Michael W. Jann
Scott R. Penzak
Lawrence J. Cohen *Editors*

Applied Clinical Pharmacokinetics and Pharmacodynamics of Psychopharmacological Agents

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ISBN 978-3-319-27881-0 ISBN 978-3-319-27883-4 (eBook)
DOI 10.1007/978-3-319-27883-4

Library of Congress Control Number: 2016932526

Springer Cham Heidelberg New York Dordrecht London

Printed on acid-free paper

Adis is a brand of Springer
Springer International Publishing AG Switzerland is part of Springer Science+Business Media (www.springer.com)

Preface and Acknowledgments

The primary purpose of the *Applied Clinical Pharmacokinetics and Pharmacodynamics of Psychopharmacological Agents* text is to offer students, clinicians, scientists, and members of the pharmaceutical industry a comprehensive yet practical information resource for medications that affect the central nervous system (CNS). Part 1 presents the background for the pharmacokinetic and pharmacodynamic principles for agents that must reach the CNS to produce their clinical actions. Drug development and clinical application for the psychopharmacological agents have progressed to incorporate biomarkers, such as positron emission tomography (PET) scans, pharmacogenomics, and sophisticated mathematical modeling with population pharmacometrics. These chapters provide the readers with a foundational background of these exciting areas. Each chapter in Part 2 offers an important focus on psychopharmacological agents that reinforces the basic principles in Part 1.

The Part 2 chapters portray a broad scope of psychopharmacological agents that are available in different formulations, such as long-acting injectable antipsychotics and oral extended-release products; these formulations promote ease of dosing administration and enhance patient adherence. Some of the earliest works of pharmacokinetic-pharmacodynamic modeling occurred with the anesthetic agents, which formed the basis of analysis for the remaining psychopharmacologic medications. Pharmacodynamic parameters assessing CNS drug effects are challenging and frequently involve a variety of measurements. These measurements include patient clinical rating scales for efficacy and adverse effects, serum drug concentrations, physiologic assessments, pharmacogenomic markers, and imaging technologies.

The chapters in Part 3 concentrate on drug-drug interactions with psychopharmacological agents. Drug-drug interactions with CNS agents can occur via pharmacokinetic and/or pharmacodynamic mechanisms. Part 3 serves as a valuable resource to aid clinicians discerning clinically significant drug-drug interactions commonly encountered in patient care.

The editors wish to acknowledge our sincere appreciation to the chapter authors who contributed their time, effort, and enthusiasm, all of which made this book possible. Finally, the editors would like to thank their spouses and family members for their support during the long hours spent completing this endeavor.

Fort Worth, TX, USA

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Part I
General Pharmacokinetic and Pharmacodynamic Principles of Psychopharmacological Agents

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Chapter 1
Pharmacokinetic Properties

Mark S. Luer and Scott R. Penzak

Abstract Pharmacokinetics is the mathematical characterization of the time course of drug absorption, distribution, metabolism, and excretion. Over the past 50 years, dramatic scientific advances have revolutionized drug development and design and clinical decision making. These include improvements in quantitating drug and metabolite concentrations in biologic matrices (plasma and tissue), measuring drug effects, and understanding how genetics, metabolic pathways, and drug transporters influences drug disposition. A major challenge for health-care professionals in clinical psychopharmacology is in understanding and adjusting for individual differences in a drug's response. Knowledge of a drug's pharmacokinetic characteristics can be leveraged to help resolve these issues and formulate rational drug therapy decisions. As an example, understanding the absorption and distribution characteristics of a drug allows one to predict the amount of an administered dose that is expected to enter the bloodstream and reach its site of action. Further, an understanding of drug metabolism and elimination allows for the prediction of drug concentrations when it is administered on a repeated basis (i.e., under steady-state conditions); this allows for the rational selection of dosing regimens. Dose and regimen selection must also take drug interactions, genetic polymorphisms, comorbid conditions, and aging into account since all of these can impact drug exposure, efficacy, and toxicity.

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M. Jann et al. (eds.), *Applied Clinical Pharmacokinetics and Pharmacodynamics of Psychopharmacological Agents*,
DOI 10.1007/978-3-319-27883-4_1

Keywords Absorption • Distribution • Metabolism • Excretion • Cytochrome P450 • Poor metabolizer • Extensive metabolizer • Ultrarapid metabolizer • Inhibition • Induction • Drug interaction

1.1 Introduction

Pharmacokinetics is the mathematical characterization of the time course of drug absorption (A), distribution (D), metabolism (M), and excretion (E) [1]. Taken together, ADME processes relate to the intensity and time course (onset, duration, etc.) of drug action, as such their understanding is important to guiding rational drug therapy. Over the past 50 years, scientific advances have revolutionized drug development and design and clinical decision making. These include improvements in quantitating drug and metabolite concentrations in biologic matrices (plasma and tissue), measuring drug effects, and understanding how genetics, metabolic pathways, and drug transporters influences drug disposition. This chapter will provide an overview of how ADME and its applications may be used clinically to enhance the efficacy and minimize the toxicity of centrally acting pharmacologic agents.

1.2 Pharmacokinetics of CNS Active Agents

A major challenge for health-care professionals in clinical psychopharmacology is in understanding and adjusting for individual differences in a drug's response. Knowledge of a drug's pharmacokinetic characteristics can be leveraged to help resolve these issues and formulate rational drug therapy decisions. As an example, understanding the absorption and distribution characteristics of a drug allows one to predict the amount of an administered dose that is expected to enter the bloodstream and reach its site of action. Further, an understanding of drug metabolism and elimination allows for the prediction of drug concentrations when it is administered on a repeated basis (i.e., under steady-state conditions); this allows for the rational selection of dosing regimens. Dose and regimen selection must also take drug interactions, genetic polymorphisms, comorbid conditions, and aging into account since all of these can impact drug exposure, efficacy, and toxicity [2].

1.3 Principles of Pharmacokinetic Models and Relationship to Psychopharmacology

From a pharmacokinetic perspective, the body is often characterized as a series of compartments that are reversibly interconnected through a central compartment. Compartments are purely mathematical locales and do not necessarily represent a specific physiologic or anatomic area, but are fashioned when organs and tissues

which display similar pharmacokinetic characteristics for a given drug are grouped together. Because of these similarities, it is assumed that a drug within each compartment is distributed homogenously, and drug movement in and out of each compartment displays consistent kinetics. By establishing these compartments, mathematical models can be created to characterize the separate aspects of ADME to describe variations in each and help predict drug actions.

Drugs that behave mathematically in the body as though they reside within a single homogenous space are described using a one-compartment model. These drugs are treated as though there is one central compartment into which they are absorbed, rapidly distributed, and eliminated. In reality, the body is not a single homogenous compartment and actual tissue concentrations will vary considerably throughout. However, in using this model, it is assumed that there is kinetic homogeneity throughout the body, and thus the rate of change of drug concentrations in one tissue will reflect a corresponding change in drug concentrations in all other tissues [3]. Typically plasma or serum drug concentration data are used as the primary reference for this compartment. Consequently, a 10 % increase in plasma drug concentrations would be reflected by a 10 % increase in tissue drug concentrations over the same time frame. For one-compartment psychopharmacologically active agents, this relative increase in tissue concentrations would include the central nervous system (CNS), which represents the site(s) of drug action.

Unfortunately, not all drugs fit well into a one-compartment model and this includes many psychopharmacologic agents. For such drugs, their tissue distribution is not necessarily rapid or uniform throughout the body; consequently, rates of change in tissue drug concentrations do not consistently match those of the central compartment. These drugs are typically described mathematically as having multiple (two or more) compartments. Such a situation can easily be observed when sufficient plasma concentrations are plotted over time following an intravenous bolus injection of a drug. Upon injection, plasma concentrations will initially be high because all of the drug is located in the blood. This is quickly followed by a period of rapid decline in plasma concentrations, due primarily to drug distribution out of the central compartment and into the tissues. This period is called the *distributive phase,* although some drug elimination (e.g., metabolism by the liver and/or excretion by the kidney) also occurs simultaneously. For drugs with three or more compartments, multiple distributive phases, each with distinct rates of decline may exist. As each distributive phase may last from minutes to hours, they can only be properly delineated with multiple plasma concentrations obtained during each phase; a process that is not typically feasible in the clinical setting. Finally as drug distribution reaches its peak, a pseudo-equilibrium is established between the individual tissues and the central compartment. The continued decline in plasma concentrations will now slow, and the subsequent changes in plasma concentrations will now largely represent drug metabolism and/or excretion. This phase is called the *elimination phase*; it is during this time that a drug's elimination half-life ($T_{1/2}$) can be calculated, and it is anticipated that subsequent changes in plasma concentrations accurately reflect changes in tissue concentrations throughout the body, similar to that of a one-compartment model.

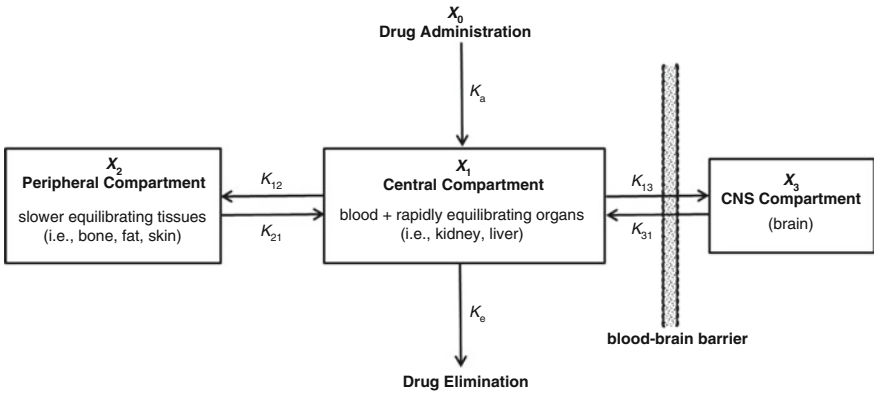

Fig. 1.1 Schematic representation of a three-compartment open model describing the kinetics of a drug that is differentially distributed between compartments. This model assumes that all drug absorption and elimination occurs via the central compartment. Arrows indicate directional movement of the drug. X_0 dose of drug, X_1 amount of drug in central compartment, X_2 amount of drug in peripheral compartment, X_3 amount of drug in CNS compartment, K_a first-order absorption rate constant, K_e elimination rate constant, and K_{12}, K_{21}, K_{13}, and K_{31} distribution rate constants of drug between compartments

For drugs acting on the CNS, pharmacokinetic modeling can be even more complicated. Let us look at an example in which a rapid intravenous bolus injection of a drug is administered into the central compartment, and the rate of drug distribution into the tissues relates principally to blood flow. In this scenario, drug concentrations in highly perfused organs and tissues such as the liver and kidney will begin to equilibrate more quickly with changes in plasma concentrations than would drug concentrations in poorly perfused tissues such as muscle and fat. These rapidly equilibrating tissues are frequently grouped together with blood since they have similar kinetic characteristics and are treated as a common central compartment where drug absorption, distribution, and elimination occur. Similarly, less well-perfused tissues are often combined into separate peripheral compartments based on their like kinetic characteristics.

Characterizing drug disposition can be difficult when considering certain organs such as the brain, which is highly perfused but is separated by a series of physiologic barriers including the blood-brain barrier (BBB) and blood-cerebral spinal fluid barriers (BCSFB). Because these barriers are lipophilic in nature, a drug's physiochemical properties can determine whether it distributes rapidly, distributes slowly, or not at all into the CNS. Consequently, the CNS may actually reside in the central compartment if a drug's distribution is rapid or a peripheral compartment if it is slower; it all depends on the drug's individual and often unique distribution characteristics.

For purposes of this discussion, psychopharmacological agents will be treated as though they reside in a dynamic system consisting of three distinct compartments (Fig. 1.1). Again, from a kinetics standpoint, these compartments are mathematical

in nature and generally do not represent a distinct anatomic location. However, in this case the CNS will be treated as a compartment separate from the others. While this three-compartment model is not universally accepted for all psychopharmacologically active agents (i.e., two compartment models may best describe the disposition of certain centrally acting agents), thinking of the body as three distinct but connected compartments makes it easier to account for differences in CNS drug disposition that may result from delayed or selective tissue uptake and/or clearance that is unique to this system. While these CNS parameters are generally not determined in the clinical setting, they can be used to rationalize drug effects in the CNS that would not otherwise be predicted based solely on a measured drug concentration in the central compartment (i.e., plasma). In addition, as the different aspects of ADME are discussed in this chapter, it will be easier to refer to the effects of each parameter on the different compartments with the understanding that changes in plasma concentrations and/or tissue distributions as reflected in the traditionally calculated pharmacokinetic parameters do not necessarily indicate corresponding changes in CNS tissue concentrations.

1.4 Pharmacokinetic Processes

Drug disposition within the CNS is dependent on both the drug's physicochemical properties and its ability to permeate physiologic barriers such as the blood-brain barrier [4]. However, ADME properties each have an impact on drug concentrations in the central compartment which are ultimately what are presented to these barriers; therefore these characteristics of ADME, either individually or collectively, affect drug concentrations in the CNS.

1.4.1 Absorption

Absorption is the entry of a drug into the body, and for psychopharmacological agents, it usually refers to drug entry into the central compartment. In most cases, these agents are administered orally or intramuscularly, but some are administered transdermally, intranasally, rectally, and occasionally intravenously. Because intravenously (IV) administered drugs are delivered directly into the central compartment, absorption is considered to be 100 %, and thus it is deemed the standard by which all other routes of drug delivery are compared. This comparison is typically done by dividing the amount of drug that is quantified in the central compartment (typically measured as area under the concentration-versus-time curve [AUC]) following non-IV administration by the amount of drug measured in this compartment following direct IV administration. This comparison is expressed as a fraction or percent of drug absorbed and is called a drug's *bioavailability*, a parameter which may vary considerably depending on the route of administration [5, 6]. Differences

in bioavailability are a substantial reason why the dose of a drug may differ so significantly from one route of administration to another.

In addition to the extent of drug absorption, the rate of drug absorption may also impact drug efficacy and clinical usefulness. The rate of absorption into the central compartment will influence the maximum plasma concentration (C_{max}) and the time at which it occurs (T_{max}). Importantly, while the rate of absorption by itself may have an effect on drug dosing because of its influence on C_{max}, it does not usually affect the steady-state concentrations or the overall maintenance dose. For this section on absorption, the focus will be on the oral and intramuscular routes of administration as they represent the primary routes by which psychopharmacological agents are dosed clinically.

1.4.1.1 Oral

For an oral drug, bioavailability is affected principally by its pharmaceutical formulation, gastrointestinal physiology, and susceptibility to presystemic metabolism in the GI tract and liver. The entire blood supply of the upper gastrointestinal tract passes through the liver before reaching the systemic circulation; therefore as drugs are absorbed into this blood supply, they may be metabolized partially or completely before ever reaching the central compartment. This process is called the "first-pass" effect and it can significantly limit the oral bioavailability of some drugs. Other considerations that can impact oral bioavailability include a compound's solubility, lipophilicity, susceptibility to degradation by pH extremes in the gastrointestinal tract, transport by uptake and efflux transporters such as organic anion transporting polypeptides (OATPs) and P-glycoprotein (P-gp), respectively, metabolism by cytochrome P450 (CYP) enzymes within the gastrointestinal wall, concomitant disease states, and drug interactions which could alter one or more of these factors. An example of the latter is the decreased oral absorption of the phenothiazine antipsychotics, fluphenazine and thioridazine, when they are coadministered with over-the-counter antacid medications. In one evaluation, solubility was reduced and the overall AUC and C_{max} of each phenothiazine were diminished 50 % or more [7].

Another consideration for oral dosing involves the rate and timing of drug absorption. In addition to formulation-specific characteristics of a drug such as extended-release preparations which intentionally slow the rate of absorption, alterations in gastric emptying can also affect an absorption profile since the majority of drugs are absorbed in the upper portion of the small intestine. Drugs such as metoclopramide, which decrease gastric emptying time (i.e., increase gastric emptying), can shorten the time to absorption (reduce T_{max}), whereas drugs that slow gastric emptying may delay the time to absorption (increase T_{max}). As an example, drugs with antimuscarinic activity such as the tricyclic antidepressants can significantly delay gastric emptying. This delay may result in a lag in the onset of action of coprescribed oral medications. A similar effect can be seen with the intake of food. High-fat meals in particular can also have a dramatic effect on gastric emptying. For

example, the absorption of valproic acid (VPA) is significantly delayed when coadministered with food. While, the overall bioavailability and ultimate pharmacologic effect is not altered, it can take hours longer to achieve peak concentrations when VPA is coadministered with a meal [8, 9]. In this case, the increased gastric emptying time does not actually slow the rate of absorption, but it does delay the time before absorption begins.

1.4.1.2 Intramuscular

When a drug is administered intramuscularly (IM), it avoids first-pass metabolism in the liver, potential degradation in the gastrointestinal tract, and depending on the drug's formulation, a quicker onset of action. For standard formulations of drugs in aqueous solutions, absorption by the IM route tends to be relatively fast, but the actual rate of absorption is dependent on blood flow. Differences in absorption rate may exist between individuals based on differences in body composition and sex. Differences in absorption rate may also exist between different muscle groups within the same individual. Obese or emaciated individuals may experience alterations in absorption, and females may experience slower absorption rates based on sex-related differences in the composition of subcutaneous fat. The IM administration of drugs in aqueous solutions is used when an immediate pharmacologic response is not necessary or feasible (e.g., no IV access), but a prompt effect is desired. One example is the use of a haloperidol lactate IM for the management of acutely agitated patients with moderate to severe symptoms.

In contrast to the rapid-onset and typically short-lived characteristics of standard aqueous solutions administered IM, long-acting IM depot formulations of drugs such as the antipsychotics have grown in popularity. These agents are most commonly long-chain esters (e.g., decanoate or palmitate) of the parent drug compounded in a vegetable oil. When injected, the compound forms a "depot" within the muscle and as the drug ester slowly diffuses into the bloodstream, the compound undergoes rapid hydrolysis to release the parent drug. Haloperidol decanoate in sesame oil is an example where such a formulation slows the rate of absorption considerably. For haloperidol decanoate, peak concentrations after IM administration may not be observed for up to 7 days, whereas after IM administration of fluphenazine decanoate, peak concentrations may be observed within 24 h of dosing; therefore, dosing of IM depot formulations of antipsychotics must be individualized [10]. Another formulation approach used to obtain this depot effect is the injectable suspension. These can be created by encapsulating a drug such as risperidone in a biodegradable copolymer that is slowly hydrolyzed in the body or by creating a microcrystalline salt such as olanzapine pamoate that is poorly water soluble on injection but freely dissociates in plasma [11]. Regardless of the technology used, these depot formulations exhibit a slow-release pattern of the drug into plasma and permit the administration of larger doses at less frequent intervals, with the intention of achieving better adherence and consistent and sustained plasma concentrations.

1.4.2 Distribution

After a drug is absorbed into the central compartment, it is distributed throughout the body and into the peripheral compartments. As mentioned previously, a drug's physiochemical properties can significantly impact its distribution characteristics. Larger molecules generally diffuse more slowly across plasma and cell membranes than smaller molecules. Drugs that are more hydrophilic tend to collect in the plasma, whereas drugs that are more lipophilic tend to accumulate in fatty tissues such as the brain. Finally, when drugs are highly bound to plasma proteins such as albumin or α_1-acid glycoprotein (AAG), the drug-protein complex formed in the plasma becomes so large that diffusion across plasma membranes is effectively prohibited leaving only the unbound or "free" drug capable of distributing out into tissues. As such, it is this unbound or free drug that is presented to the receptor site and is considered to be the pharmacologically active moiety [12].

When it comes to drug distribution into the CNS, the BBB and BCSFB are often considered the primary obstacles to entry. Because the BBB has capillary endothelial cells with tight intercellular junctions and is covered by a layer of glial cells, it is lipophilic in nature and usually restricts larger and more water-soluble molecules from crossing [13]. The BCSFB has comparably structured choroid plexus epithelial cells and likewise can restrict drug distribution. Previously, the BBB was considered to be the dominant barrier to CNS drug accumulation, but this has come into question as there is evidence that the BCSFB may have a surface area in the same order of magnitude as the BBB [13, 14]. The implications of this are not clear; nonetheless, it is less relevant whether a drug preferentially enters the CNS through one barrier versus another so long as clinically relevant drug concentrations are obtained at the site of action.

For a drug to distribute into the CNS after reaching systemic circulation, it must traverse the BBB and/or BCSFB via one of several pathways: simple diffusion, facilitated transport, or receptor-mediated transport [15, 16]. In terms of CNS drug distribution, the most prevalent process is simple diffusion. This bidirectional movement is governed by the drug's concentration gradient across the membrane and is impacted by drug-specific characteristics such as molecular size, lipophilicity, and protein binding as previously noted [13]. Increasing the amount of drug in the bloodstream or central compartment will result in an increase in the concentration of drug that is presented to the luminal side of the BBB or BCSFB and thus the amount of drug available for diffusion into the brain. As drug accumulates in the CNS, a pseudo-equilibrium will eventually be established as concentrations equilibrate on both sides of the barrier. Then as plasma concentrations decline secondary to redistribution, metabolism, and/or excretion, the drug will diffuse out of the CNS and back into the central compartment according to the concentration gradient. Typically, smaller, more lipophilic molecules tend to cross the BBB more readily in both directions. A classic example demonstrating this fact is a comparison of the CNS distribution of diazepam and lorazepam. Given intravenously, the more lipophilic diazepam distributes into CNS tissues more quickly than lorazepam and has

a slightly more rapid onset of action [17]. However, diazepam, because of his high lipophilicity, will continue to distribute into other tissues as well. This continued distribution into other (non-CNS) tissues causes diazepam concentrations in the plasma to decline such that CNS concentrations are comparatively higher. In keeping with the concentration gradient, diazepam diffuses out of the CNS, and within 15–20 min its neuropharmacological effects can be lost. In comparison lorazepam, which is less lipophilic than diazepam, distributes out of the central compartment and into all tissues more slowly; consequently lorazepam does not display the same degree of redistribution as diazepam. Hence, when administered as an IV bolus, diazepam will have a rapid onset of action that is likely to be short-lived. Conversely, lorazepam administered as an IV bolus will have a slightly slower onset on action, yet its pharmacologic effect may persist for hours [17, 18]. This difference has led some clinicians to prefer lorazepam over diazepam for the treatment of status epilepticus although clinical data demonstrating that one drug is more efficacious than the other in this setting are conflicting [19, 20].

While most drugs gain entry to the CNS via simple diffusion, to a lesser extent drugs may enter the CNS through facilitated diffusion or passive carrier-mediated transport. This process is similar to simple diffusion in that it works along a concentration gradient, but it requires a helper protein to "facilitate" the transport process through the membrane. The greatest difference from simple diffusion is that with facilitated diffusion, the helper protein is finite in number, and thus the process is subject to being capacity limited. Examples of natural substances which utilize this method of uptake are amines, amino acids, and small peptides. Thus for drugs such as gabapentin which have been associated with neutral amino acid transport, saturable uptake into the CNS may occur [21].

The third pathway for centrally acting drugs to gain access to the CNS is receptor-mediated transport or more specifically receptor-mediated endocytosis and transcytosis [16, 22]. Receptor-mediated transport has generated a tremendous amount of interest in recent years and is aggressively being explored as a mechanism for delivering larger drug macromolecules and therapeutic proteins into the CNS. This approach capitalizes on existing transport systems in the BBB and could revolutionize treatment options for all types of neurologic disorders. At this time however, the utility of receptor-mediated transport to facilitate drug delivery in the CNS is largely investigational and mostly limited to preclinical studies [16, 22]. Further discussion of this process and its potential implications will be discussed later in this chapter.

A fourth transport system for crossing the BBB does exist, but its role in drug transport is thought primarily to limit CNS drug uptake, not facilitate it. The system is comprised of a group of naturally occurring, membrane-bound proteins that act as active efflux transporters to move substrates across membranes and against concentration gradients in an energy-dependent manner. Importantly, many drugs serve as substrates or modifiers for these transporters. One of the most prominent active efflux transporters in the BBB is P-glycoprotein (P-gp), which can significantly limit the CNS uptake of many lipophilic drugs that would otherwise be predicted to have significant distribution into the brain based on their physicochemical properties alone [23–25]. This mismatch in distribution patterns for some lipophilic drugs

has been a challenge to CNS drug development for years; because a drug must not only be able to cross the BBB, it must reside in the CNS long enough to exert its desired pharmacological effects [26, 27]. In short, these efflux transporters may not be able to prevent a drug's diffusion into the CNS, but they do appear to limit its accumulation and thus minimize its effectiveness as a neuropharmacological agent. The reader is referred to Chap. 5 for a detailed description of drug transporters and the role they play in the BBB as well as overall drug therapy.

For most psychopharmacological agents which are lipophilic in nature, the concentration gradient at the BBB and BCSFB is principally what governs CNS drug disposition. In general, the rate of CNS drug uptake or loss will be proportional to this gradient, so increases or decreases in plasma concentrations will likely lead to respective changes in concentration-dependent CNS drug activity. This dynamic relationship highlights the importance of ADME, since changes in any one of the ADME parameters can alter plasma concentrations causing changes to CNS concentrations and ultimately a drug's neuropharmacological effects.

1.4.3 Metabolism

The majority of psychopharmacologically active agents are removed from the body through metabolic processes. Most drug metabolism occurs in the liver and is usually categorized as phase I or phase II reactions. Phase I involves the processes of oxidation, reduction, and hydrolysis, and phase II involves conjugation. In general, metabolism results in the biotransformation of a parent compound or drug into one or more metabolites, the purpose of which is to make the compound more polar in nature (i.e., water soluble) and thus easier to eliminate from the body by the liver and/or kidney [2, 27]. The resultant metabolite(s) may be inactive, less active, or even more pharmacologically active than the parent compound.

A drug that is metabolized may have as few as one or more than 50 metabolites, some of which may be pharmacologically and/or pharmacokinetically active. From a pharmacologic perspective, the metabolite(s) can contribute significantly to the overall efficacy and/or toxicity profile of the parent drug, and from a pharmacokinetic standpoint, the metabolite may alter (i.e., restrict or enhance) its clearance. A few examples where a metabolite is active and contributes to the drug's overall therapeutic effect are amitriptyline's conversion to nortriptyline, fluoxetine's conversion to nor-fluoxetine, and primidone's conversion to two active metabolites (phenobarbital and phenylethylmalonamide) [28–30]. In those situations when the metabolite itself is the pharmacologically active moiety, the parent drug is referred to as a prodrug. Tramadol, codeine, and fosphenytoin are each prodrugs where metabolic conversion is necessary for their desired pharmacological effect. Tramadol, for instance, is transformed to *O*-desmethyltramadol (*O*-DSMT) which is considerably more potent as a mu opioid agonist and has been shown to have a far greater analgesic effect than the parent drug, tramadol [31, 32].

Of all the metabolic pathways, the cytochrome P450 (CYP) superfamily of metabolizing enzymes is the most important to the metabolism and clearance of drugs and is a major source of variability in pharmacokinetics and plasma drug concentrations [33–38]. Table 1.1 provides an overview of many of the antipsychotics, antidepressants, anxiolytics, anticonvulsants, opioids, and hypnotics relative to their role as a CYP subfamily substrate, inhibitor, or inducer. The data compiled for this table are intended to serve as a reference point from which the discussion on metabolism will now shift to those specific intrinsic and extrinsic factors that affect CYP drug metabolism.

1.4.3.1 Genetic Variability

All enzymes involved in drug metabolism are regulated by genes and gene products (e.g., proteins and RNA). Consequently, an individual's genetic makeup plays an important role in determining the amount and activity of each enzyme system including CYP. This genetic factor accounts for significant interindividual variability in both drug metabolism and metabolite formation. Gene mutations result in enzyme variants with increased, decreased, or no activity. When a gene variant represents at least 1 % of the general population, it is considered a pharmacogenetic polymorphism [39]. Genetically, a wide spectrum of variants may occur in a population that could potentially create a broad range of enzyme activities, but in practice these variants are typically categorized into four general pharmacokinetic phenotypes:

- Poor metabolizers (PM) refer to individuals with variants resulting in highly dysfunctional or inactive CYP enzymes.
- Intermediate metabolizers (IM) refer to individuals with variants resulting in below normal CYP enzyme activity.
- Extensive metabolizers (EM) refer to individuals with the normal phenotype and represent the majority of the population. The EM is the reference phenotype by which others are compared as it is considered normal CYP enzyme activity.
- Ultrarapid metabolizers (UM) refer to individuals with variants that produce much higher than normal CYP enzyme activity [37].

Polymorphic CYP enzymes of clinical relevance for psychopharmacological agents include CYP2C9, CYP2C19, and CYP2D6 [37, 40]. While there are also variants in other important drug-metabolizing enzymes such as CYP1A2 and CYP3A4, extremes in metabolism such as PM and UM are rare [37]. The clinical impact of any pharmacogenetic polymorphism must be considered within the context of the drug(s) being used. Equivalent dosing in PM will result in higher plasma concentrations and possible toxicity relative to EM, while the opposite will occur in UM (i.e., lower plasma concentrations and a possible lack of efficacy). Differential effects also occur if the drug must be metabolically activated (i.e., prodrug); in this case PM will not convert the parent compound to its active metabolite, thus rendering the drug potentially ineffective [37, 40]. Conversely, when a prodrug is

Table 1.1 Reported psychopharmacological agents that act as substrates, inhibitors, or inducers of cytochrome P450 metabolism

CYP1A2	*CYP2B6*	*CYP2C8*	*CYP2C9*	*CYP2C19*	*CYP2D6*	*CYP3A4*
Substrates						
Amitriptyline	Bupropion	Benzphetamine	Amitriptyline	Amitriptyline	Amitriptyline	Alprazolam
Asenapine	Ketamine	Carbamazepine	Clomipramine	Citalopram	Amphetamine	Amitriptyline
Caffeine	Methadone	Phenytoin	Dronabinol	Clomipramine	Aripiprazole	Aripiprazole
Chlordiazepoxide	Sertraline	Zopiclone	Fluoxetine	Desipramine	Asenapine	Buprenorphine
Chlorpromazine			Hexobarbital	Diazepam	Atomoxetine	Buspirone
Clozapine			Imipramine	Escitalopram	Chlorpromazine	Cafergot
Imipramine			Ketamine	Hexobarbital	Clomipramine	Caffeine
Nortriptyline			Mephenytoin	Imipramine	Clozapine	Cannabinoids
Olanzapine			Phenobarbital	Lacosamide	Codeine	Carbamazepine
Perphenazine			Phenytoin	S-Mephenytoin	Desipramine	Chlordiazepoxide
Riluzole			Quetiapine	R-Mephenytoin	Dexfenfluramine	Citalopram
Tacrine			Sertraline	R-Mephobarital	Dextromethorphan	Clomipramine
Zolpidem			THC	Moclobemide	Donepezil	Clonazepam
			Valproic Acid	Nortriptyline	Duloxetine	Clorazepate
				Phenobarbital	Fluphenazine	Clozapine
				Phenytoin	Fentanyl	Cocaine
				Sertraline	Fluoxetine	Codeine
				Thioridazine	Fluvoxamine	Dextromethorphan
					Galantamine	Diazepam
					Haloperidol	Donepezil
					Hydrocodone	Dronabinol
					Iloperidone	Eszopiclone
					Imipramine	Ethosuximide
					Maprotiline	Fentanyl
					Meperidine	Flurazepam
					Methadone	Galantamine

					Methamphetamine	Haloperidol
					Methoxyamphetamine	Hydrocodone
					Minaprine	Iloperidone
					Mirtazapine	Imipramine
					Morphine	Ketamine
					Nortriptyline	Methadone
					Olanzapine	Midazolam
					Oxycodone	Mirtazapine
					Paroxetine	Modafinil
					Perphenazine	Oxycodone
					Propoxyphene	Quetiapine
					Quetiapine	Ramelteon
					Risperidone	Sertraline
					Sertraline	Sibutramine
					Thioridazine	Sufentanil
					Tramadol	Temazepam
					Trazodone	THC
					Venlafaxine	Tiagabine
						Tramadol
						Trazodone
						Triazolam
						Valproic Acid
						Zaleplon
						Ziprasidone
						Zolpidem
						Zonisamide

(continued)

Table 1.1 (continued)

CYP1A2	*CYP2B6*	*CYP2C8*	*CYP2C9*	*CYP2C19*	*CYP2D6*	*CYP3A4*
Inhibitors						
Citalopram			Fluoxetine	Citalopram	Asenapine	Fluoxetine
Fluvoxamine			Fluvoxamine	Felbamate	Bupropion	Fluvoxamine
			Modafinil	Fluoxetine	Chlorpromazine	Nefazadone
			Paroxetine	Fluvoxamine	Citalopram	Norfluoxetine
			Sertraline	Modafinil	Clomipramine	Sertraline
			Tacrine	Oxcarbazepine	Cocaine	
				Topiramate	Desipramine	
					Dozepine	
					Duloxetine	
					Escitalopram	
					Fluoxetine	
					Fluphenazine	
					Haloperidol	
					Levomepromazine	
					Methadone	
					Moclobemide	
					Nefazodone	
					Norfluoxetine	
					Paroxetine	
					Perphenazine	
					Propoxyphene	
					Sertraline	
					Thioridazine	