)**. Conversely, UMs display very low steady-state parent drug concentrations and an abbreviated time to steady state.

Codeine is biotransformed by CYP2D6 to the potent active metabolite morphine, so its effects are blunted in PMs and exaggerated in UMs. Deaths due to respiratory depression in children given codeine after tonsillectomy have been attributed to the UM trait, and the U.S. Food and Drug Administration (FDA) has revised the package insert to include a prominent "black box" warning against its use in this setting, and, in fact, forbidding its use in children less than 12 years old. In the case of drugs with beta-blocking properties metabolized by CYP2D6, greater signs of beta blockade (e.g., bronchospasm, bradycardia) have been reported in PM subjects than in EMs. This can be seen not only with orally administered beta blockers such as metoprolol and carvedilol, but also with ophthalmic timolol and with the sodium channel–blocking antiarrhythmic propafenone, a CYP2D6 substrate with beta-blocking properties. UMs may require very high dosages of nortriptyline and other tricyclic antidepressants to achieve a therapeutic

effect. Tamoxifen undergoes CYP2D6-mediated biotransformation to an active metabolite, so its efficacy may be in part related to this polymorphism. In addition, the widespread use of selective serotonin reuptake inhibitors (SSRIs) to treat tamoxifen-related hot flashes may also alter the drug's effects because many SSRIs, notably fluoxetine and paroxetine, are also CYP2D6 inhibitors (Table 67-2).

CYP2C19 The PM phenotype for CYP2C19 is common (20%) among Asians and rarer (2–3%) in other populations; the frequency of the PM trait is especially high (>50%) in Oceania. The impact of polymorphic CYP2C19-mediated metabolism has been demonstrated with the proton pump inhibitor omeprazole, where ulcer cure rates with "standard" dosages were much lower in EM patients (29%) than in PMs (100%). Thus, understanding the importance of this polymorphism would have been important in developing the drug, and knowing a patient's *CYP2C19* genotype could improve therapy. CYP2C19 is responsible for bioactivation of the antiplatelet drug clopidogrel, and several large retrospective, and more recently prospective, studies have documented decreased efficacy (e.g., increased myocardial infarction after placement of coronary stents or increased stroke or transient ischemic attacks) among subjects with one or two reductions of function alleles. In addition, some studies suggest that omeprazole and possibly other proton pump inhibitors phenocopy this effect by inhibiting CYP2C19.

CYP2C9 There are common variants in *CYP2C9* that encode proteins with reduction or loss of catalytic function. These variant alleles are associated with increased rates of neurologic complications with phenytoin, hypoglycemia with glipizide, and reduced warfarin dose required to maintain stable anticoagulation. Rare patients homozygous for loss-of-function alleles may require very low warfarin dosages. Up to 50% of the variability in steady-state warfarin dose requirement is attributable to polymorphisms in *CYP2C9* and in the promoter of *VKORC1*, which encodes the warfarin target with lesser contributions by genes such as *CYP4F2* controlling vitamin K metabolism. The angiotensin receptor blocker losartan is a prodrug that is bioactivated by CYP2C9; as a result, PMs and those receiving inhibitor drugs may display little response to therapy.

DPYD Individuals homozygous for loss-of-function alleles in dihydropyrimidine dehydrogenase, encoded by *DPYD*, are at increased risk for severe toxicity when exposed to the substrate anticancer drug 5-fluorouracil (5-FU), as well as to capecitabine and tegafur, which are metabolized to 5-FU. Dose reductions have been recommended in intermediate metabolizers.

Transferase Variants Thiopurine *S*-methyltransferase (TPMT) bioinactivates the antileukemic drug 6-mercaptopurine (6-MP), and 6-MP is itself an active metabolite of the immunosuppressive azathioprine. Homozygotes for alleles encoding inactive TPMT (1/300 individuals) predictably exhibit severe and potentially fatal pancytopenia on standard doses of azathioprine or 6-MP. On the other hand, homozygotes for fully functional alleles may display less anti-inflammatory or antileukemic effect with standard doses of the drugs. GWA studies have also identified loss-of-function variants in *NUDT15* that reduce degradation of thiopurine metabolites and, thereby, also increase risk of excessive myelosuppression.

N-acetylation is accomplished by hepatic *N*-acetyl transferase (NAT), which represents the activity of two genes, *NAT1* and *NAT2*. Both enzymes transfer an acetyl group from acetyl coenzyme A to the drug; polymorphisms in *NAT2* are thought to underlie individual differences in the rate at which drugs are acetylated and thus define "rapid acetylators" and "slow acetylators." Slow acetylators make up ~50% of European and African populations but are less common among East Asians. Slow acetylators have an increased incidence of the drug-induced lupus syndrome during procainamide and hydralazine therapy and of hepatitis with isoniazid.

Individuals homozygous for a common promoter polymorphism that reduces transcription of uridine diphosphate glucuronosyltransferase (*UGT1A1*) have benign hyperbilirubinemia (Gilbert's syndrome; **Chap. 337**). This variant has also been associated with diarrhea and increased bone marrow depression with the antineoplastic prodrug irinotecan, whose active metabolite is normally detoxified by UGT1A1-mediated glucuronidation. The antiretroviral atazanavir is a UGT1A1 inhibitor, and individuals with the Gilbert's variant develop higher bilirubin levels during treatment. While this is benign, the hyperbilirubinemia can complicate clinical care because it may raise the question of whether coexistent hepatic injury is present.

Transporter Variants The risk for myotoxicity with simvastatin and possibly other statins appears increased with variants in *SLCO1B1*. Variants in *ABCB1*, encoding the drug efflux transporter P-glycoprotein, may increase digoxin toxicity. Variants in the uptake transporters *MATE1* and *MATE2* have been reported to modulate metformin's glucose-lowering activity.

GENETIC VARIANTS AFFECTING PHARMACODYNAMICS

A variant in the *VKORC1* promoter, especially common in Asian subjects (Table 68-1), reduces transcriptional activity and warfarin dose requirement. Multiple polymorphisms identified in the β_2-adrenergic receptor appear to be linked to specific drug responses in asthma and congestive heart failure, diseases in which β_2-receptor function might be expected to determine drug response. Polymorphisms in the β_2-receptor gene have also been associated with response to inhaled β_2-receptor agonists, while those in the β_1-adrenergic receptor gene have been associated with variability in heart rate slowing and blood pressure lowering. In addition, in heart failure, the arginine allele of the common β_1-adrenergic receptor gene polymorphism R389G has been associated with decreased mortality and decreased incidence of atrial fibrillation during treatment with the investigational beta blocker bucindolol.

Drugs may also interact with genetic pathways of disease to elicit or exacerbate symptoms of the underlying conditions. In the porphyrias, CYP inducers are thought to increase the activity of enzymes proximal to the deficient enzyme, exacerbating or triggering attacks **(Chap. 416)**. Deficiency of glucose-6-phosphate dehydrogenase (G6PD), most often in individuals of African, Mediterranean, or South Asian descent, increases the risk of hemolytic anemia in response to the antimalarial primaquine **(Chap. 100)** and the uric acid-lowering agent rasburicase, which does not cause hemolysis in patients with normal amounts of the enzyme. Patients with mutations in *RYR1* encoding the skeletal muscle intracellular release calcium (also termed type 1 ryanodine receptor) are asymptomatic until exposed to certain general anesthetics, which can trigger the rare syndrome of malignant hyperthermia. Certain antiarrhythmics and other drugs can produce marked QT prolongation and torsades de pointes **(Chap. 246)**, and in a minority of affected patients, this adverse effect represents unmasking of previously subclinical congenital long QT syndrome.

Immunologically Mediated Drug Reactions The Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) is a potentially fatal skin and systemic reaction now increasingly recognized to be linked to specific HLA alleles (Table 68-2). Cases of drug-induced hepatotoxicity and of the drug rash with eosinophilia and systemic symptoms (DRESS) syndrome have also been linked to variants in this region. The frequency of risk alleles often varies by ancestry (Table 68-1). The HLA risk alleles appear to be necessary but not sufficient to elicit these reactions. For example, HLA-B*57:01 is a risk allele for abacavir-related SJS/TEN and flucloxacillin-related hepatotoxicity. However, while 55% of abacavir-exposed subjects will develop a reaction, only 1/10,000 subjects exposed to flucloxacillin develop hepatotoxicity. Thus, a third factor, the nature of which has not yet been established, seems necessary.

Tumor and Infectious Agent Genomes The actions of drugs used to treat infectious or neoplastic disease may be modulated by variants in these nonhuman germline genomes. Genotyping tumors is a rapidly evolving approach to target therapies to underlying mechanisms and to avoid potentially toxic therapy in patients who would derive

no benefit (Chap. 71). Trastuzumab, which potentiates anthracycline-related cardiotoxicity, is ineffective in breast cancers that do not express the Herceptin receptor. Imatinib targets a specific tyrosine kinase, BCR-Abl1, that is generated by the translocation that creates the Philadelphia chromosome typical of chronic myelogenous leukemia (CML). Imatinib is also an inhibitor of another kinase, c-kit, and the drug is remarkably effective in c-kit-driven cancer, such as gastrointestinal stromal tumors (Chap. 71). Vemurafenib does not inhibit wild-type *BRAF* but is active against the V600E mutant form of the kinase. Crizotinib is highly effective in non-small cell lung cancers harboring anaplastic lymphoma kinase (ALK) mutations.

INCORPORATING PHARMACOGENETIC INFORMATION INTO CLINICAL PRACTICE

The discovery of common variant alleles with relatively large effects on drug response raises the prospect that these variants could be used to guide therapy. Desired outcomes could be better ways of choosing likely effective drugs and dosages, or avoiding drugs that are likely to produce severe adverse drug events or be ineffective in individual subjects. Indeed, the FDA now incorporates pharmacogenetic data into package inserts meant to guide prescribing. A decision to adopt pharmacogenetically guided dosing for a given drug depends on multiple factors. The most important are the magnitude and clinical importance of the genetic effect and the strength of evidence linking genetic variation to variable drug effects (e.g., anecdote versus post-hoc analysis of clinical trial data versus randomized clinical trial [RCT]). The evidence can be strengthened if statistical arguments from clinical trial data are complemented by an understanding of underlying physiologic mechanisms. Cost versus expected benefit may also be a factor.

Point of Care Versus Preemptive Approaches Two approaches to pharmacogenetic implementation have been put in place at "early adopter" institutions and are currently being evaluated. In the first, variant-specific assays are ordered at the time of drug prescription and delivered rapidly (often within an hour or two), and the results are then used to guide therapy with that specific drug. The alternative to this "point-of-care" approach is a "preemptive" approach in which pharmacogenetic testing for large numbers of potential variants across many drugs is undertaken prior to prescription of any such drug. The data are then available in electronic health record (EHR) systems and coupled to real-time clinical decision support (CDS). When a drug whose effects are known to be influenced by pharmacogenetic variants is prescribed, the EHR system looks up whether variants likely to affect response are present; if so, CDS will alert health care providers that an alternate drug or a different dose may be required.

Challenges There are multiple challenges in putting in place either system. Assay validity and reproducibility have been issues in the past, but are less likely now. National consortia are now being put in place to develop standards for pharmacogenetic CDS. While common variants in genes such as those listed in Table 68-1 have been clearly associated with variable drug responses, the effect of rare variants, now readily discoverable by large-scale sequencing, is unknown. The extent to which a dose adjustment might be recommended may vary depending on whether zero, one, or two variant alleles are present, and whether such variants are reduction of function, loss of function, or gain of function. The Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group have developed and published guidelines for multiple drug-gene pairs focusing on the question of what might be an appropriate drug dose adjustment given the availability of genetic data. These resources do not directly address the question of when or how such genetic testing should be undertaken.

Developing Evidence That Pharmacogenetic Testing Alters Drug Outcomes A major issue is whether pharmacogenetic testing affects important drug response outcomes. When the evidence is compelling, alternate therapies are not available, and there are clear recommendations for dosage adjustment in subjects with variants, there is a strong argument for deploying genetic testing as a guide to prescribing; HLA-B*57:01 testing for abacavir is an example described below. In other situations, the arguments are less compelling: the magnitude of the genetic effect may be smaller, the consequences may be less serious, alternate therapies may be available, or the drug effect may be amenable to monitoring by other approaches.

One school argues that the physiology and pharmacology are known and that RCTs are, therefore, unnecessary (and conceivably unethical). The analogy is sometimes drawn to well-recognized dose adjustment of renally excreted drugs in the presence of renal dysfunction. RCTs have not been conducted and the idea of such dose adjustment is well accepted in the medical community and recommended in FDA-approved drug labels. Others have argued that the effect of genetic variants is generally modest and variability in drug actions has many nongenetic sources, so genetic testing might provide marginal benefit at best.

Efforts to demonstrate the value of pharmacogenetic testing have met with mixed results. An RCT clearly showed that HLA-B*57:01 testing eliminates SJS/TEN due to abacavir. Similarly, regulatory authorities in some countries in Southeast Asia mandated HLA-B*15:02 testing prior to initiation of carbamazepine; however, in this case, an unfortunate outcome in some jurisdictions was that prescribers stopped using carbamazepine, often substituting phenytoin (another drug associated with SJS/TEN), so the incidence of the severe ADR was unchanged.

RCTs evaluating the effect of using pharmacogenetically guided therapy to optimize warfarin treatment have shown either no effect or a modest benefit of incorporating genetic information into prescribing the drug. Initial RCTs focused on time in therapeutic range in the first 4–12 weeks of treatment, whereas one more recent trial demonstrated that genotype-guided therapy could reduce the frequency of over-anticoagulation. Retrospective analyses of bleeding cases versus non-bleeding controls in EHRs and administrative databases have suggested a role for CYP2C9*3 or for the V433M variant in *CYP4F2* in mediating this risk.

Two large trials have randomized patients with acute coronary syndromes to newer antiplatelet therapies (ticagrelor or prasugrel) or clopidogrel if *CYP2C19* variants were absent; in one, clopidogrel was superior, and in the second, a trend in the same direction, which did not reach the prespecified endpoint, was observed.

New effective alternate therapies to warfarin and clopidogrel that appear to lack important pharmacogenetic variants have emerged. One approach to therapy, therefore, is to use pharmacogenetic testing to identify subjects in whom variants are absent and therefore standard doses of the conventional inexpensive drugs are likely to be effective and to reserve alternate more expensive therapies for subjects likely to have variant responses to warfarin or clopidogrel.

GENETICS AND DRUG DEVELOPMENT

Genetic tools are now being increasingly used to identify or validate new drug targets. Initial studies suggest that a new drug development program is more likely to succeed if evidence from human genetics supports the role of a possible drug target in disease pathogenesis and suggests that the risk of toxicity due to high-risk pharmacokinetics or other mechanisms is small. Furthermore, studies of the relationships between variants in genes encoding drug target molecules and a range of phenotypes (e.g., those in EHRs) are being used for drug "repurposing," identifying new indications for existing drugs.

Finding Protective Alleles Can Identify Drug Targets One example of using genetics to identify a new drug target started with the discovery that very rare gain-of-function variants in *PCSK9* are a rare cause of familial hypercholesterolemia. Subsequently, population studies showed that carriers of loss-of-function SNPs (2.5% of African Americans) had decreased low-density lipoprotein cholesterol, decreased incidence of coronary artery disease, and no deleterious consequences in other organ systems. These data triggered the development of PCSK9 monoclonal antibodies, which were marketed <10 years after the initial population studies. Other targets implicated by similar population genetic studies include HSD17B13 for

prevention of chronic liver disease, SLC30A8 for the prevention of type 2 diabetes, and APOC3 for hypertriglyceridemia. Discovering rare protective alleles may require very large data sets (>100,000), such as EHR systems coupled to DNA biobanks or epidemiologic cohorts like the UK Biobank.

Cancer In cancer, tumor sequencing has identified new targets for drug development, often constitutively active kinases. A problem in this area has been the rapid emergence of drug resistance, often after extraordinary initial responses. For example, 40% of melanomas appear to be driven by the V600E mutant form of *BRAF*, and the specific inhibitor vemurafenib can produce clinically spectacular remission. However, durable responses are rare, and it is now apparent that combination therapy, often with inhibitors of the MEK pathway, can provide improved therapy. Another approach that is rapidly gaining wide use in cancer involves drugs that reverse immune system inhibition **(Chap. 73)**. In some patients, the release of this "brake" can provide durable remissions, whereas in others, severe adverse events, including colitis, pneumonitis, and myocarditis, have been reported. Understanding the mechanisms underlying variability to these therapies is a major emerging challenge in the field.

Using Multiple Data Types The development of methods to understand associations across multiple large data sets is another approach that is being explored in drug development. For example, a GWA study of risk of rheumatoid arthritis identified multiple risk loci, and many encode proteins that are known targets for intervention in the disease. Interestingly, others encode proteins that are targets for drugs used in other conditions, such as certain cancers, raising the question of whether such drugs could be "repurposed" for rheumatoid arthritis.

While the field has, to date, focused on individual high effect size variants (that are often common in a population), newer approaches combining many (dozens to millions) common variants into polygenic risk scores to predict drug responses are also being explored. An extension of this approach is the broader issue of systems pharmacology, in which multiple sources of data are used to identify potential molecules or pathways that would be amenable to treatment, by new drugs or by existing agents, using analysis of genomic, transcriptomic, proteomic, and other large data sets. Similar approaches are being developed to predict toxicity expected from targeting specific genes or disease pathways.

SUMMARY

The science of pharmacogenomics has evolved from isolated examples of rare adverse drug actions to a more comprehensive view of the role of genetic variation in mediating the effects of most drugs. Current principles include:

- Genetic variants with an important effect on drug actions can be common, and their frequencies often vary by ancestry.
- One common mechanism is modulation of drug concentrations.
- No practitioner can be expected to remember all variants important for all drugs. Electronic data systems can now be accessed to describe this information. Ultimately, this information will be used by linking individual pharmacogenetic data to smart EHR systems.
- Incorporating genetic approaches into drug development projects holds the promise of more rapid development of targeted, safe, and effective therapies.

FURTHER READING

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