

Introduction to Clinical Pharmacology

Introduction to Clinical Pharmacology:

From Symptoms to Treatment

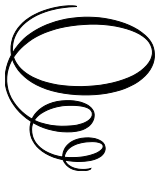
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PREFACE

VICTOR UTESHEV

The teacher-centric didactic method of learning excessively focuses on memorizing data and has been viewed as inadequate for medical education. (Neufeld and Barrows 1974) As a result, the student-centric self-directed learning method termed Problem-Based Learning (PBL) has been introduced as a superior strategy (Barrows 1983) which facilitates the acquisition of pre-clinical knowledge and skills and allows medical, professional, and graduate students to learn how to approach and solve real-world problems. (Barrows and Tamblyn 1980) In 1965-1968, an innovative concept of *simulated patients* was developed for pre-clinical teaching of medical students by Dr. Howard S. Barlow and colleagues. (Barrows 1968) Those efforts gradually led to the PBL. Following the PBL guidance, in this textbook, each chapter is built around patient presentation advancing from symptoms through diagnosis to treatment as anticipated in clinical practice.

It is anticipated that this textbook will give medical, pharmacy, and graduate students a guided understanding of how practicing physicians think when facing symptoms and determining treatments by working through multiple steps including differential diagnoses, imaging, and lab results before achieving a final diagnosis. Tracking the pharmacology of a particular type of drug as pertaining to specific symptoms is a unique feature of this book. Each section discusses specific symptom-based mechanisms and drug treatments followed by relevant cases/questions. The main objective is to provide concise, focused information on pharmacological treatments and mechanisms of action as related to specific symptoms and patient presentation. The prime target audience includes medical students preparing for the United States Medical Licensing Examination (USMLE), the Comprehensive Osteopathic Medical Licensing Examination (COMLEX) in the United States, or similar exams in other countries, pharmacy students, pharmacology/physiology students, practicing physicians and pharmacists, and pre-medical students preparing for medical school. Certain important topics are not covered in this edition including oncology, dermatology, and substance abuse. These and other subjects will be addressed in future editions.

This textbook is an invited contribution of world experts in medical research and education. As this project is approaching its final stage, I am pleased to see that this tribute generously offered by Cambridge Scholars Publishing was enthusiastically used by the authors and I hope that their efforts will find an adequate positive response among medical, professional, and graduate students around the world.

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November 25th, 2022*

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CHAPTER 1

THE CONCEPT AND BRIEF HISTORY OF PHARMACOLOGY

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Pharmacology is the study of the composition, potential therapeutic effects and toxicity, therapeutic index, molecular mechanisms, cellular interaction, and overall impact of chemicals on the body. The two components that make up pharmacology are pharmacodynamics (what the drug does to the body) and pharmacokinetics (what the body does to the drug) of the chemical component (see Chapter 2). Pharmacology is essential for the drug development process. Pharmaceutical scientists create novel therapeutic compounds, whereas pharmacologists study the absorption, distribution, metabolism, excretion, and chemical effects on the body. The pharmacologist then can begin to understand the mechanism of the drug action by looking at the side effects, drug interactions, effects on pregnancy, age- and sex-dependent dosages, and the effects on different races, sexes, and ethnicities before any of the novel compounds make it to clinical trials (U.S. Department of Health and Human Services 2021).

The usage and search for therapeutic chemical components have been around for thousands of years worldwide. The precursors of this field trace back to the oldest known medicinal texts. These include the Sumerian clay slab from Nagpur, The Pen Ts'ao (a Chinese medicinal book written by Emperor Shen Nung) (Petrovska 2012), and The Ebers Papyrus, an Egyptian medical scroll that dates back to 1552 B.C., containing remedies to cure illnesses (Major 1930). These texts include recipes for drugs that use various herbs and plants available to their respective civilizations at the time of writing, demonstrating that humans have used various naturally occurring chemical compounds to cure and treat diseases for most, if not all, of recorded history.

Many people influenced the field of pharmacology and toxicology as we know it today. This dates back to Philippus Aureolus Theophrastus Bombastus von Hohenheim, a German-Swiss physician and alchemist, known as Paracelsus (1493-1541) (Michaleas et al. 2021). Born in Einsiedeln, Switzerland, he played a significant role in shaping our modern understanding of toxicology. Following the death of his mother, the family moved to Villach in Carinthia, where his father Wilhelm Bombast von Hohenheim, a physician and an alchemist (Borzelleca 2000), taught chemistry. While in Villach, Paracelsus worked in the mines. This gave Paracelsus knowledge of metallurgy, which likely influenced his later discoveries. In 1507, Paracelsus began traveling through Europe in search of world-renowned professors. During this time, Paracelsus attended various universities. Finally, in 1510, he received his baccalaureate in medicine from the University of Vienna, and in 1516 received his doctoral degree from the University of Ferrara. This is when he began using the name Paracelsus (Michaleas et al. 2021).

Paracelsus was disappointed with his academic endeavors as he believed, in his own words, "the universities do not teach all things" (Borzelleca 2000). He began to broaden his education by traveling through Europe, ultimately becoming an army surgeon (Hartmann 1896). During this search, he expanded his knowledge of alchemy and how to use what he termed "the latent forces of Nature." This experience led him to question the fundamental medical ideologies of the time (Cintas 2003). In 1524, Paracelsus returned to Villach, was appointed the town's physician, and became a lecturer at the University of Basel. His reputation for curing disease led to his lectures being well attended. In his classes, Paracelsus discussed the healing powers of nature. He also denounced several methods of treatment, which caused him to dispute with the local doctors, causing him to leave Basel in 1528 and travel once again. It was then when Paracelsus contributed significantly to the field of medicine. He went against the treatments of the time and described new treatment options. An example of this was when he used specified mercury compound doses to treat Syphilis, making him a pioneer in the application of minerals and metals for medicinal purposes. He emphasized that "a poison in the body would be cured by a similar poison," but the dosage is what makes it therapeutic. He expanded on this idea of dose responses in his work "Third Defense." Paracelsus greatly influenced toxicology with his ideology of learning and understanding that "the dose determines that a thing is not a poison" (Borzelleca 2000).

The study of pharmacology has progressed greatly from the times of Paracelsus to our current understanding of modern experimental pharmacology. Almost 300 years later, Rudolf Buchheim (1820-1879) set up the first pharmacology laboratory and later established an institute of pharmacology. Buchheim was a medical student when he began working as a research assistant to Ernst Heinrich Weber (1795-1878), a famous physiologist (Muscholl et al. 1995). His supervisor, Karl Gotthelf Lehmann (1812-1863), introduced him to the medicinal aspect of chemicals, leading him to his future studies. His scholastic endeavors allowed him to become a professor at the University of

Dorpat, where he lacked funding and decided to build a laboratory in the basement of his house. In 1860, he relocated to the newfound institute of pharmacology, where he mentored many students, some of whom became his successors (Scheidlin 2001). Buchheim established the basics of pharmacology by establishing that physiology and pathology are the roots of pharmacology. He correctly believed that a chemical's processes controlled an organism's functions and classified them by their mechanisms of action rather than their chemical class and origin (Muscholl et al. 1995).

Although Buchheim established the basic principles of pharmacology, his student Oswald Schmiedeberg (1838-1921) is recognized as the father of modern experimental pharmacology. Schmiedeberg was a devoted scientist who first introduced pharmacodynamics and pharmacokinetics, making pharmacology an autonomous scientific discipline (Pokrovskii et al. 2017). He received his Doctor of Medicine from Dorpat after submitting his thesis about chloroform measurements in the blood and succeeded Buchheim at Dorpat in 1869 (Scheidlin 2001).

In 1872, after receiving government funding and building an astonishing pharmacology institute, Schmiedeberg became a professor of pharmacology at the University of Strassburg. He taught there for 46 years, where he excelled in the field. It was during this time that he identified that muscarine evoked similar effects on the heart as the vagus nerve, used urea derivatives as a hypnotic, discovered nicotine's ability to block cardiac vagal ganglia, and found the toxic activity of heavy metals, among other findings (Muscholl et al. 1995). He also trained numerous successful pharmacologists. One of his apprentices was John Jacob Abel (1857-1938), the first chair of pharmacology at the University of Michigan, who later went to Johns Hopkins University, where he accomplished isolating epinephrine from extracts of adrenal glands and histamine isolation from the pituitary (Scheidlin 2001).

But The Best Treatment is Prevention

Chronic diseases such as heart disease, stroke, and diabetes are the leading causes of death and disabilities. In 2014, 60% of the adult population in America had one chronic condition, and 42% had multiple chronic diseases. These diseases affect the quality of life of the patient and their families. A person with a chronic illness has various limitations, which can lead to depression and losing their ability to cope with pain, resulting in worse disease outcomes. People with chronic diseases are also more likely to spend more on prescription drugs than those without. These diseases can also make it difficult for the patients to work, coinciding with lower incomes and, thus, impacting their finances (Levine et al. 2019).

Chronic diseases are the driving force of the rising costs of health care, which are expected to increase dramatically in the next few decades. It is estimated that 86% of healthcare-related expenses are due to the treatment of chronic diseases (Holman HR 2020). In 2016, treatment costs were more than \$1 trillion, with Diabetes, Alzheimer's, and Osteoarthritis being the leaders of the increased costs. As the world population ages, these costs are projected to increase. Over 80 million Americans will have at least three chronic diseases by 2030 (Levine et al. 2019).

The prevention of disease requires drastic lifestyle changes and education across the general public, as the cause of disease is largely in part due to human behavior, including fitness and health considerations. The best course of action is to stop the onset of disease before it progresses, as there are lasting emotional and physical impacts from disease, which for some, can amount to death.

The degrees of clinical preventative strategies for disease consist of primary, secondary, and tertiary prevention. In primary prevention, healthcare providers intervene before the appearance of disease. In secondary prevention, health providers detect the disease in the early stages and begin treatment. Finally, in tertiary prevention, healthcare providers work with the patient to reduce or stop the progression of disease (Levine et al. 2019). These interventions can mitigate the detrimental implications of disease on the body. However, the lack of implementation of these preventive measures further contributes to disease progression. Nonetheless, chronic diseases can be prevented by healthier lifestyle routines such as exercising, healthy eating habits, refraining from excessive alcohol, and avoiding tobacco use.

Dietary changes help prevent and manage chronic diseases, such as Type 2 Diabetes, as well as cardiovascular diseases. This includes having a balanced diet with various vegetables, lean proteins, fruits, and whole grains. Additionally, limiting food high in sugars, sodium, and saturated fats will have a positive impact on health. In addition, eating balanced meals has been shown to improve insulin sensitivity. Whereas, having a diet with a high intake of processed meats (hot dogs, deli meats, etc.) has been shown to increase the risk of cardiovascular diseases, and high consumption of unprocessed red meats has an associated increased rate of colon cancer and cardiovascular mortality. A diet based on fish, poultry, and unprocessed red meat thus serves as a healthier alternative (Yu et al. 2018). This kind of preventative care is medically and financially beneficial, as heart disease costs the United States roughly \$219 billion annually (Office of the Associate Director for Policy and Strategy 2021).

Observational trials show that exercise contributes to the primary and secondary prevention of cardiovascular disease. Health benefits can be seen with light to moderate intensity exercise on most days of the week for about 20 to 60 minutes, averaging at least 150 minutes per week (Warburton et al. 2008). Regular physical activity can decrease a

patient's blood pressure and improve cholesterol. This can reduce the risk of developing Type 2 Diabetes. If a patient does muscle-strengthening activities such as weightlifting, they can increase strength, muscle, and bone density, decreasing the risk of Osteoporosis (Centers for Disease Control and Prevention 2022). Increased physical activity has a plethora of health benefits, even for a short time, as it can help prevent and manage existing chronic diseases.

Limiting tobacco and alcohol use can aid in lowering the risk of various comorbidities that can lead to chronic diseases. For example, excess drinking can lead to liver disease, stroke, high blood pressure, and heart disease. This can be reduced by decreasing alcohol intake. Smoking can also lead to serious health problems. By quitting smoking, individuals are reducing the risk of lung disease, Type 2 Diabetes, and the risk of heart disease (Centers for Disease Control and Prevention, 2022).

Using Drugs Only as The Last Resort

People generally require more medications as they age. These can include statins to lower cholesterol levels, alpha-blockers for high blood pressure, proton-pump inhibitors for acid reflux, and painkillers for pain management related to injury, among other medications. All medications carry risks, resulting in unwanted or unexpected side effects, which can range from headaches, dizziness, fatigue, rash, and nausea to more severe side effects such as liver failure, abnormal heart rhythms, and increased risk of bleeding. A few of these medications can be avoided through dietary lifestyle changes.

When taking prescribed drugs, a patient can also risk experiencing unwanted side effects due to drug interactions. The interactions can appear in the form of two drugs interacting together, such as aspirin and blood thinners. It can also occur with drugs and food, such as eating grapefruit, an inhibitor of cytochrome p450 CYP3A4, which can increase the toxicity of statins, such as atorvastatin; thus, consumption of grapefruit juice should be avoided while on CYP3A4-sensitive medications (Ramkumar et al. 2016). There are also drug and supplement interactions that can occur. For example, taking ginkgo (a dietary supplement) and blood thinners can cause an interaction resulting in adverse side effects (U.S. Department of Health and Human Services 2020). Interactions with drugs and medical conditions can also occur, such as taking aspirin while having stomach ulcers, furthering the risk of stomach bleeding. Therefore, patients must go over medications with their doctors and pharmacists to avoid problems with drug interactions.

Due to genetic polymorphism (different genetic makeup of individuals, which can cause them to metabolize drugs differently), prescription drugs can work differently for each individual, even if it is the same dose. For example, isoniazid is a drug used to treat tuberculosis that is metabolized by acetylation. However, the rate of acetylation varies from one individual to another due to genetic differences, which define the amount of unmetabolized isoniazid available for therapeutic effects (Ramachandran and Swaminathan 2012). Another example is clopidogrel, a blood-thinning prodrug metabolized to its active form by CYP2C19. Decreased response to clopidogrel has been noticed in Asian communities due to genetic polymorphisms that cause an inadequate metabolism of the drug (Brown et al., 2018).

Although drugs can help treat diseases, the outcomes are only sometimes beneficial or pleasant. Therefore, it is advantageous for the patient to use medications only as a last resort and instead attempt to prevent the diseases to avoid the need for medications and, thus, potential toxicity and side effects.

"All Drugs are Toxic, It's the Dose that Makes Them Therapeutic" (Paracelsus)

It was Paracelsus who first realized the importance of the dose in determining the drug's therapeutic effects and toxicity. Thus, even a poison can be therapeutically effective if given at an appropriately low dose. An important parameter called the therapeutic index, determines how appropriate and risky a drug is for clinical use. The therapeutic index is defined as a ratio of LD50 (lethal dose of a drug for 50% of the population) over ED50 (the minimum effective dose for 50% of the population). The dose window between the LD50 and the ED50 depends on the medication. The wider the window (i.e., the greater the ratio, LD50/ED50), the safer the drug (Tamargo et al. 2015). However, if the window is small, the drug has little difference between its therapeutic and toxic doses. Nevertheless, that does not eliminate certain drugs or drug classes from clinical use, as long as the patient takes certain precautions. For example, most general anesthetics have a low therapeutic index, yet clinical practices widely use them. Other drugs with a small therapeutic index are warfarin, phenytoin, and levothyroxine. Using medications with a low therapeutic index requires exceptional vigilance (see Chapter 2) and should be individualized for each patient. Note that the TD50 (toxic dose for 50%) instead of the LD50 can be used to define the therapeutic index (see Chapter 2).

In summary, pharmacology was created under the influence of various great physicians and scientists, including Paracelsus, who created the idea of using drugs for treatment and differentiating between the quantity that makes such treatments toxic or therapeutic, and Oswald Schmiedeberg, who introduced pharmacodynamics and pharmacokinetics. The combined ideas of these individuals, among others, led to the formation of this field. Although there are ways to prevent the necessity of drug treatment, such as eating a well-balanced diet and exercising, science has increased the benefits and progressively reduced the risk of using prescribed medication under observation from a medical provider,

as this remains the best option to aid in the treatment of a patient. As Paracelsus said, "All drugs are toxic. It is the dose that makes them therapeutic," which defines the role of a pharmacologist to study drugs in order to understand how they can best be therapeutic to a patient (see Chapter 2).

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CHAPTER 2

GENERAL PRINCIPLES OF PHARMACOLOGY, PHARMACODYNAMICS, PHARMACOKINETICS AND PHARMACOVIGILANCE

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General Background

Pharmacology is the study of agents that are capable of altering the body's physiological processes in a manner that may be therapeutic and/or toxic. The application of pharmacology ranges from drug discovery/design to clinical practice. The clinical application of pharmacology rests on three major components or pillars: the **ABCs of Pharmacology**. These three pillars are **A) Pharmacodynamics (PD)** – knowledge of what a drug does to affect the pathophysiology, **B) Pharmacokinetics (PK)** – knowledge of how the body processes a drug, and **C) Pharmacovigilance (PV)** – knowledge of the adverse and toxic effects of a drug. Understanding the ABCs of a given drug and the relevant characteristics of a specific patient, such as age or sex, are essential to reach an acceptable balance between the benefits and risks of a particular drug in that particular patient. Using the ABCs of Pharmacology, as detailed below, can help assure the rational use of drugs in the treatment of specific patient disorders while limiting untoward effects on the patient. Most drugs are given systemically to improve a pathology at a specific organ system, such as the heart, but a majority of drugs exert additional direct or indirect effects on other organ systems of the body beyond the systems being targeted. Therefore, as the father of pharmacology, Paracelsus, wrote over 500 years ago, it is critical to emphasize that even the most effective drugs are poisons if the dose is too high (see Chapter 1).

Pharmacology is a highly dynamic field due, in part, to the frequent introduction of new drugs with novel mechanisms of action, which has recently been occurring at the rate of over 50 novel agents a year. So, in addition to consulting with textbooks and online drug information sources, it is useful for each practitioner to develop their conceptual scaffold or **Tree of Pharmacology Knowledge** (Figure 1) to mentally map out the various classes of drugs targeting specific types of medical conditions and organ systems. Pharmacology knowledge can then be acquired into a mental database or conceptual scaffold that includes drug class, names, mechanism of action, pharmacodynamics (PD), and critical adverse events or toxicities (PV), allowing any new drug to be placed within this database to build onto their existing knowledge of familiar drugs. Thus, each novel drug becomes a new leaf on the specific branch of this tree that applies to the medical conditions in the mental database of the practitioner. The intentional and well-reasoned development of such a mental database/conceptual scaffold establishes an integrated understanding of pharmacology and facilitates the assimilation of new knowledge.

Often pharmacological knowledge is considered secondary to developing an understanding of pathophysiology, but this delay in developing a pharmacological knowledge base is a missed opportunity. Rather, once basic anatomical and physiological knowledge is in place, actively developing pharmacological reasoning and a knowledge base for treatment (and/or diagnosis) in parallel to understanding pathophysiology and disease can be mutually beneficial. For example, a clear understanding of why angiotensin receptor blockers are effective in heart failure facilitates an integrated view of smooth muscle contraction, intracellular signal transduction mechanism, neurohormonal control of blood pressure, the renin-angiotensin-aldosterone system, cardiac output, and hypertension, among others.

Integrating the Three Pillars in the ABCs of Pharmacology

Once the diagnosis is established and treatment goals are identified, the drug category needed to treat the patient's condition or the specific branch on the Tree of Pharmacology Knowledge is identified. For example, if a patient is diagnosed with an infectious disease and the causative organism is established by microbiological techniques, the specific chemotherapeutic branch on the Tree that specifies the agent useful to treat that infection will be selected. Then the three major pillars of pharmacology are addressed individually based on the options within that branch: What drugs are available that are therapeutically effective? What are their pharmacological properties at the dosages administered? What are the potential risks to the patient? Here, each question is the overarching question answered by an understanding of PD, PK, and PV. Within these pillars, important factors can be evaluated by working through a series of additional questions designed to address the most important issues within each pillar to eventually answer the

important broader question: How do the potential benefits outweigh the risks of an implemented drug treatment to improve a patient’s health and well-being? More details and an overview of practical considerations for the ABCs are listed below, but drug-specific information and safety should always be consulted when questions or uncertainty are present (Faingold and Dunaway, 2002; Dunaway and Faingold, 2002).

A. Pharmacodynamics (PD)

The first pillar of pharmacology is **pharmacodynamics (PD)**, referring to the actions of a drug on the body or a system. This is typically the first guiding principle of drug choice based on a leading **diagnosis** of the pathophysiological state.

Diagnosis

Incorporating *presentation, associated signs and symptoms, risk factors, lab tests, and exams*, is the key to choosing the correct drug to treat the accurately diagnosed pathophysiological condition to be addressed. Successful drug therapy is directly dependent on a thorough understanding of the pathophysiology underlying the presenting medical problem(s) that require(s) pharmacological intervention. Also, note that a comprehensive pharmacological knowledge base may be useful in developing a diagnosis by evaluating patient responses to specific drugs (e.g. administering a bronchodilator or bronchoconstrictor after obtaining baseline pulmonary function test values to identify obstructive lung diseases). Upon obtaining a diagnosis with the clearest possible understanding of the driving pathophysiology, goals for treatment should be developed. In many cases, these treatment goals may be able to provide a curative approach resulting in a complete correction of the pathophysiological state. In other cases, there may be no curative option, and a pharmacological approach that limits symptoms or delays mortality may be the sole option. Using the questions below, consider how drug action, specificity, and compensatory changes that may occur are used to refine the list of drug options.

1. *What drug classes are available that exert pharmacological effects needed to achieve treatment goals?*

Regardless of the condition, drugs within specific classes are identified based on their ability to affect change in certain systems to achieve identified goals, whether curative, preventive, or palliative. These drug-induced changes correspond to the biological sites where each drug acts, typically by binding to a site to produce some change in or interfere with an ongoing process, collectively referred to as the drug’s mechanism of action.

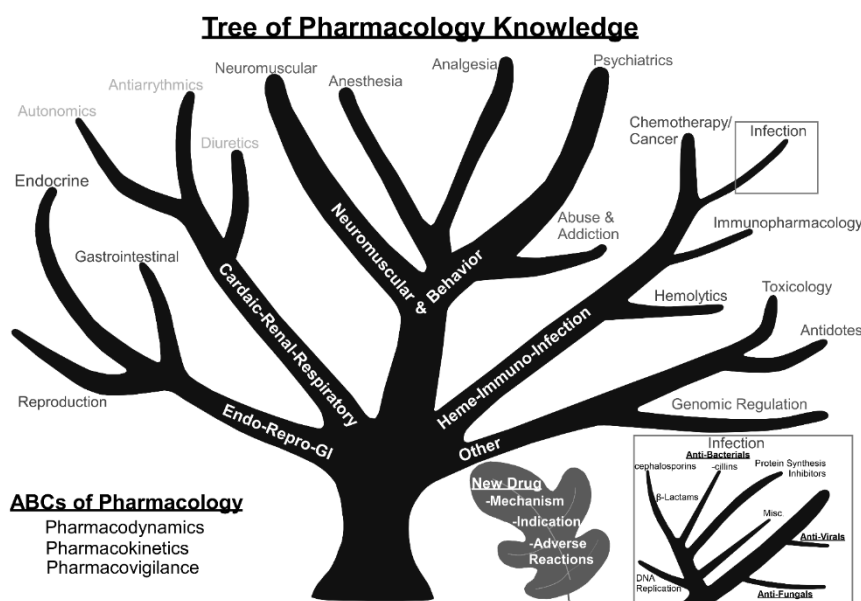


Figure 1. Tree of Pharmacology Knowledge

2. *What are the mechanisms of action of this drug?*

a. *specificity/selectivity of the drug-receptor interaction*

Guided by the need to induce specific changes in system function, the understanding of that system’s physiology is essential to guide the choice of drug class based on the site and nature of that drug’s interaction with the system(s) targeted for manipulation. In a case where a process may need to be enhanced, activating a receptor that drives such a process may be beneficial. Also, inhibiting a different opposing mechanism that slows that same process may be just

as beneficial or even more so to achieve the desired effects. In addition to the direction of change, each class of drug should be evaluated based on its specificity or the drug's ability to affect only the intended signaling/system with little-to-no change in other signaling/systems. Drugs in clinical use today fall within an incredibly broad spectrum, ranging from monoclonal antibodies that selectively bind specific epitopes on specific receptor subtypes to small molecule neuropsychiatric medications that interact with several major signaling pathways within the nervous system. It is also important to distinguish within the latter, a drug that interacts with multiple effector classes (e.g. atypical antipsychotic clozapine) relative to drugs that interact with specific receptors/effectors that happen to be widely expressed (e.g. fentanyl and mu-opioid receptors or digoxin and Na⁺/K⁺-ATPase).

Across this spectrum of drugs that produce highly specific to non-specific effects, there is a general correlation with a drug's ability to affect change, where many drugs with poor selectivity are often the ones most effective at altering or restoring normal physiological status. However, increased off-target interactions of drugs with reduced binding specificity lead to more adverse or unintended effects. It is at this stage that the first risk-benefit analysis must be conducted to identify whether changes due to non-specific interactions of a drug are acceptable based on the potential to reach treatment goals. Doing so will further refine treatment options to those that will be best tolerated and/or produce only limited or acceptable adverse drug effects.

b. *dose-response relationship, effective dose versus toxic dose*

In most cases, higher drug doses/concentrations more readily produce the desired effects to achieve treatment goals. Unfortunately, the specificity of a drug is often reduced with increasing drug dose/concentrations. To quantify flexibility and safety across the dose range for a specific drug, a **therapeutic index (TI)** for each drug is determined as a ratio of the TD₅₀/ED₅₀. The ED₅₀ (effective dose for 50%) is the concentration at which a drug produces a desired effect in 50% of the population whereas the TD₅₀ (toxic dose for 50%) is the dose at which 50% of the population experiences toxic or adverse effects. Similarly, the dose range between where beneficial effects emerge but before toxic or adverse effects are observed is considered to be the **therapeutic window** of a drug for the population for which data are available. Using these population-based values of the therapeutic index and therapeutic window, which increases with lower doses needed to achieve effects or with higher doses needed to reach toxicity, a starting point and flexibility across a drug dose range can be considered to include/exclude a drug or choose a starting dose. Because these values are derived from populations that may have considerable variability, an individual may need to increase or decrease doses of a specific drug to simultaneously produce the greatest benefit with the fewest adverse effects that occur more frequently at higher doses.

c. *cell signaling*

Limitations or refinement of a potential list of drugs to produce a particular result may be significantly limited by drug specificity and therapeutic index. Therefore, it is valuable to consider a broader view of the pathophysiology and the multiple factors that can shape a physiological change. As indicated in section A.2.a., producing a particular effect may be achieved in several ways, including direct activation of a receptor or enzyme, inhibition of an opposing receptor or enzyme, and actions at distinct stages downstream or upstream of the site of disruption. One example of a system with multiple targetable cellular and molecular sites to achieve an intended result is blood pressure. Lowering blood pressure may be achieved by multiple approaches that include blocking the generation of angiotensin II, directly antagonizing the angiotensin receptor, preventing the degradation of cAMP, activating alpha 2 adrenergic receptors that reduce the release of norepinephrine, and stimulating nitric oxide production. With an integrated view of system physiology, cellular signaling mechanisms, and sites that may be targeted by specific drugs, treatment options may be expanded to rationally target a mechanism to produce an effect that may reduce adverse drug reactions (side effects) and needs to use higher doses/concentrations.

B. Pharmacokinetics

3. *What pharmacokinetic-related factors can alter the patient's responsiveness to a drug?*

Once any drug or agent is administered to the body, the body and organ systems will immediately begin to redistribute it into certain compartments and/or change its molecular structure or composition. These actions the body takes on the drug are unique to each compound and are referred to as the **pharmacokinetic (PK)** properties of a drug. Drug PK, or what the body does to the drug, is characterized by four major processes that include **absorption, distribution, metabolism, and elimination** (i.e. **ADME**). Each of these components may be shaped by either active or passive processes and may vary greatly between individuals based on their age, sex, mass, genetics, health status, and exposure to other experiences or substances. These individual variations within components that shape these processes may produce cumulative or synergistic effects on how much drug remains within the body or compensate for one another.

Generally, the cumulative effects of each of these processes are quantified by assessing the concentration of the drug in the plasma at regular intervals. Other reservoirs may be more appropriate in some cases (e.g. cerebrospinal fluid).

This evaluation of drug concentration over time after a single dose, repeated doses, or continuous delivery (pump or transdermal) is used to evaluate the time it takes for a specific amount of active drug to be removed from the body or that reservoir. This change in drug concentration follows one of two patterns: zero-order kinetics or first-order kinetics. In the case of **zero-order kinetics**, the processes involved in the body's ability to reduce the amount of the drug are saturated and only a finite *amount* of the drug is removed per unit of time (e.g., alcohol). In the case of **first-order kinetics**, the processes involved in changing the concentration of the drug are dependent on the concentration present, i.e. a fixed *proportion* or *percentage* of the drug is removed per unit of time rather than an amount. In other words, with first-order kinetics, the more drug present in the body means that a greater amount will be removed in a given time, whereas less drug in the body results in a lower amount of drug removed in a given time. Generally, drugs with zero-order elimination kinetics tend to bring a higher risk of overdose since the processes involved in drug removal are saturated, whereas drugs eliminated with first-order kinetics carry less overdose risk since the body removes more drug when more drug is present.

Regardless, variations from the "average" patient due to any of the above factors may require a change in drug dose and/or drug choice. Below are major physiological determinants of drug pharmacokinetic profiles to consider in drug and dosage choice. This list is not comprehensive, but rather a general guideline for thinking critically about each concept.

a. site and route of administration

Chemical limitations to the compound formulation and compound stability in certain states (aqueous, solid, etc.) that also facilitate the body's ability to absorb a drug (see below) together determine the possible formulations for all compounds, molecules, peptides, antibodies, etc. that may be administered to patients as drugs. These determinants and other aspects related to controlling the temporal component of drug delivery then limit whether a drug may be administered through intravenous, subcutaneous, transdermal, inhaled, intramuscular, and/or oral routes. This combination of a drug's state and its route of administration both impact the **bioavailability** of a drug, or the percentage of drug administered that is retained by the body. By definition, drugs that are delivered intravenously are considered to be 100% bioavailable since the serum is the common reference for the concentration of drugs in the body. Relative to intravenous administration, other routes of administration typically result in a lower bioavailability of a given drug.

b. drug absorption

Drug absorption refers to the mechanism, rate, and capacity for a drug to transition from its administered form to being present within biological tissues and fluid reservoirs or compartments. One major determinant of drug absorption is its ionization (or charged) state, which may differ based on its environment, especially pH, with the latter varying wildly based on the site of administration (e.g. gastric pH ~ 1.5, blood pH ~7.4). Using pH as an example, several factors may affect environmental pH and absorption, as is the case for gastric pH following oral administration or diabetes and subsequent metabolic acidosis in the case of blood pH. A second major determinant of drug absorption is the mechanism by which drugs move through biological barriers like membranes. Drugs may move passively (e.g. diffusion) or actively (e.g. transporter proteins) across barriers or compartments, the degree to which is a function of the interaction between the drug state and availability of requisite biological processes or environments.

c. drug distribution in the body

Once a drug is absorbed at its site of administration, some proportion of the drug may remain there and some may move to other compartments. These compartments include those where the drug remains free or in an aqueous state, bound to specific proteins, or some combination of the two. For example, some drug present in the blood may be free or unbound to any protein and a separate fraction may be bound to albumin. In this case, changes in blood pH may change the charge of the drug to make it more or less likely to remain free or be transported across membranes, while changes in albumin levels (e.g. glomerulonephritis) will alter the capacity of the drug to remain in the blood and bound rather than free. Other compartments where a drug may accumulate or redistribute include cerebrospinal fluid, intracellular space, interstitial/extracellular space, binding to specific proteins (e.g. serum albumin), fat in the case of lipophilic drugs, and bone, among others. This is largely governed by an interaction between a drug's chemical or thermodynamic properties and biological processes. Differences across individuals that affect such processes may produce individual variability in how a drug distributes within the body and in which compartments it accumulates. Therefore, an understanding of how underlying genetic (e.g. mutations in a transporter protein gene), environmental exposure (e.g. other prescription drugs), or pathophysiological conditions (e.g. hormone-secreting tumors/paraneoplastic syndromes) may be important to understanding how a drug appropriately or inappropriately distributes within the body of an individual to impact the amount of drug available to interact with the therapeutic site.

d. drug metabolism/biotransformation

For many drugs or exogenous compounds to be eliminated from the body, they must first be modified by a biological process in the body to reach routes of elimination (discussed below). This process of modifying drugs to facilitate their

removal from the body is collectively referred to as drug **metabolism** or biotransformation and is typically the most significant determinant of how much active drug is available in the body and shapes zero- or first-order kinetic. In addition to inactivating or promoting the elimination of drugs, some may need to be modified by the body after administration to render them pharmacologically *active* or able to interact with and alter targeted biological processes. This group of drugs that require some biological transformation (biotransformation) to be active are administered as **prodrugs**. Whether for metabolism or biotransformation, the chemical or structural alteration of drugs occurs through a multitude of processes, but most often involves two phases. Phase 1 reactions involve the addition of a functional group through reduction, oxidation, or hydrolysis to inactivate/activate a drug, whereas Phase 2 reactions involve the conjugation of an additional molecule to promote water solubility for elimination. The enzymes responsible for Phase I and transferases for Phase 2 reactions are differentially expressed through the body and organ systems but are most abundant in the gastrointestinal system and liver. It is the primary role of enzymes found in the liver in metabolizing so many drugs that often cause a major proportion of drugs to be eliminated rather quickly after intravenous administration giving rise to what is called the 'first pass effect'. It is important to keep in mind that changes in the anatomy or physiology of the gastrointestinal, hepatic, or other systems that are important sites of metabolism/biotransformation of a particular drug may result in major changes in drug concentration for an individual given a particular dose. Because the rate and mechanism of drug metabolism are specific and the largest determinant of drug concentration and lifetime in the body, factors that affect these processes, whether genomic (e.g. pharmacogenomics) or pathophysiological (e.g. hepatitis, surgical removal), are important to consider in establishing drug choice and dose.

e. drug elimination from the body

While some drugs require metabolism by the body to reach a route that facilitates their removal or **elimination** from the body, many may be eliminated in the same form in which they are initially administered. Regardless of their form, nearly all drugs or their metabolites are removed from the body by being accumulated into waste compartments either in the urine by the kidneys or feces by the gastrointestinal and biliary tracts, with only a limited amount accumulating in other compartments for removal (e.g. sweat, breast milk, lungs etc.). As discussed previously, the movement into and accumulation of drugs or their metabolites in compartments may be passive or active, which will affect the capacity for drug elimination. For example, any changes (genomic or pathological) in glomerular filtration rate (e.g. as in hypertension or chronic kidney disease) or the environment and transporter activity in the proximal (drug secretion) or distal tubule (drug reabsorption) and collecting duct will alter how much drug is moved to and retained in the urine for eventual elimination. Similar mechanisms for diffusion and transport that accumulate drugs into the gastrointestinal lumen and/or packaging of drugs or metabolites with bile for recycling or excretion are also sensitive to disruption in these physiological processes (e.g. increased motility, cholecystectomy).

f. pharmacogenomic determinants of drug action

Pharmacogenomics refers to how individual variability in functionally-relevant genes that encode either drug targets or processes involved in establishing a drug's pharmacokinetic profile can determine the potency, efficacy, specificity, and temporal nature of the drug and body/system interaction. Whether single or multiple nucleotide insertions, deletions, substitutions, or translocations are present, any functionally-relevant change or mutation in a gene encoding for a particular protein may affect its function(s) in an individual. Mutated genes that encode sites at which drugs interact to produce some functional change may impact drug pharmacodynamics by increasing or decreasing the ability of the drug to bind or the degree to which downstream effectors are activated. Similarly, mutations in genes that encode transporters and enzymes responsible for drug absorption, distribution, metabolism, or excretion may increase or decrease the amount of drug present in the body or affect how long it takes the body to reduce the concentration of a drug. One of the most common sites where genomics affects pharmacokinetic properties is in mutations of genes encoding any one of the 12 major cytochrome P450 (CYP450) enzymes, which is a superfamily of proteins responsible for phase I metabolic reactions for many kinds of drugs or exogenous compounds. The presence of a dominant or homozygous loss of function mutations in CYP450 genes may easily go undetected for a lifetime until an individual experiences a toxic accumulation of a novel drug due to the reduced metabolism of that drug by a deficient CYP450 enzyme. The area of pharmacogenomics is complex and evolving, but awareness of potential genomic determinants of drug actions may be used to identify potential genetic causes of aberrant responses to a particular drug or screen preventively for mutations associated with such aberrant responses in the larger population, which is well outside the scope of this chapter.

g. race or ethnicity

Similar to pharmacogenomics but more wide-reaching, many unique functionally-relevant differences in genes encoding drug-relevant proteins are common within some groups having shared ethnic, racial, or regional backgrounds (e.g., the anticonvulsant, carbamazepine in certain Asian populations). Databases and references are available to guide drug choice or dose based on these commonly occurring variations in genes that encode drug targets or mechanisms for metabolism or elimination. However, be aware that some rationales for differentiating pharmacotherapeutic approaches based on racial or ethnic background persist in the literature despite a lack of appropriately powered and

controlled studies, the implementation of which may lead to health disparities. Therefore, caution should be exercised when factoring in the rationale for drug choice and dose changes based on patient background.

h. target organ/effector cell sensitivity

Primarily considered a component of pharmacodynamics, changes in the sensitivity of a drug target or some component of the downstream effector (e.g. second messenger) of that target may vary between individuals or over time in a given individual due to genetics or experience. In addition to previously discussed pharmacogenomic implications (see B.3.f), genetic determination of a drug's affinity, potency, or efficacy at the target site may require increases or decreases in dosing to achieve the goal. An individual's history of exposure to prescribed or recreational drugs also affects drug targets and related signaling (see sections B.4 and C.7.b).

i. hypersensitivity (allergy) or idiosyncratic reactions of the patient

Some drug hypersensitivity or allergic reactions can be characterized as immunologic if they are mediated by immunoglobulins. They can be further classified into those that are rapid and mediated by immunoglobulins such as IgE (Type I) and those that are delayed and mediated by non-IgE (Type II-IV). In contrast, non-immunogenic/pseudo-hypersensitivity reactions are mediated by other known or unknown (idiopathic) mechanisms that are drug/class dependent, not by immunoglobulins. An individual's hypersensitivity or allergic reaction to a drug is often considered a clear contraindication for that drug and will require the identification of an alternative. Because drugs of a similar class often share a similar chemical structure, it may be ideal to choose a drug from an alternative class to achieve the treatment goal to avoid provoking a reaction by similar compounds (e.g. sulfa-containing drugs). In some instances, the hypersensitivity or allergic reaction is specific to one drug within a class and not the entire class, and using another drug within that class may still be safe. In other cases where a hypersensitivity reaction is not severe, uncertain, or delayed (Type II-IV) and the benefits of the drug are profound, it may be reasonable to implement the use of that drug with appropriate supervision, support, and/or a second drug to reduce the adverse effect. Sensitivity testing and a protocol to develop desensitization of the immune response to a drug may also be useful if the use of a specific drug or class of drugs is unavoidable.

j. weight of the patient

As individual body mass varies, so does the overall water volume, size of specific compartments and reservoirs, and a drug's general **volume of distribution**. Generally, an individual with lower total body mass will require less drug to achieve an effective concentration of that drug as it has a smaller volume over which to be distributed. Except for some extreme variations in individual total body mass, most adults may be administered a standard initial dose for a particular drug or started on a low dose, especially for drugs with limited acute adverse reaction profiles. Then, based on the progress toward a treatment goal and any observed adverse drug reactions, the dose may be increased or decreased from what is given initially. Likewise, those with greater body mass will likely require higher doses to achieve the necessary therapeutic concentrations. Of course, relative to a typical adult, children have lower body mass and body mass often decreases in the elderly. Separate from age-specific considerations (discussed below), the dose of many drugs may need to be reduced from a typical adult dose to account for body mass changes alone.

k. body composition of the patient (normal, lean, or obese)

Body composition referring to the relative percentage of an individual's mass made up of fat is primarily a determinant of drug distribution. Lipophilic drugs, unlike hydrophilic drugs, accumulate in adipose tissue and leave little in the plasma/blood/water volume. This effectively raises the volume of distribution and potentially sequesters away drug from non-adipose sites of action. As a result, lipophilic drugs will likely have an increased volume of distribution and reduced efficacy in obese individuals, while the opposite is true for leaner individuals. Although not a consideration for a majority of patients, those with body composition extremes of obese and very lean, their composition should be considered especially for lipophilic drugs (e.g. diazepam, propranolol, estrogen).

l. age of the patient

In addition to changes in body mass throughout the aging process, many other physiological parameters (e.g. muscle, fat composition) and physiological processes (e.g. kidney function/glomerular filtration rate) change throughout the lifetime. Pediatric and geriatric populations are not simply differently-sized adults – there are significant changes that occur in the pharmacodynamic and pharmacokinetic properties of many drugs across the lifespan. As such, incorporating patient age as one variable to determine drug choice and dose is an essential consideration, especially early and late in life.

In addition to differences in body mass of children relative to adults mentioned previously, the underlying physiology of children is often still developing and produces quite different PK and PD profiles for certain drugs relative to adults. Mechanisms affecting drug absorption and distribution (muscle/fat ratio, transporter function, volume of distribution, protein binding), metabolism (e.g. CYP450, transferase expression), and elimination (e.g. glomerular filtration rate)

have all been found to vary across childhood and adolescence in addition to being different from adults depending on the drug used (Batchelor and Marriott, 2015). Children are also uniquely susceptible to specific drug-induced adverse reactions or toxicities, including opioid-induced respiratory depression (e.g. codeine) or damage to tooth enamel by tetracyclines, making the use of these and other drugs in pediatric populations problematic despite a favorable safety profile in adults.

Geriatric populations pose a particular set of pharmacological challenges due to changes in pharmacokinetic and pharmacodynamic properties, but also due to the challenge of polypharmacy as dysfunction of systems accumulates with age. A few examples of pharmacokinetic considerations in older populations include the decrease in the muscle/fat ratio that impacts the volume of distribution for lipophilic drugs (e.g. fentanyl) and how drugs that require hepatic (e.g. metoprolol) or renal (e.g. gabapentin) mechanisms may be cleared from the body more slowly and accumulate. While it is arguably more difficult to predict the pharmacodynamic properties that change with age consistently, one common observation is the elevated sensitivity of older individuals to the anticholinergic adverse effects of many drugs, especially drugs that are commonly prescribed to treat aging-related conditions (e.g. antihistamines, antipsychotics, antidepressants, among others). Further complicating drug choice and dosing in geriatric populations is the need to achieve multiple goals like reducing blood pressure, improving depression, relieving pain, treating heart failure, and/or improving sleep. Achieving these goals often requires the administration of drugs unique to those goals, with some drugs exacerbating underlying issues, producing additive adverse reactions, or even provoking an entirely new problem. This issue of polypharmacy, occurring at greater rates with advancing age, is a longstanding problem. However, efforts to increase monitoring of an individual's complete medication list and identify drugs that are particularly problematic for older individuals (Beers Criteria, Merck Manual on Drug Therapy in Older Adults) are the first steps in reducing the unnecessary or inappropriate use of drugs or drug classes in elderly patients.

m. sex of the patient

Pharmacokinetic and pharmacodynamic properties of many drugs may vary based on sex since the underlying physiology of males and females is unique and those that are transitioning or have transitioned to one sex or the other may display drug-relevant aspects of each (Soldin and Mattison, 2009). Some important factors that affect drug absorption and distribution include body mass, body water, the fraction of extracellular/intracellular water, muscle/fat ratio, changes due to menopause or pregnancy, and the presence of soluble drug-binding proteins. Drug absorption, distribution, and metabolism are also unique based on sex-specific variations in transporter and enzyme activity (e.g. alcohol dehydrogenase).

n. preexisting or concurrent diseases

The impact of concurrent pathophysiology on drug effects and pharmacokinetic profiles has been mentioned above in other contexts and can be a major determinant of drug efficacy, adverse reactions, and potential for excessive accumulation of drugs in the body. Although this may seem obvious, it is often overlooked. For example, individuals with reduced kidney function should be cautiously administered certain antibiotics with regular assessment of plasma drug concentrations while others should avoid nephrotoxic antibiotics like aminoglycosides when possible. Individuals with diabetes should not be administered corticosteroids, thiazide diuretics, or beta-blockers due to their hyperglycemia-inducing properties. A list of drug-disease interactions is beyond the scope of this chapter, but the most important aspect of accounting for drug interactions with preexisting conditions is for the provider and potentially the pharmacist to have a comprehensive understanding of an individual's pathophysiological state and condition. The time taken to develop this understanding will help ensure drugs or drug classes are avoided that may be problematic in a given setting.

4. What factors alter target cell responsiveness over time for this drug?

Much of this chapter so far has discussed the implementation of a pharmacological regimen in a static context, i.e. the situation is not changing. However, the physiology of an individual almost always changes in response to drug administration. This arises from the efforts of the body to maintain a homeostatic balance and 'set point', which often produces unintended consequences that may be misinterpreted as an additional disease or disorder. So, when this imbalance is corrected by drug administration the body will work to restore the situation to a pre-drug state even if this state is pathophysiological. This reconfiguring of its systems and function in the setting of a new drug or drugs are often referred to as plasticity or adaptation. The mechanisms that can change to produce adaptation in response to the drug are extensive and encompass pharmacokinetic and/or pharmacodynamic changes based on the administered drug(s).

While many of the adaptive responses to a drug can be complex and affect multiple systems, one of the most common observations is **tolerance** – a reduced response to a drug over time. Drug tolerance may develop due to pharmacokinetic or pharmacodynamic changes. Pharmacokinetic changes that may produce drug tolerance can include increased expression of a transporter that enhances the movement of the drug to the gastrointestinal renal tubule lumen to promote excretion. Commonly, the expression of an enzyme essential for drug metabolism may increase with

increasing exposure to a drug (e.g. alcohol dehydrogenase in chronic alcohol use). Both situations would facilitate more rapid degradation of this drug so that its effects on physiological systems are reduced. Tolerance to other drugs may rely on changes in the drug's pharmacodynamic properties, as there may be a reduction in the receptors and/or its downstream effectors that are being targeted, or there may be an increase in a separate system that compensates for the actions of the drug. One classic example of pharmacodynamic adaptations that occur to produce tolerance is **desensitization** in opioid receptor signaling. This involves a decrease in mu-opioid receptor expression and an increase in adenylyl cyclase/cAMP/protein kinase A (PKA) expression to compensate for the overactivation of mu-opioid receptors and inhibition of adenylyl cyclase. Similarly, the loop diuretic furosemide is often much more effective in the first few days of administration than it is weeks later due to an increase in expression of the NKCC2 transporter that is blocked by furosemide and increases in ion reabsorption at other sites within the renal tubule. Similar compensatory adaptations to produce tolerance do, or have the potential to occur, with almost every drug in use today, resulting in the need to escalate the dose and/or introduce additional drugs to achieve the treatment goal over time.

Drug-specific mechanisms that promote tolerance develop over time, because the continued presence may alter the function of the targeted system. As a result, the physiological state of the system/body is reliant upon the presence of the drug, also known as **dependence**. In addition to the need for a higher dose or other drugs to achieve the treatment goal, this 'new normal' in the presence of the drug also means that when the drug is withheld, the homeostatic balance of the system will be lost because the receptor desensitization and compensatory adaptations that developed over time will be unopposed in absence of the drug. **Withdrawal** refers to the physical or psychological symptoms due to the activation of dependence mechanisms and processes in the absence of a drug. This may vary from mildly uncomfortable to life-threatening, depending on the drug and duration of exposure. For example, a potentially life-threatening withdrawal condition can occur when the antihypertensive drug and alpha 2 adrenergic agonist, clonidine, is withheld. Continual activation of alpha 2 adrenergic receptors by clonidine causes desensitization through downregulation of the receptor, which is physiologically important to provide feedback inhibition of norepinephrine release. As a result, reduced receptor number without continual activation by an administered drug results in excessive norepinephrine release without the same degree of feedback inhibition, causing a hypertensive crisis. Unfortunately, drug tolerance, desensitization, dependence, and withdrawal are unavoidable consequences of pharmacotherapy in many instances, but with time and attention, it is possible to manage these risks to ensure patient safety and health.

C. Pharmacovigilance

In addition to the multitude of factors that comprise the pharmacodynamic and pharmacokinetic properties of a drug, it is essential to also account for the safety profile of a drug. Pharmacovigilance (PV) refers to the incorporation of a drug's toxic or adverse effects into the rationale for choosing a drug and its dose. As discussed previously, drug toxicity and adverse drug reactions stem from a drug's pharmacodynamic and/or pharmacokinetic properties, underscoring the interdependent nature of the three ABCs of Pharmacology. In some cases, adverse drug reactions arise due to non-specificity or off-target binding of a drug to produce a physiological response in a system outside of the one that is targeted for therapeutic benefit, as noted above. In other instances, the amount of drug in the body may accumulate to toxic levels due to decreases in the activity of an enzyme responsible for that drug's metabolism, either due to genetics, disease, or environmental factors. It is also important to note that pharmacovigilance is not a static factor or one that only needs to be considered only when initiating a new treatment regimen. Rather, it is dynamic, and an individual's therapeutic response to a drug must continually be weighed relative to the development of any adverse reactions. The need for continual pharmacovigilance is because the body's or system's status quo is continually changing over time. This may involve changes in underlying physiological processes, the emergence of new pathologies, the administration of a new drug to treat a new or different condition, or sensitized immune responses.

5. *What is the Risk/Benefit ratio of therapy (therapeutic index) of this drug?*

As discussed in detail in section A.2.b, the relationship between the dose at which adverse drug reactions or toxicities and the concentration of a drug at which beneficial changes occur is important to understand the potential risk/benefit of a given drug. The further apart these therapeutic and toxic dose ranges are, the wider the **therapeutic window** and the greater the **therapeutic index**. In contrast, when these concentrations are closer the therapeutic window and index both decrease. This means that it will be more difficult to find a concentration of a drug that is capable of achieving therapeutic goals without causing too many untoward effects. Ideally, the therapeutic window/index should be as large as possible to allow the most flexibility in choosing the maximally beneficial drug dose with minimal adverse drug reactions.

6. *What are the contraindications (absolute/relative) of this drug?*

In addition to common mild adverse reactions, which occur with the use of almost every drug in the general population, some drugs have been found to induce adverse reactions in specific settings. Sometimes these contraindicated situations are physiological (e.g. age), pathophysiological (e.g. renal failure), or due to interaction between two drugs (see below). Depending on how frequently a drug is used in a problematic setting, data collected

during clinical trials or over years of use in clinical practice are what determine whether a contraindication exists and is listed in drug packaging and on professional databases (e.g. UpToDate, Medscape, Clinical Pharmacology, Drugs.com). Some of these contraindications are 'relative contraindications' that will produce mild adverse reactions if a drug is administered in the presence of that contraindication. Other contraindications are 'absolute' and administration of a drug in that setting could be life-threatening or fatal (e.g., ventricular fibrillation for digoxin). Regardless, a significant aspect of pharmacovigilance is the awareness and communication of drug contraindications, which again is a shared responsibility of a provider and pharmacist.

7. *What adverse (side) effects are caused by this drug?*

According to the Institute of Medicine (US) Committee on Quality of Health Care in America, adverse drug reactions (ADRs) are a major public health problem. Recent Centers for Disease Control and Prevention (CDC) data indicate that more than 700,000 Emergency Department visits (120,000 hospitalizations) for ADRs occur per year, with adults over 65 twice as likely to visit the Emergency Department for ADRs, often due to overdose. Roughly half of the medical error causes of death are drug-related, and ADRs are the 5th-8th leading cause of death in U.S. hospitals. ADRs may occur immediately (e.g. allergic reaction) or take months to years to develop (e.g. amiodarone-induced pulmonary fibrosis). They also may range from mild to life-threatening, and they stem from physiological, pathophysiological, or environment/experience-dependent changes in pharmacodynamic (see section B.3.h) or pharmacokinetic (B.3.a-e) processes. Some adverse effects are also difficult to predict due to the complex and dynamic physiological changes that occur over time in the presence of other drugs or exposures, as previously discussed (see Section B.4). Regardless, awareness and continual monitoring of adverse drug effects are essential to responsible drug prescribing and patient safety.

a. hypersensitivity and pseudo-hypersensitivity

Many types of adverse effects (side effects) have been mentioned above. One of the major concerns with the initial administration of a new drug or class of drugs to an individual is the possibility that an immune-mediated hyperreactivity reaction may occur that produces an immunoglobulin-mediated Type I-IV response. Often drugs with shared functional groups (e.g. sulfa-containing drugs) may induce similar reactions based on host immune detection of like antigens, despite falling in different pharmacotherapeutic classes (e.g. glipizide for Type II diabetes mellitus and the antibacterial sulfamethoxazole). Therefore, appropriate pharmacovigilance requires awareness of allergic reactions to drugs that may fall within different therapeutic classes but have shared chemical structures. In addition to awareness of hypersensitivity/allergic reactions, other drugs may cause pseudo-hypersensitivity in some individuals due to direct stimulation of a system (e.g. complement pathway) that mimics an immune-mediated reaction (Zhang et al., 2018). The groups of agents that trigger pseudo-hypersensitivity typically fall into a limited group of clinically relevant drugs, including opioids and non-steroidal anti-inflammatory drugs (NSAIDs). Note that, in some cases, it is the metabolite of a drug that triggers its hypersensitivity/hyperreactivity, which may result in a delayed reaction.

b. drug-drug interactions

One of the most common environment/experience-dependent causes of an adverse drug effect is due to interactions between two drugs. These drug-drug interactions do not necessarily refer to physical interactions of two substances, but rather the effects of one drug that impact the pharmacokinetics or pharmacodynamics of another drug. Regarding pharmacodynamics, drugs of one class may directly or indirectly affect the site of action or the effector mechanism for another drug. In individuals with asthma who use drugs that activate beta-adrenergic receptors (e.g. albuterol) to produce bronchodilation, administration of a non-selective beta-adrenergic receptor blocker (e.g. propranolol) to treat hypertension will antagonize this effect and exacerbate asthma. In addition to pharmacodynamically antagonistic drug-drug interactions, others may be pharmacodynamically additive. This can occur with the combined administration of a selective serotonin reuptake inhibitor like fluoxetine for depression and the anti-migraine drug sumatriptan because they both enhance the activity of serotonin (5-hydroxytryptamine) receptors and increase the risk of potentially life-threatening serotonin syndrome. Fortunately, a clear understanding of the drug mechanism of action makes it possible to predict and account for pharmacodynamic drug-drug interactions.

In contrast, drugs that interact to affect the pharmacokinetic properties of one another often do so by more complicated and less obvious mechanisms that may have to do with drug absorption, distribution, elimination, or metabolism. For example, commonly prescribed gastric proton pump inhibitors (e.g. omeprazole) work by decreasing gastric proton concentration, which negatively affects the absorption and eventual effectiveness of certain drugs that require an acidic environment (e.g. antifungal posaconazole). Reductions in drug elimination may cause elevations in drug concentrations that exceed therapeutic concentrations and reach toxic levels. For example, renal elimination of methotrexate, a cancer chemotherapeutic agent, is reduced when glomerular filtration rates decline in response to NSAIDs (e.g., aspirin), producing a drug-drug interaction that results in nausea, vomiting, and/or myelosuppression. While pharmacokinetic drug-drug interactions that occur through induced changes in absorption, distribution, or elimination may be simpler to predict, incorporating an understanding of interactions that alter drug metabolism is more challenging. This challenge stems from the fact that many of the metabolic processes or enzymes responsible for

drug activation or inactivation are dynamic and not static. The activity of enzymes (CYP450s or transferases) responsible for drug transformation may be inhibited or induced, and their expression levels may be increased or reduced by several factors, especially other agents or drugs. As a result, concentrations of drugs that rely on a specific transferase or CYP450s to be metabolized for excretion may be elevated to toxic if those enzymes are inhibited or their expression is reduced. In contrast, elevation in the activity or expression of these enzymes may prevent that same drug from reaching therapeutic levels. Decades of data are now available that describe which drugs inhibit or induce specific enzymes/processes responsible for drug metabolism. Known CYP2C9 inhibitors like amiodarone or fluoxetine may cause prolonged elevation of CYP2C9 substrates like carvedilol or losartan. Likewise, CYP3A4 inducers like rifampin may lead to reduced levels of the antihypertensive drug, amlodipine, requiring higher amlodipine doses to achieve appropriate blood pressure control.

Whether due to pharmacodynamic or pharmacokinetic changes, drug-drug interactions become more common in older individuals and individuals with significant pathophysiologies, since both situations require administration of different drugs/classes to address accumulating pathologies. Therefore, the need to consider drug-drug interactions becomes more important as more drugs are administered. Accounting for and avoiding drug-drug interactions is complex, but the regular reference of drug-drug interactions in package inserts, available databases, and working closely with pharmacists are all approaches that should be leveraged to maximize patient benefits and safety.

c. overdose toxicity

As noted previously (see above and Chapter 1), Paracelsus, who is credited as the father of toxicology, made it clear that every drug is a poison if the dose is excessive. Even water can be toxic if taken in excessive doses, which can result in fatal cerebral edema, and water drinking games and excessive water intake related to athletic competitions have resulted in death even in relatively young and previously healthy individuals. The drugs associated with the highest rates of fatalities include opiates, which are a severe public health problem. In addition, other drugs of abuse, sedative-hypnotics, antipsychotics, CNS stimulants, alcohol, cardiovascular drugs, and even acetaminophen are all associated with a large degree of fatalities. For example, acetaminophen, also known as paracetamol, is a safe drug in therapeutic doses. However, it is found in a great number of over-the-counter products for pain and also in cold remedies, in which it is a major ingredient. These products have been taken together for decades, which has resulted in fatal overdose toxicity involving liver failure. A drug that has a toxic dose that is relatively close to its therapeutic dose is considered to have a low therapeutic index, as described above. The organ system that mediates the toxicity is often not the organ system that is the therapeutic target, as seen with acetaminophen which targets the nervous system for pain relief but targets the liver to produce toxicity.

8. What drug-related disease-like symptoms (including those due to drug abuse) can be mistaken for additional disease symptoms?

Many drug-induced changes in system processes or functions have the potential to mimic certain disease states or other problematic issues with acute or chronic use. For example, anticoagulants may appear to mimic spousal abuse. An adverse effect of these drugs is extensive bruising of the skin (ecchymosis). A patient with a history of marital discord taking an anticoagulant for a clotting problem who is consulting with a new healthcare professional could be erroneously thought to be suffering from spousal abuse. The key to mitigating this problem is the awareness of these possibilities based on understanding drug pharmacodynamic properties and potential adverse events, along with accumulation of data on an individual.

9. What alterations of clinical laboratory tests can be caused by this drug?

Just as many drugs can produce other pathologies, based on their mechanism of action it is possible to also predict how laboratory test values may be affected. Therefore, when a new drug has been added to the regimen and laboratory data suggest a deviation from previous or typical values, it is often best to first determine whether a drug may be the cause. For example, a patient who has a routine blood test that shows hypokalemia or low potassium might be taking a thiazide diuretic, since this is an adverse response to this class of drugs.

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Quiz Questions

1. Pharmacovigilance issues do NOT include:
 - A. Drug toxicity
 - B. Drug adverse effects
 - C. Drug-drug interactions
 - D. Drug mechanism of action
 - E. Drug-induced symptoms that resemble another disease
2. Which of the following is NOT true about adverse drug effects in the hospital?
 - A. Lead to ED visits and hospitalizations
 - B. Cause half of the medical error-induced death in the US
 - C. Always occur within 1-2 hrs of drug administration
 - D. Cause hospitalization most commonly in the older adult demographic
3. Which of the following will have the greatest effect on the pharmacokinetic profile of a drug?
 - A. Downregulation of drug-activated effector mechanism
 - B. Reduced drug binding affinity due to mutation in the drug binding site
 - C. Inhibition of a phase I type enzyme activity responsible for prodrug transformation
 - D. Increases in target enzyme expression with prolonged administration of a drug
4. Which of the following changes in pharmacokinetic properties may lead to drug toxicity?
 - A. Decreased absorption due to elevated gastric pH
 - B. Increased volume of distribution due to elevated adipose tissue levels
 - C. Increased rate of drug metabolism due to induction of CYP2C9
 - D. Decrease in renal elimination due to dysfunctional organic anion transporter 3
5. Which of the following necessitates a re-evaluation of drug choice or dosage when they occur after initiation of a new pharmacotherapeutic regimen?
 - A. Thrombocytopenia
 - B. Pulmonary fibrosis
 - C. Cough
 - D. Orthostatic Hypotension
 - E. Anaphylaxis
 - F. All the above

Quiz Answers

1. D. Pharmacovigilance refers to the knowledge of what contributes to the adverse effects of a drug. Option D refers to a drug's mechanism of action, which is typically considered a pharmacodynamic concept as it deals with what the drug does to the body, but not necessarily what leads to an adverse event or negative reaction to a drug.
2. C. All options are true for adverse drug effects or events in the US, except C. Adverse drug events may occur in the short term and/or over long periods of time due to accumulating effects of a drug over weeks, months, or years.
3. C. Options A and B refer to changes that would primarily impact a drug's pharmacodynamic properties, while option D refers to pharmacodynamic changes that occur with drug exposure – none of which will necessarily affect absorption, distribution, metabolism, or elimination (pharmacokinetics) of a drug.
4. D. For drug toxicity to develop, it is implied that the drug concentration in the body must increase. Therefore, anything that leads to an increase in drug concentration in the body may cause toxicity. Options A-C would all decrease the amount of free drug in the body and therefore reduce the potential for toxicity to develop. Decreasing the elimination of a drug will likely lead to unexpected accumulation of the drug in the body and lead to potential toxicity.
5. F. The occurrence of any new physiological change after beginning a new drug should always be evaluated further as potentially being caused by the new drug, whether serious (anaphylaxis) or mild (cough). Even in the case of mild adverse events/effects, this may signify an individual's natural high sensitivity to or reduced ability to eliminate a drug. The emergence of these adverse events indicates a need to consider other drugs or changes in dose to ensure patient safety.

**SYMPTOMS 1 –
IMMUNO-INFECTIOUS SYMPTOMS
TO TREATMENT**

CHAPTER 3

DRUGS FOR INFECTIONS

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**Symptoms: Immuno-Infectious
Musculoskeletal
Neurological**

ANTIBACTERIAL DRUG LIST

Penicillins:

β -lactam ring-containing bacterial cell wall synthesis inhibitors

penicillin G

given intramuscular or intravenously; PBP transpeptidase inhibitor

penicillin V

given orally; PBP transpeptidase inhibitor

ampicillin

an aminopenicillin with an extended spectrum; given with **sulbactam**

amoxicillin

an aminopenicillin with an extended spectrum; given with **clavulanate**

piperacillin

“*anti-pseudomonal*” penicillin; often given with **tazobactam**

nafcillin, oxacillin, dicloxacillin

“*anti-staphylococcal*” penicillins; PBP transpeptidase inhibitors

Cephalosporins:

β -lactam ring-containing cell wall synthesis inhibitors

cefazolin, cephalexin, cephalothin

1st generation cephalosporins; PBP transpeptidase inhibitors

cefuroxime, cefoxitin, cefotetan

2nd generation cephalosporins; PBP transpeptidase inhibitors

ceftriaxone, cefotaxime, ceftazidime

3rd generation cephalosporins; PBP transpeptidase inhibitors

cefepime

4th generation cephalosporin; PBP transpeptidase inhibitor

ceftaroline fosamil

5th generation cephalosporin; PBP transpeptidase inhibitor

Carbapenems:

β -lactam ring-containing cell wall synthesis inhibitors

imipenem

given with **cilastatin** (anti-dehydropeptidase adjuvant)

doripenem, ertapenem, meropenem

broad-spectrum inhibitors of bacterial PBP transpeptidases

Monobactams:

β -lactam ring-containing cell wall synthesis inhibitors

aztreonam

monocyclic; narrow spectrum PBP transpeptidase inhibitor

Non- β -lactam drugs:**Inhibitors of cell wall synthesis / membrane integrity****vancomycin**

glycopeptide; binds and blocks peptidoglycan precursors

bacitracin

cyclic peptide; inhibits peptidoglycan precursor delivery

polymyxin B

cyclic peptide; alters bacterial membrane permeability

Folate antagonists:**Inhibitors of bacterial purine production / DNA synthesis****sulfamethoxazole (SMX),****sulfadiazine, mafenide**

sulfonamides ("sulfa" drugs) that inhibit dihydropteroate synthase

trimethoprim (TMP)dihydrofolate reductase inhibitor; usually given as **TMP-SMX** combination**pyrimethamine**dihydrofolate reductase inhibitor; usually given in combination with a **sulfa****Tetracyclines:****Inhibitors of bacterial protein synthesis****tetracycline**

30S ribosomal subunit inhibitor

doxycycline

30S ribosomal subunit inhibitor

minocycline

30S ribosomal subunit inhibitor

tigecycline

30S ribosomal subunit inhibitor; broader spectrum

sarecycline

30S ribosomal subunit inhibitor; narrower spectrum

Aminoglycosides:**Inhibitors of bacterial protein synthesis****streptomycin**

30S ribosomal subunit inhibitor

gentamicin

30S ribosomal subunit inhibitor

tobramycin

30S ribosomal subunit inhibitor

amikacin

30S ribosomal subunit inhibitor; successor to kanamycin

neomycin

30S ribosomal subunit inhibitor; topical agent only

paromomycin

30S ribosome inhibitor; antiparasitic and anthelmintic uses

chloramphenicol:

inhibitor of bacterial protein synthesis via 50S subunit

Macrolides and Ketolides:**Inhibitors of bacterial protein synthesis****erythromycin**

50S ribosomal subunit inhibitor

azithromycin

50S ribosomal subunit inhibitor

clarithromycin

50S ribosomal subunit inhibitor

telithromycin

50S ribosomal subunit inhibitor; ketolide

clindamycin (a lincosamide):

inhibitor of bacterial protein synthesis via 50S subunit

mupirocin (a mixture of pseudomonic acids):

inhibitor of bacterial isoleucine-tRNA ligase; used topically

fidaxomicin (a macrocyclic):inhibitor of bacterial RNA polymerase; used for *C. diff* only

Fluoroquinolones:**Inhibitors of bacterial DNA gyrase and topoisomerase IV****ciprofloxacin****levofloxacin**

a “respiratory fluoroquinolone”

moxifloxacin

a “respiratory fluoroquinolone”

gemifloxacin

a “respiratory fluoroquinolone”

nitrofurantoin (a nitrofuran):reduced to highly reactive intermediates damaging to bacterial DNA;
concentrated in the urine to bactericidal levels**Nitroimidazoles:****DNA-damaging drugs (anaerobic bacteria / protozoa)****metronidazole**

forms reactive nitroso radical within reducing environment

tinidazole

forms reactive nitroso radical within reducing environment

ANTIMYCOBACTERIAL DRUG LIST

First-line drugs for tuberculosis

- **isoniazid (INH)**
- **Rifamycins: rifampicin (a.k.a. Rifampin), rifapentine**
- **ethambutol**
- **pyrazinamide**

Second-line drugs for MDR-/XDR-tuberculosis

- Fluoroquinolones: **levofloxacin, moxifloxacin**
- Add-on agents: **bedaquiline; delamanid; p-aminosalicylic acid**
- Injectables: **amikacin, streptomycin; capreomycin; carbapenems + clavulanate**
- **pretomanid + bedaquiline & linezolid**

First-line drugs for Hansen’s disease (“leprosy”)

- **dapsone**
- **rifampicin**
- **clofazimine**

ANTIFUNGAL DRUG LIST

terbinafine:

inhibitor of ergosterol biosynthesis

azoles:

inhibitors of ergosterol biosynthesis

ketoconazole

imidazole, fungal CYP450 inhibitor; generally a topical application

miconazole

imidazole, fungal CYP450 inhibitor; generally a topical application

clotrimazole

imidazole, fungal CYP450 inhibitor; generally a topical application

fluconazoletriazole, fungal CYP450 inhibitor; narrower spectrum (~*Candida*)**itraconazole**triazole, fungal CYP450 inhibitor; broader spectrum (+*Aspergillus*)**voriconazole**triazole, fungal CYP450 inhibitor; broader spectrum (+*Aspergillus*)**posaconazole**triazole, fungal CYP450 inhibitor; broader spectrum (+*Aspergillus*)**isavuconazole**triazole, fungal CYP450 inhibitor; broader spectrum (+*Aspergillus*)