INTRODUCTION

Drugs used to treat psychiatric disorders have become among the most prescribed classes of pharmaceutical agents. Antidepressants are second only to lipid-lowering agents in prescription volume in the United States. Antipsychotic drugs are among the fastest growing classes of drugs. Benzodiazepines and similarly acting agents that reduce anxiety and promote sleep are perennially among the most widely prescribed medications. In addition to agents with Food and Drug Administration (FDA) approval for use as primary interventions for mental disorders, many other drugs are used “off label.” In fact, many of the chapters that follow discuss compounds that are intended to treat general medical or neurologic conditions in addition to mental illness.

There are three general terms, used interchangeably, that describe drugs that treat psychiatric disorders—psychotropic drugs, psychoactive drugs, and psychotherapeutic drugs. Traditionally, these agents have been divided into the following four categories: (1) antipsychotic drugs or neuroleptics used to treat psychosis, (2) antidepressant drugs used to treat depression, (3) antimanic drugs or mood stabilizers used to treat bipolar disorder, and (4) antianxiety drugs or anxiolytics used to treat anxious states (which are also effective as hypnotics in high dosages). Such categoric distinctions, however, have become less valid for the following reasons:

1. Many drugs of one class are used to treat disorders previously assigned to another class. For example, most antidepressant drugs are now also used to treat a broad range of anxiety disorders.
2. Drugs introduced as treatments for schizophrenia, agents such as the serotonin–dopamine antagonists (SDAs), are also indicated for the management of bipolar disorder and appear to have some antidepressant activity.
3. Drugs from all four categories are used to treat symptoms and disorders such as insomnia, eating disorders, behavioral disturbances associated with dementia, and impulse-control disorders.
4. Drugs such as clonidine (Catapres), propranolol (Inderal), verapamil (Isoptin), modafinil (Provigil), and gabapentin (Neurontin) can effectively treat a variety of psychiatric disorders and do not fit easily into the traditional classification of drugs.
5. Some descriptive psychopharmacologic terms are arbitrary and overlap in meaning. For example, anxiolytics decrease anxiety, sedatives produce a calming or relaxing effect, and hypnotics produce sleep. However, most anxiolytics function as sedatives and at high doses can be used as hypnotics, and all hypnotics at low doses can be used for daytime sedation.
CLASSIFICATION

This book uses a classification in which each drug is discussed according to its pharmacologic category. Each drug is described in terms of its pharmacologic actions, including pharmacodynamics and pharmacokinetics. Indications, contraindications, drug–drug interactions, and adverse side effects are also discussed.

Table A (see p. xi) lists each psychotherapeutic drug according to its generic name, trade name, and chapter title and number in which it is discussed.

PHARMACOLOGIC ACTIONS

The main determinants of the clinical effects of a drug on an individual are determined by its pharmacokinetic and pharmacodynamic properties. In simple terms, pharmacokinetics describes what the body does to the drug, and pharmacodynamics describes what the drug does to the body. Pharmacokinetic data trace the absorption, distribution, metabolism, and excretion of the drug in the body. Pharmacodynamic data measure the effects of the drug on cells in the brain and other tissues of the body.

Pharmacokinetics

Absorption. Drugs reach the brain through the bloodstream. Orally administered drugs dissolve in the fluid of the gastrointestinal (GI) tract—depending on their lipid solubility and the GI tract’s local pH, motility, and surface area—and are then absorbed into the blood.

Stomach acidity may be reduced by proton pump inhibitors, such as omeprazole (Prilosec), esomeprazole (Nexium), and lansoprazole (Prevacid); by histamine H₂ receptor blockers, such as cimetidine (Tagamet), famotidine (Pepcid), nizatidine (Axid), and ranitidine (Zantac); or by antacids. Gastric and intestinal motility may be either slowed by anticholinergic drugs or increased by dopamine receptor antagonists (DRAs), such as metoclopramide (Reglan). Food can also increase or decrease the rate and degree of drug absorption.

As a rule, parenteral administration can achieve therapeutic plasma concentrations more rapidly than can oral administration. However, some drugs are deliberately emulsified in an insoluble carrier matrix for intramuscular (IM) administration, which results in the drug’s gradual release over several weeks. These formulations are called depot preparations. Intravenous (IV) administration is the quickest route for achieving therapeutic blood concentrations, but it also carries the highest risk of sudden and life-threatening adverse effects.

Distribution and Bioavailability. Drugs that circulate bound to plasma proteins are called protein bound, and those that circulate unbound are called free. Only the free fraction can pass through the blood–brain barrier.

The distribution of a drug to the brain is governed by the brain’s regional blood flow, the blood–brain barrier, and the drug’s affinity with its receptors in the brain. High cerebral blood flow, high lipid solubility, and high receptor affinity promote the therapeutic actions of the drug.
A drug’s volume of distribution is a measure of the apparent space in the body available to contain the drug, which can vary with age, sex, adipose tissue content, and disease state. A drug that is very lipid soluble, such as diazepam (Valium), and thus is extensively distributed in adipose tissue, may have a short duration of clinical activity despite a very long elimination half-life.

Bioavailability refers to the fraction of the total amount of administered drug that can subsequently be recovered from the bloodstream. Bioavailability is an important variable because FDA regulations specify that the bioavailability of a generic formulation can differ from that of the brand-name formulation by no more than 30%.

**Metabolism and Excretion**

**Metabolic Routes.** The four major metabolic routes for drugs are oxidation, reduction, hydrolysis, and conjugation. Metabolism usually yields inactive metabolites that are readily excreted. However, metabolism also transforms many inactive prodrugs into therapeutically active metabolites.

The liver is the principal site of metabolism, and bile, feces, and urine are the major routes of excretion. Psychotherapeutic drugs can also be excreted in sweat, saliva, tears, and breast milk.

**Quantification of Metabolism and Excretion.** Four important parameters regarding metabolism and excretion are time of peak plasma concentration, half-life, first-pass effect, and clearance.

The time between the administration of a drug and the appearance of peak plasma concentrations varies according to the route of administration and rate of absorption.

A drug’s half-life is the amount of time it takes for metabolism and excretion to reduce a particular plasma concentration by half. A drug administered steadily at time intervals shorter than its half-life will reach 97% of its steady-state plasma concentration after five half-lives.

The first-pass effect refers to the initial metabolism of orally administered drugs within the portal circulation of the liver, and is described as the fraction of absorbed drug reaching the systemic circulation unmetabolized.

Clearance is a measure of the amount of the drug excreted from the body in a specific period of time.

**Cytochrome P450 Enzymes.** The cytochrome P450 (CYP) enzyme system is responsible for the inactivation of most psychotherapeutic drugs. It is so named because the heme-containing enzymes strongly absorb light at a wavelength of 450 nm. Although present throughout the body, these enzymes act primarily in the endoplasmic reticulum of the hepatocytes and the cells of the intestine. Therefore, cellular pathophysiology, such as that caused by viral hepatitis or cirrhosis, may affect the efficiency of drug metabolism by the CYP enzymes.

The human CYP enzymes comprise several distinct families and subfamilies. In the CYP nomenclature, the family is denoted by a numeral, the subfamily by a capital letter, and the individual member of the subfamily by a second numeral (e.g., 2D6). Persons with genetic polymorphisms in the CYP genes that encode inefficient versions of CYP enzymes are considered poor metabolizers.
There are two mechanistic processes involving the CYP system: induction and inhibition (Table 1–1):

**Induction.** Expression of the CYP genes may be induced by alcohol, certain drugs (barbiturates, anticonvulsants), or smoking. For example, an inducer of CYP3A4, such as cimetidine, may increase the metabolism and decrease the plasma concentrations of a substrate of 3A4, such as alprazolam (Xanax).

**Inhibition.** Certain drugs are not substrates for a particular enzyme but may nonetheless indirectly inhibit the enzyme and slow its metabolism of other drug substrates. For example, concurrent administration of a CYP2D6 inhibitor, such as fluoxetine (Prozac), may inhibit the metabolism and thus raise the plasma concentrations of CYP2D6 substrates, including amitriptyline (Elavil). If one CYP enzyme is inhibited, then its substrate accumulates until it is metabolized by an alternate CYP enzyme. Table 1–2 lists representative psychotropic drug substrates of human CYPs along with representative inhibitors.

**Pharmacodynamics**

The major pharmacodynamic considerations include molecular site of action; the dose-response curve; the therapeutic index; and the development of tolerance, dependence, and withdrawal symptoms.

**Molecular Site of Action.** Psychotropic drugs may act at any of several molecular sites in brain cells. Some activate (agonists) or inactivate (antagonists) receptors for a specific neurotransmitter. Other drugs, particularly antidepressant drugs, bind to and block transporters that normally take up serotonin or norepinephrine from the synaptic cleft into the presynaptic nerve ending (reuptake inhibitors).

Some drugs block the passage of cations or anions through ion channels embedded in cellular membranes (channel inhibitors or blockers). Other drugs bind to and inhibit catabolic enzymes that normally inactivate neurotransmitters, thereby prolonging the life span of the active neurotransmitters (e.g., monoamine oxidase inhibitors). Finally, several drugs have numerous molecular sites of action, although the sites that are therapeutically relevant may remain unknown.

**Dose-Response Curves.** The dosage-response curve plots the clinical response to the drug as a function of drug concentration (Figure 1–1). Potency refers to comparisons of the dosages of different drugs required to achieve a certain effect. For
### Table 1–2
Representative Psychotropic Drug Substrates of Human Cytochrome P450's Along with Representative Inhibitors

<table>
<thead>
<tr>
<th>CYP3A</th>
<th>CYP2D6</th>
<th>CYP2C19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substrates</td>
<td>Substrates</td>
<td>Substrates</td>
</tr>
<tr>
<td>Triazolam (Halcion)</td>
<td>Desipramine (Norpramin)</td>
<td>Diazepam&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Alprazolam (Xanax)</td>
<td>Nortriptyline (Aventyl)</td>
<td>Amitriptyline&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Midazolam (Versed)</td>
<td>Paroxetine (Paxil)</td>
<td>Citalopram&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Quetiapine (Seroquel)</td>
<td>Venlafaxine (Effexor)</td>
<td>Inhibitors</td>
</tr>
<tr>
<td>Nefazodone (Serzone)</td>
<td>Tramadol (Ultram)</td>
<td>Fluvoxamine</td>
</tr>
<tr>
<td>Buspirone (BuSpar)</td>
<td>Fluoxetine&lt;sup&gt;a&lt;/sup&gt; (Prozac)</td>
<td>Omeprazole (Prilosec)</td>
</tr>
<tr>
<td>Trazodone (Desyrel)</td>
<td>Citalopram&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Ramelteon (Rozerem)</td>
<td>Inhibitors</td>
<td></td>
</tr>
<tr>
<td>Zolpidem&lt;sup&gt;a&lt;/sup&gt; (Ambien)</td>
<td>Quinidine (Cardioquin)</td>
<td></td>
</tr>
<tr>
<td>Amitriptyline&lt;sup&gt;a&lt;/sup&gt; (Endep)</td>
<td>Fluoxetine</td>
<td></td>
</tr>
<tr>
<td>Imipramine&lt;sup&gt;a&lt;/sup&gt; (Tofranil)</td>
<td>Paroxetine</td>
<td></td>
</tr>
<tr>
<td>Haloperidol&lt;sup&gt;a&lt;/sup&gt; (Haldol)</td>
<td>Bupropion (Wellbutrin, Zyban)</td>
<td></td>
</tr>
<tr>
<td>Citalopram&lt;sup&gt;a&lt;/sup&gt; (Celexa)</td>
<td>Terbinafine (Lamisil)</td>
<td></td>
</tr>
<tr>
<td>Clozapine&lt;sup&gt;a&lt;/sup&gt; (Clozaril)</td>
<td>Diphenhydramine (Benadryl)</td>
<td></td>
</tr>
<tr>
<td>Diazepam&lt;sup&gt;a&lt;/sup&gt; (Valium)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ritonavir (Norvir)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketoconazole (Nizoral)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itraconazole (Sporanox)</td>
<td></td>
<td></td>
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<tr>
<td>Nefazodone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine (Luvox)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythromycin (E-Mycin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin (Biaxin)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Partial substrate.

### Examples of Dose-Response Curves

**Figure 1–1.** The dosage-response curves plot the therapeutic effect as a function of increasing dose, often calculated as the log of the dose. Drug A has a linear dosage response, drugs B and C have sigmoidal curves, and drug D has a curvilinear dosage-response curve. Although smaller doses of drug B are more potent than are equal doses of drug C, drug C has a higher maximum efficacy than does drug B. Drug D has a therapeutic window such that both low and high doses are less effective than midrange doses.
example, haloperidol (Haldol) is more potent than chlorpromazine (Thorazine) because about 2 mg of haloperidol is required to achieve the same therapeutic effect as 100 mg of chlorpromazine. However, haloperidol and chlorpromazine are equal in their clinical efficacy—that is, the maximum achievable clinical response.

**Therapeutic Index.** The therapeutic index is a relative measure of a drug’s toxicity or safety. It is defined as the ratio of the median toxic dosage ($TD_{50}$)—the dosage at which 50% of persons experience toxic effects—to the median effective dosage ($ED_{50}$)—the dosage at which 50% of persons experience therapeutic effects. For example, haloperidol has a high therapeutic index, as evidenced by the wide range of dosages in which it is prescribed without monitoring of plasma concentrations. Conversely, lithium (Eskalith, Lithobid, Lithonate) has a low therapeutic index, thereby requiring the close monitoring of plasma concentrations to avoid toxicity.

Persons exhibit both interindividual and intraindividual variation in their responses to a specific drug. An individual may be hyporeactive, normally reactive, or hyperreactive to a particular drug. For example, whereas some persons require 50 mg a day of sertraline, other persons require 200 mg a day for control of their symptoms. An unpredictable, non–dosage-related drug response is called idiosyncratic. For example, diazepam administered as a sedative paradoxically causes agitation in some persons.

**Tolerance, Dependence, and Withdrawal Symptoms.** A person who becomes less responsive to a particular drug over time is said to develop tolerance to the effects of the drug. The development of tolerance can be associated with the appearance of physical dependence, which is the necessity to continue administering the drug to prevent the appearance of withdrawal symptoms (also called discontinuation syndrome).

**DRUG INTERACTIONS**

Drug interactions may be either pharmacokinetic or pharmacodynamic, and they vary greatly in their potential to cause serious problems. Pharmacokinetic drug interactions concern the effects of drugs on their respective plasma concentrations, and pharmacodynamic drug interactions concern the effects of drugs on their respective receptor activities.

Pharmacodynamic drug–drug interactions causing additive biochemical changes may trigger toxic adverse effects. For example, monoamine oxidase inhibitors (MAOIs) when coadministered with either tricyclic antidepressants or selective serotonin reuptake inhibitors (SSRIs), may precipitate a serotonin syndrome in which serotonin is metabolized slowly and thus accumulates in excessive concentrations. The interaction of disulfiram (Antabuse) and alcohol is another example of toxicity caused by pharmacodynamic drug interactions.

Some clinically important drug interactions are well studied and well proven; other interactions are well documented but have only modest effects; and still other interactions are true but unproven, although reasonably plausible. Clinicians must remember that (1) animal pharmacokinetic data are not always readily generalizable to humans; (2) in vitro data do not necessarily replicate the results obtained under in vivo conditions; (3) single-case reports can contain misleading information; and
(4) studies of acute conditions should not be uncritically regarded as relevant to chronic, steady-state conditions.

An additional consideration is one of phantom drug interactions. The person may be taking only drug A and then later receive both drug A and drug B. The clinician may then notice some effect and attribute it to the induction of metabolism. In fact, what may have occurred is that the person was more compliant at one point in the observation period than in another or there may have been some other effect of which the clinician was unaware. The clinical literature may contain reports of phantom drug interactions that are rare or nonexistent.

Informed clinicians need to keep these considerations in mind and to focus on the clinically important interactions, not on the ones that may be mild, unproven, or entirely phantom. At the same time, clinicians should maintain an open and receptive attitude toward the possibility of pharmacokinetic and pharmacodynamic drug interactions.

**DRUG SELECTION**

There is no psychotropic drug that is effective in all patients with a given diagnosis. The ability of a drug to prove effective is only partially predictable and depends on the properties of the drug and the biology of the patient. Decisions about drug selection and use are made on a case-by-case basis, relying on the individual judgment of the physician. There are three factors in drug selection: (1) the drug, (2) the patient, and (3) the expertise and judgment of the prescribing physician. Each of these components affects the probability of a successful outcome.

An often-overlooked consideration in drug selection involves possible long-term consequences of being on a particular drug. For example, when starting antidepressant treatment in a young woman, thought needs to be given to which drug would be less problematic should she become pregnant and need to remain on medication. Paroxetine (Paxil), as an example, carries a higher risk of birth defects and would not be the best choice of medication in this instance. Another reason that paroxetine would not be the most appropriate agent for this patient group is its more severe withdrawal syndrome, which would make it more difficult for a woman who wants to discontinue medication in order to become pregnant. Similarly, drugs such as quetiapine (Seroquel) or citalopram (Celexa) that can prolong the QT interval may be reasonable choices for a healthy adult with no congenital long QT interval, but may be problematic if that patient needs to be treated for a medical problem with other medications that prolong the QT interval. Thinking long-term is important because many psychiatric disorders are chronic and involve treatment over extended periods.

**THERAPEUTIC INDICATIONS**

A therapeutic indication is a psychiatric diagnosis, as defined in the 10th revision of the *International Statistical Classification of Diseases and Related Health Problems* (ICD-10) or the fifth edition of the *Diagnostic and Statistical Manual of Mental*
Disorders (DSM-5), for which a specific drug ameliorates signs or symptoms. Drugs are approved on the basis of carefully designed large-scale clinical trials that prove the drug is safe and that clinical improvement is attributable to the drug and not to the placebo. The FDA then grants a manufacturer the official right to advertise the drug as safe and effective for that therapeutic indication.

Clinicians must distinguish between official and unofficial therapeutic indications. This is necessary because many drugs are in fact safe and effective for treating not only those indications proven in FDA-scale trials but also for a much broader range of indications described in smaller trials.

Drug Approval Process in the United States

Under the Federal Food, Drug, and Cosmetic (FD&C) Act, initially passed in 1938 and subsequently heavily amended, the FDA has the authority to (1) control the initial availability of a drug by approving only those new drugs that demonstrate both safety and effectiveness and (2) ensure that the drug’s proposed labeling is truthful and contains all pertinent information for the safe and effective use of that drug. An additional concentration of government regulation is directed by the Drug Enforcement Administration (DEA), which classifies drugs according to their abuse potential (Table 1–3). Clinicians are advised to exercise increased caution when prescribing controlled substances.

In general, the FDA not only ensures that a new medication is safe and effective but also that a new medication compares favorably with existing agents used for the same indications. The new agent is usually not approvable unless it is at least equivalent in safety and efficacy to existing agents, if not superior. Table 1–4 summarizes the phases of research that lead to approval of a new drug.

Off-Label Uses

After a drug has been approved for commercial use, the clinician may, as part of the practice of medicine, lawfully prescribe a different dosage for a person or otherwise vary the conditions of use from what is approved in the package labeling without notifying the FDA or obtaining its approval. In other words, the FD&C Act does not limit the manner in which a clinician may use an approved drug.

However, although clinicians may treat persons with an approved drug for unapproved purposes—that is, for indications not included on the drug’s official labeling—without violating the FD&C Act, this practice exposes the clinician to increased risk for medical malpractice liability. This is a significant concern because the failure to follow the FDA-approved label may create an inference that the clinician is varying from the prevailing standard of care. Clinicians may, however, prescribe medication for any reason they believe to be medically indicated for the welfare of the person. This clarification is important in view of the increasing regulation of clinicians by federal, state, and local governmental agencies.
Table 1-3
Characteristics of Drugs at Each DEA Level

<table>
<thead>
<tr>
<th>Schedule (Control Level)</th>
<th>Characteristics of Drug at Each Schedule</th>
<th>Examples of Drugs at Each Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>High abuse potential</td>
<td>LSD, heroin, marijuana, peyote,</td>
</tr>
<tr>
<td></td>
<td>No accepted use in medical</td>
<td>PCP, mescaline, psilocybin,</td>
</tr>
<tr>
<td></td>
<td>treatment in the United States at the</td>
<td>nicocodeine, nicomorphine</td>
</tr>
<tr>
<td></td>
<td>present time; therefore, not for</td>
<td></td>
</tr>
<tr>
<td></td>
<td>prescription use</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Can be used for research</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>High abuse potential</td>
<td>Amphetamine, opium, morphine,</td>
</tr>
<tr>
<td></td>
<td>Severe physical dependence liability</td>
<td>codeine, hydromorphone,</td>
</tr>
<tr>
<td></td>
<td>Severe psychological dependence liability</td>
<td>phennetrazine, amobarbital,</td>
</tr>
<tr>
<td></td>
<td>No refills; no telephone prescriptions</td>
<td>seccobarbital, pentobarbital,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ketamine, methylphenidate</td>
</tr>
<tr>
<td>III</td>
<td>Abuse potential lower than levels I and</td>
<td>Glutethimide; methyprylon;</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>nalorphine; sulfurmethane;</td>
</tr>
<tr>
<td></td>
<td>Moderate or low physical dependence</td>
<td>benzphetamine; phendimetrazine;</td>
</tr>
<tr>
<td></td>
<td>liability</td>
<td>chlorphentermine; compounds</td>
</tr>
<tr>
<td></td>
<td>High psychological liability</td>
<td>containing codeine, morphine,</td>
</tr>
<tr>
<td></td>
<td>Prescriptions must be rewritten after 6</td>
<td>opium, hydrocodone,</td>
</tr>
<tr>
<td></td>
<td>months or five refills</td>
<td>alfhydromorphone, diethylpropion;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>dronabinol</td>
</tr>
<tr>
<td>IV</td>
<td>Low abuse potential</td>
<td>Phenobarbital, benzodiazepines, a</td>
</tr>
<tr>
<td></td>
<td>Limited physical dependence liability</td>
<td>chloral hydrate, ethchlorvynol,</td>
</tr>
<tr>
<td></td>
<td>Limited psychological dependence</td>
<td>ethinamate, meprobamate,</td>
</tr>
<tr>
<td></td>
<td>liability</td>
<td>paraldehyde</td>
</tr>
<tr>
<td></td>
<td>Prescriptions must be rewritten after 6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>months or five refills</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>Lowest abuse potential of all controlled</td>
<td>Narcotic preparations containing</td>
</tr>
<tr>
<td></td>
<td>substances</td>
<td>limited amounts of nonnarcotic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>active medicinal ingredients</td>
</tr>
</tbody>
</table>

DEA, Drug Enforcement Administration; LSD, lysergic acid diethylamide; PCP, phencyclidine.  
In New York State, benzodiazepines are treated as schedule II substances, which require a triplicate prescription for a maximum of 3 months’ supply.

Table 1-4
Phases of Drug Development

Nonclinical (Preclinical) Studies. Nonclinical studies that are sufficient to establish a tolerable dose and to identify the target organs of toxicity for a new drug must be conducted before first use of a new chemical entity in humans. A standard battery of animal studies and in vitro studies is required.

Phase I. Phase I studies represent the initial introduction of the new drug into humans. These studies, usually conducted in healthy volunteers, typically in closely monitored (often inpatient) settings, serve to characterize the absorption, distribution, metabolism, and excretion of the compound; to identify overt toxicities associated with drug administration; and to establish a tolerable dose for use in further studies.

Phase II. Phase II includes the initial controlled clinical efficacy studies. These studies typically include carefully selected patients with the disease or condition under study and are usually well controlled, closely monitored, and optimized for the collection of efficacy data. In phase II, exploratory work is undertaken to help determine the optimal doses of the drug.

Phase III. After preliminary evidence suggesting the effectiveness of the drug has been established in phase II trials, additional information about effectiveness and safety is needed to evaluate the overall risk-benefit relationship of the drug and to provide an adequate basis for product labeling. Phase III studies, expanded controlled and uncontrolled trials, provide this information.

Phase IV. After the drug has been approved, subsequent postmarketing activities may be conducted in phase IV. Studies to elucidate new indications or adverse effects and risks occur in this phase.
Off-label drug use for treatment of mental disorders most frequently occurs when a patient has repeatedly failed to experience an adequate response to, or could not tolerate, standard therapies. A good example of recent off-label drug use involves utilization of drugs that are believed to act on the glutamate system. A growing body of evidence suggests that glutamate (glutamic acid), the most abundant excitatory neurotransmitter in the brain, is involved in the pathophysiology of several disorders. The most notable example, glutamate-modulating drug therapy, is the use of ketamine infusions to treat treatment-refractory depression. Another is the use of riluzole (Rilutek) in cases of severe obsessive-compulsive disorder. Other glutamatergic drugs being used outside of their FDA-approved indication include topiramate (Topamax) for weight loss, pregabalin (Lyrica) for anxiety, and memantine (Namenda) for depression. At the moment, the degree to which any of these drugs benefit a large number of patients in need of an unconventional pharmacological intervention remains to be determined. With all of these drugs, symptom severity and a history of failure of conventional pharmacotherapy typically determine whether it is decided to use these agents.

When using a drug for an unapproved indication or in a dose outside the usual range, the clinician should document the reason for these treatment decisions in the person’s chart. If a clinician is in doubt about a treatment plan, he or she should consult a colleague or suggest that the person under treatment obtain a second opinion.

PRECAUTIONS AND ADVERSE EFFECTS

Overall, psychotropic drugs are remarkably safe, especially during short-term use. Only a few drugs—such as lithium, clozapine (Clozaril), valproic acid (Depakene), and carbamazepine (Tegretol)—require close laboratory monitoring. It has also become evident that the newer antipsychotic agents require regular blood tests to monitor changes in blood glucose and lipid levels.

Precautions

Before use of a drug, it is important to be prepared to safely manage any expected adverse effects. Clinicians should be fully aware of any warnings and precautions in the product literature and should anticipate how to respond at least to the more common adverse effects listed.

Adverse Effects

Adverse effects are an unavoidable risk of medication treatment. Although it is impossible to have an encyclopedic knowledge of all possible adverse drug effects, prescribing clinicians should be familiar with the more common adverse effects as well as those with serious medical consequences. Even though the FDA requires that
product information contain the results of clinical trials, many of the listed adverse effects are not actually causally associated with use of the drug, and it is common for adverse effects to be missed during clinical trials. It is thus important for clinicians to follow reports of treatment-associated adverse events during the postmarketing period. No single text or document, including the product information, contains a complete list of possible treatment-emergent events.

It is always best to anticipate expected adverse effects, as well as rare but potentially problematic adverse effects, and to consider whether those effects will be unacceptable to the patient. For example, sexual dysfunction, weight gain, daytime sedation, sweating, nausea, and constipation may predictably cause some patients to discontinue treatment. It is thus important to discuss potential adverse effects with the patient and to determine if a problem with compliance is likely to arise. Persons generally have decreased trouble with adverse effects if they have been warned to expect them.

Drug adverse effects can largely be explained by their interactions with several neurotransmitter systems, both in the brain and in the peripheral nervous system. Older psychotherapeutic drugs, for example, commonly cause anticholinergic effects (Table 1–5) or bind to dopaminergic, histaminergic, and adrenergic receptors, resulting in the adverse effects listed in Table 1–6.

Newer agents tend to have either more specific neurotransmitter activity or combinations of effects that make them better tolerated than older agents. Nevertheless, some of the adverse effects of the newer agents remain problematic (Table 1–7), and in some cases—such as nausea, weight gain, and sexual dysfunction, all the result of serotonergic activity—these effects are more common than with the older drugs. It is usually not possible to predict which persons will not tolerate a serotonergic agent.

**Treatment of Common Adverse Effects**

Psychotherapeutic drugs may cause a wide range of adverse effects. The management of a particular adverse effect is similar, regardless of which psychotherapeutic drug the person is taking. If possible, another drug with similar benefits but
Table 1–6
Potential Adverse Effects of Psychotherapeutic Drugs and Associated Neurotransmitter Systems

<table>
<thead>
<tr>
<th>Antidopaminergic</th>
<th>Antihistaminergic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine dysfunction</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>Sedation</td>
</tr>
<tr>
<td>Menstrual dysfunction</td>
<td>Weight gain</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td>Multiple neurotransmitter systems</td>
</tr>
<tr>
<td>Movement disorders</td>
<td>Agranulocytosis (and other blood dyscrasias)</td>
</tr>
<tr>
<td>Akathisia</td>
<td>Allergic reactions</td>
</tr>
<tr>
<td>Dystonia</td>
<td>Anorexia</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>Cardiac conduction abnormalities</td>
</tr>
<tr>
<td>Tardive dyskinesia</td>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td>Antidadrenergic (primarily α)</td>
<td>Seizures</td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
</tr>
<tr>
<td>Postural hypotension</td>
<td></td>
</tr>
<tr>
<td>Reflex tachycardia</td>
<td></td>
</tr>
</tbody>
</table>

Table 1–7
Common Adverse Effects Associated with Newer Psychotropic Drugs

Movement disorders
First-generation antipsychotics (the DRAs) are the most common cause of medication-induced movement disorders. The introduction of SDAAs has greatly reduced the incidence of these adverse effects, but varying degrees of dose-related parkinsonism, akathisia, and dystonia still occur. Risperidone (Risperdal) most closely resembles the older agents in terms of these adverse effects. Olanzapine (Zyprexa) also causes more EPS than clinical trials suggested. There have been rare reports of SSRI-induced movement disorders, ranging from akathisia to tardive dyskinesia.

Sexual dysfunction
The use of psychiatric drugs may be associated with sexual dysfunction—decreased libido, impaired ejaculation and erection, and inhibition of female orgasm. In clinical trials with the SSRIs, the extent of sexual adverse effects was grossly underestimated because data were based on spontaneous reports by patients. The rate of sexual dysfunction in the original fluoxetine (Prozac) product information, for example, was <5%. In subsequent studies in which information about sexual adverse effects was elicited by specific questions, the rate of SSRI-associated sexual dysfunction was found to be between 35% and 75%. In clinical practice, patients are not likely to report sexual dysfunction spontaneously to the physician, so it is important to ask about this adverse effect. In addition, some forms of sexual dysfunction may be related to the primary psychiatric disorder. Nevertheless, if sexual dysfunction emerges after pharmacotherapy has begun and the primary response to treatment has been positive, it may be worthwhile to attempt to treat the symptoms. Long lists of possible antidotes to these adverse effects have evolved, but few interventions are consistently effective, and few have more than anecdotal evidence to support their use. The clinician and patient should consider the possibility of sexual adverse effects with a patient when selecting a drug and switching treatment to another drug that is less or not at all associated with sexual dysfunction if this adverse effect is not acceptable to the patient.

Weight gain
Weight gain accompanies the use of many psychotropic drugs as a result of retained fluid, increased caloric intake, decreased exercise, or altered metabolism. Weight gain may also occur as a symptom of disorder, as in bulimia or atypical depression, or as a sign of recovery from an episode of illness. Treatment-emergent increase in body weight is a common reason for noncompliance with a drug regimen. No specific mechanisms have been identified as causing weight gain, and it appears that the histamine and serotonin systems mediate changes in weight associated with many drugs used to treat depression and psychosis. Metformin (Glucophage) has been reported to facilitate weight loss among patients whose weight gain is attributed to use of serotonin–dopamine reuptake inhibitors and valproic acid (Depakene). Valproate and olanzapine have been linked to the development of insulin resistance, which could induce appetite increase, with subsequent weight increase.

(continued)
Weight gain is a noteworthy adverse effect of clozapine (Clozaril) and olanzapine. Genetic factors that regulate body weight, as well as the related problem of diabetes mellitus, seem to involve the 5-HT2c receptor. There is a genetic polymorphism of the promoter region of this receptor, with significantly less weight gain in patients with the variant allele than in those without this allele. Drugs with a strong 5-HT2c affinity would be expected to have a greater effect on body weight of patients with a polymorphism of the 5-HT2c receptor promoter region.

**Weight loss**

Initial weight loss is associated with SSRI treatment but is usually transient, with most weight being regained within the first few months. Bupropion (Wellbutrin) has been shown to cause modest weight loss that is sustained. When combined with diet and lifestyle changes, bupropion can facilitate more significant weight loss. Topiramate (Topamax) and zonisamide (Zonegran), marketed as treatments for epilepsy, produce sometimes substantial, sustained loss of weight.

**Glucose changes**

Increased risk of glucose abnormalities, including diabetes mellitus, is associated with weight increase during psychotropic drug therapy. Data are not conclusive, but olanzapine is associated with more frequent reports than other SDAs of abnormalities in fasting glucose levels, as well as in reported cases of hyperosmolar diabetes and ketoacidosis.

**Hyponatremia**

Hyponatremia is associated with oxcarbazepine (Trileptal) and SSRI treatment, especially in elderly patients. Confusion, agitation, and lethargy are common symptoms.

**Cognitive**

Cognitive impairment means a disturbance in the capacity to think. Some agents, such as the benzodiazepine agonists, are recognized as causes of cognitive impairment. However, other widely used psychotropics, such as the SSRIs, lamotrigine (Lamictal), gabapentin (Neurontin), lithium (Eskalith), TCAs, and bupropion, are also associated with varying degrees of memory impairment and word-finding difficulties. In contrast to the benzodiazepine-induced anterograde amnesia, these agents cause a more subtle type of absent-mindedness. Drugs with anticholinergic properties are likely to worsen memory performance.

**Sweating**

Severe perspiration unrelated to ambient temperature is associated with TCAs, SSRIs, and venlafaxine (Effexor). This adverse effect is often socially disabling. Attempts can be made to treat this adverse effect with agents, such as terazosin (Hytrin) and oxybutynin (Ditropan).

**Cardiovascular**

Newer agents are less prone to having direct cardiac effects. Many older agents, such as TCAs and phenothiazines, affected blood pressure and cardiac conduction. The drug thioridazine (Mellaril), which has been in use for decades, has been shown to prolong the QTc interval in a dose-related manner and may increase the risk of sudden death by delaying ventricular repolarization and causing torsades de pointes. Newer drugs are now routinely scrutinized for evidence of cardiac effects. A promising treatment for psychosis, sertrindole (Serlect), was not marketed because the FDA would have required a black box warning. Slight QTc effects noted with ziprasidone (Geodon) delayed the marketing of that drug. High-normal and high-dose olanzapine may cause prolongation of the PR interval and atrioventricular conduction delay. The management of specific adverse effects for individual drugs is covered in their respective chapters.

**Rash**

Any medication is a potential source of a drug rash. Some psychotropics, such as carbamazepine (Tegretol) and lamotrigine, have been linked to an increased risk of serious exfoliative dermatitis, so patients should be informed about the seriousness of widespread lesions that occur above the neck and involve the mucous membranes. If such symptoms manifest, a patient should be instructed at the time the medication is prescribed to go immediately to an emergency department and not to first attempt to contact the prescribing psychiatrist.
fewer adverse effects should be used instead. In each drug section in this text, common adverse effects and their treatments are described in detail.

**Sexual Dysfunction.** Some degree of sexual dysfunction may occur with the use of many psychotropic drugs. This is by far the most common adverse effect associated with the use of SSRIs. About 50% to 80% of persons taking an SSRI report some sexual dysfunction, such as decreased libido, impaired ejaculation and erection, or inhibition of female orgasm.

As a rule, the best approach to pharmacologic management of sexual dysfunction involves either switching from the SSRI to mirtazapine (Remeron) or bupropion (Wellbutrin), drugs that are unlikely to cause sexual dysfunction. If it is thought that use of an SSRI is indicated, adding a prosexual agent such as bupropion may be enough to reverse the sexual inhibition caused by SSRIs. The best tolerated and most potent prosexual drugs currently available are the phosphodiesterases (PDEs), such as sildenafil (Viagra).

**Anxiety, Akathisia, Agitation, and Insomnia.** Many persons initiating treatment with serotonergic antidepressants (e.g., fluoxetine) experience an increase in psychomotor activation in the first 2 to 3 weeks of use. The agitating effects of SSRIs modestly increase the risk of acting out suicidal impulses in persons at risk for suicide. During the initial period of SSRI treatment, persons at risk for self-injury should maintain close contact with the clinician or should be hospitalized, depending on the clinician’s assessment of the risk for suicide.

The insomnia and anxiety associated with use of serotonergic drugs can be countered by administration of a benzodiazepine or trazodone (Desyrel) for the first several weeks. If the agitation is extreme or persists beyond the initial 3-week period, another type of antidepressant drug, such as mirtazapine or a tricyclic agent, should be considered. Both typical and atypical antipsychotic medications are associated with movement disorders.

**Gastrointestinal Upset and Diarrhea.** Most of the body’s serotonin is in the GI tract, and serotonergic drugs, particularly sertraline (Zoloft), venlafaxine (Effexor), and fluvoxamine (Luvox), may therefore produce mildly to moderately severe stomach pain, nausea, and diarrhea, usually only for the first few weeks of therapy. Sertraline is most likely to cause loose stools, and fluvoxamine is most likely to cause nausea.

These symptoms may be minimized by initiating treatment with a very small dosage and administering the drug after eating. Dietary alteration, such as the BRAT diet (bananas, rice, apples, and toast), may reduce loose stools. These symptoms usually abate over time, but some persons never accommodate and must switch to another drug.

**Gastrointestinal Bleeding.** Drugs that inhibit the serotonin reuptake transporter, most notably the SSRIs and serotonin–norepinephrine reuptake inhibitors (SNRIs), are associated with increased tendency toward bleeding. Most commonly, this involves GI bleeding. Patients who are taking anticoagulant drugs or who use aspirin or nonsteroidal antiinflammatory drugs are most at risk and should be monitored for this adverse effect, and those agents should be used only if needed.
Headache. A small fraction of persons initiating therapy with any psychotherapeutic drug may experience mildly to moderately severe headache. These headaches often respond to over-the-counter analgesics, but it may be necessary for some persons to switch to another medication.

Anorexia. SSRIs may produce a short-term suppression of appetite. The same is true of bupropion. In patients who are already dangerously underweight, these agents should be used with caution and treatment closely monitored. Fluoxetine (60 mg per day) in the context of a comprehensive program of behavioral management is an approved treatment for bulimia and is also useful for treatment of anorexia nervosa. Unless a comprehensive therapeutic program is available, SSRIs should be used cautiously by persons with eating disorders.

Weight Gain. Most commonly used drugs cause weight gain. The mechanisms can be as diverse as fluid retention, stimulation of appetite, or alteration in metabolism. Olanzapine (Zyprexa), clozapine, and mirtazapine are associated with early, frequent, and sometimes extreme or persistent increases in body weight. SSRIs may be associated with more gradual or late-emergent weight gain that may be resistant to weight loss through diet and exercise. In these instances, some form of diet and exercise regimen should be attempted to salvage an otherwise effective treatment regimen. No drug has yet been shown to suppress the appetite safely in all persons. The most effective appetite suppressants, the amphetamines, are not used generally because of concerns about abuse. The addition of topiramate, 25 to 200 mg daily, or zonisamide (Zonegran), 50 to 150 mg daily, may help to reverse drug-induced weight gain that results from increased caloric intake.

Edema can be treated by elevating the affected body parts or by administering a diuretic. If the person adds a diuretic to a regimen of lithium or cardiac medications, the clinician must monitor blood concentrations, blood chemistries, and vital signs.

Orlistat (Xenical) does not suppress appetite; instead, it blocks absorption of fat from the intestine. Therefore, it reduces caloric intake from fatty foods but not from carbohydrates or proteins. Because orlistat causes retention of dietary fats in the intestines, it frequently causes excessive flatulence.

Somnolence. Many psychotropic drugs cause sedation. Some persons may self-medicate this adverse effect with caffeine, but this practice may worsen orthostatic hypotension.

It is important for the clinician to alert the patient to the possibility of sedation and to document that the person was advised not to drive or operate dangerous equipment if sedated by medications. Fortunately, some of newer generations of antidepressant and antipsychotic drugs are much less likely to cause sedation than were their predecessors, and the newer drugs should be substituted for the sedating medications when possible. Modafinil (Provigil) can be added to counteract residual sedative effects of psychotropic drugs.

Dry Mouth. Dry mouth is caused by the blockade of muscarinic acetylcholine receptors. When persons attempt to relieve the dry mouth by constantly sucking on sugar-containing hard candies, they increase their risk for dental cavities. They can avoid the problem by chewing sugarless gum or sucking on sugarless hard candies.

Some clinicians recommend the use of a 1% solution of pilocarpine (Salagen), a cholinergic agonist, as a mouthwash three times daily. Other clinicians suggest
bethanechol tablets, another cholinergic agonist, 10 to 30 mg once or twice daily. It is best to start with 10 mg once a day and to increase the dose slowly. Adverse effects of cholinomimetic drugs, such as bethanechol, include tremor, diarrhea, abdominal cramps, and excessive eye watering.

**Blurred Vision.** The blockage of muscarinic acetylcholine receptors causes mydriasis (pupillary dilation) and cycloplegia (ciliary muscle paresis), resulting in blurred vision. The symptom can be relieved by cholinomimetic eyedrops. A 1% solution of pilocarpine can be prescribed as one drop, four times daily. Alternatively, bethanechol can be used as it is used for dry mouth. Topiramate, an anticonvulsant often used to treat drug-induced weight gain, can cause glaucoma and subsequent blindness. Patients should be informed to immediately report any change in vision when using topiramate.

**Urinary Retention.** The anticholinergic activity of many psychotherapeutic drugs can lead to urinary hesitation, dribbling, urinary retention, and increased urinary tract infections. Elderly persons with prostatic enlargement are at increased risk for these adverse effects. Ten milligrams to 30 mg of bethanechol three to four times daily is usually effective in the treatment of the urologic adverse effects.

**Constipation.** The anticholinergic activity of psychotherapeutic drugs can cause constipation. The first line of treatment involves the prescribing of bulk laxatives, such as Citrucel, FiberCon, Konsyl, or Metamucil. If this treatment fails, cathartic laxatives, such as Milk of Magnesia, or other laxative preparations can be tried. Prolonged use of cathartic laxatives can result in a loss of their effectiveness. Bethanechol, 10 to 30 mg three to four times daily, can also be used.

**Orthostatic Hypotension.** Orthostatic hypotension is caused by the blockade of $\alpha_2$-adrenergic receptors. Elderly people are at particular risk for development of orthostatic hypotension. The risk of hip fractures from falls is significantly elevated in persons who are taking psychotherapeutic drugs.

Most simply, the person can be instructed to get up slowly and to sit down immediately if dizziness is experienced. Treatments for orthostatic hypotension include avoidance of caffeine, intake of at least 2 L of fluid per day, addition of salt to food (unless proscribed by a physician), reassessment of the dosages of any antihypertensive medications, and wearing support hose. Fludrocortisone (Florinef) is rarely needed.

### Overdose

An extreme adverse effect of drug treatment is an attempt by a person to commit suicide by overdosing on a psychotherapeutic drug. Clinicians should be aware of the risk and attempt to prescribe the safest possible drugs.

It is good clinical practice to write nonrefillable prescriptions for small quantities of drugs when suicide is a consideration. In extreme cases, an attempt should be made to verify that persons are taking the medication and not hoarding the pills for a later overdosage attempt. Persons may attempt suicide just as they are beginning to get better. Clinicians, therefore, should continue to be careful about prescribing large quantities of medication until the person has almost completely recovered, and such patients should be seen at least weekly.
Another consideration for clinicians is the possibility of an accidental overdose, particularly by children in the household. Persons should be advised to keep psychotherapeutic medications in a safe place.

**Discontinuation (Withdrawal) Syndromes**

The transient emergence of mild symptoms upon discontinuation or reduction of dosage is associated with a number of drugs, including paroxetine, venlafaxine, duloxetine (Cymbalta), sertraline, fluvoxamine, and the tricyclic and tetracyclic drugs. More severe discontinuation symptoms are associated with lithium (rebound mania), DRAs (tardive dyskinesias), and benzodiazepines (anxiety and insomnia).

Signs and symptoms of the discontinuation syndrome after SSRI use consist of agitation, nausea, dysequilibrium, and dysphoria. The syndrome is more likely to occur if the plasma half-life of the agent is brief, if the drug is taken for at least 2 months, or if higher dosages are used and if the drug is stopped abruptly. The symptoms are time limited and can be minimized by a gradual reduction of the dosage.

**DOSAGE AND CLINICAL GUIDELINES**

**Diagnosis and the Identification of Target Symptoms**

Treatment with psychotherapeutic drugs begins with formation of a therapeutic bond between the doctor and the person seeking treatment. The initial interview is devoted to defining the clinical problem as comprehensively as possible, with special attention paid to the identification of specific target symptoms whose improvement will indicate that the drug therapy is effective.

**Medication History.** Past and present medication history discusses the use of all prescription, nonprescription, herbal, and illicit drugs ever taken, including caffeine, ethanol, and nicotine; the sequence in which the drugs were used; the dosages used; the therapeutic effects; the adverse effects; details of any overdosages; and the reasons for discontinuing any drug.

Persons and their families are often ignorant about what drugs have been used before, in what dosages, and for how long. This ignorance may reflect the tendency of clinicians not to explain drug trials before writing prescriptions. Clinicians should provide written records of drug trials for each person to present to future caregivers.

A caveat to obtaining a history of drug response from persons is that because of their mental disorders, they may inaccurately report the effects of a previous drug trial. If possible, therefore, the persons’ medical records should be obtained to confirm their reports.

**Explaining Rationale, Risks, Benefits, and Treatment Alternatives**

The use of psychotropic drugs should not be oversimplified into a one diagnosis–one pill approach. Many variables impinge on a person’s psychological response to drug
treatment. Some persons may view a drug as a panacea, and other persons may view a drug as an assault. Compliance with the dosing regimen is improved by providing a person with ample opportunities to ask questions at the time of prescribing, distributing written material that reinforces proper use of the medication, streamlining the medication regimen to the extent possible, and ensuring that office visits begin at the scheduled appointment time.

Choice of Drug

**Previous Drug History.** A specific drug should be selected according to the patient’s history of drug response (compliance, therapeutic response, and adverse effects), the person’s family history of drug response, and the profile of adverse effects expected for that particular person. If a drug has previously been effective in treating a person or a family member, the same drug should be used again unless there is some specific reason not to use the drug.

**Adverse Effect Profile.** Psychotropic drugs of a single class are equally efficacious but do differ in their adverse effect profile. A drug should be selected that is least likely to exacerbate any preexisting disorders, whether medical or psychiatric, and that has probable adverse effects that are acceptable to the patient. Nevertheless, idiosyncratic reactions may occur.

Assessment of Outcome

Clinical improvements that occur during the course of drug treatment may not necessarily be related to the pharmacological effects of the drug. For example, psychological distress often improves with the simple reassurances of a medical caregiver. Many disorders remit spontaneously, so “feeling better” may be the result of coincidence rather than medication. Therefore, it is important to identify unambiguously the nature and expected time course of clinical improvements caused by the pharmacological effects of the medications.

In clinical practice, a person’s subjective impression of a beneficial drug effect is the single most consistent indicator of future response to that drug. Assessments of clinical outcome in randomized, double-blind, placebo-controlled clinical trials rely on quantitative psychiatric rating scales, such as the Brief Psychiatric Rating Scale, Positive and Negative Syndrome Scale, Montgomery-Asberg Depression Rating Scale, Hamilton Rating Scale for Depression, Hamilton Anxiety Rating Scale, or Global Assessment of Functioning Scale.

**Therapeutic Trials.** A common question a patient typically asks is, “How long do I need to take the medication?” Patients can be given a reasonable explanation of the probabilities but told that it is best to first see if the medication works for him or her and whether the adverse effects are acceptable. Any more definitive discussion of duration of treatment can be held for when the degree of success is clear. Even patients with a philosophical aversion to the use of psychotropic drugs may elect to stay on medication indefinitely if the magnitude of improvement is great.
Treatment is conceptually broken down into three phases: the initial therapeutic trial, the continuation, and the maintenance phase. The initial period of treatment should last at least 4 to 6 weeks because of the delay in therapeutic effects that characterizes most classes of psychotropic drugs. The required duration of a “therapeutic trial” of a drug should be discussed at the outset of treatment so the patient does not have unrealistic expectations of an immediate improvement in symptoms. Unfortunately, patients are more likely to experience adverse effects in the course of pharmacotherapy earlier than any relief from their disorder. In some cases, medication may even exacerbate some symptoms. Patients should be counseled that a poor initial reaction to medication is not an indicator of the ultimate outcome of treatment. For instance, many patients with panic disorder develop jitteriness or an increase in panic attacks after starting on tricyclic or SSRI treatment. Benzodiazepine agonists are an exception to the rule that there is a delay in clinical onset. In most cases, their hypnotic and antianxiety effects are evident immediately.

Ongoing use of medication does not provide absolute protection against relapse. However, continuation therapy may provide significant protective effects against relapse.

**Possible Reasons for Therapeutic Failures**

The failure of a specific drug trial should prompt the clinician to consider a number of possibilities.

First, was the original diagnosis correct? This consideration should include the possibility of an undiagnosed coexisting disorder or illicit drug or alcohol abuse.

Second, did the person take the drug as directed?

Third, was the drug administered in sufficient dosage for an appropriate period of time? Persons can have varying drug absorption and metabolic rates for the same drug, and, if available, plasma drug concentrations should be obtained to assess this variable.

Fourth, did the drug’s adverse effects produce signs and symptoms unrelated to the original disease? If so, did these effects counteract any therapeutic response? Antipsychotic drugs, for example, can produce akinesia, which resembles psychotic withdrawal; akathisia and neuroleptic malignant syndrome resemble increased psychotic agitation. SSRIs can produce fatigue, insomnia, and emotional blunting, symptoms that resemble manifestations of depression.

Fifth, did a pharmacokinetic or pharmacodynamic interaction with another drug the person was taking reduce the efficacy of the psychotherapeutic drug?

Regardless of optimal drug selection and use, some patients fail to respond to repeated trials of medication.

Poorly understood is the phenomenon of drug “poop out,” in which patients who have been taking a drug for long periods of time, with good effect, suddenly have a return of symptoms. A number of possibilities have been suggested as causing loss of therapeutic effect. These include:

- Pharmacodynamic or pharmacokinetic tolerance (tachyphylaxis)
- Side effects (apathy, anhedonia, emotional blunting)
• Onset of a comorbid medical disorder
• Increase in disease severity or change in disease pathogenesis (progression)
• Depletion of effector substance (neurotransmitter?)
• Serum drug levels that have drifted below or above that drug’s therapeutic window
• Accumulation of detrimental metabolites
• Initial misdiagnosis
• Loss of placebo response
• Lack of bioequivalence when compared to a generic version.

Strategies for Increasing Efficacy

The most fruitful initial strategy for increasing the efficacy of a psychotherapeutic drug is to review whether the drug is being taken correctly. A fresh clinical evaluation of the psychiatric symptoms and the rationale of the drug therapy is one of the psychopharmacologist’s most valuable tools for revealing previously unappreciated impediments to drug efficacy.

Adding a drug with another indication is termed augmentation. Augmentation often entails use of a drug that is not primarily considered a psychotropic. For example, in treating depression, it is common to add thyroid hormone to an approved antidepressant. In a typical scenario, a patient has little or no response to a medication, so the physician adds a second agent to induce a better response. In some cases, the use of multiple medications is the rule. Almost all patients with bipolar disorder take more than one psychotropic agent. Combination treatment with drugs that treat depression has long been held as preferable in patients with psychotic depression. Similarly, SSRIs typically produce partial improvement in patients with obsessive-compulsive disorder (OCD), so the addition of an SDA may be helpful.

In addition, drugs may be combined to counteract side effects, to treat specific symptoms, and as a temporary measure to transition from one drug to another. It is common practice to add a new agent without the discontinuation of a prior drug, particularly when the first drug has provided partial benefit. This can be done as part of a plan to transition from an agent that is not producing a satisfactory response or as an attempt to maintain the patient on combined therapy.

One limitation of augmentation is increased noncompliance and adverse effects, and the clinician may not be able to determine whether it was the second drug alone or the combination of drugs that resulted in a therapeutic success or a particular adverse effect. Combining drugs can create a broad-spectrum effect and change the ratio of metabolites.

The merits of going to a single drug with a different pharmacological profile include a lower risk of drug–drug interactions, simplicity, and lower cost. It is less burdensome to take one medication than two or three and is less likely to meet resistance from the patient. Many patients are ambivalent about taking even one medication, let alone two.
COMBINED PSYCHOTHERAPY AND PHARMACOTHERAPY

Many patients are best treated with a combination of medication and psychotherapy. In many cases, the results of combined therapy are superior to those of either type of therapy alone. For example, pharmacotherapy alleviates the depression that often interferes with the introspection and focus that are needed for psychotherapy. Conversely, patients who are engaged in ongoing therapy are more likely to continue taking medication.

Duration of Treatment

Use of the Correct Dosage. Subtherapeutic dosages and incomplete trials should not be prescribed solely to assuage the clinician’s anxiety about the development of adverse effects. The prescription of drugs for mental disorders must be made by a knowledgeable practitioner and requires continuous clinical observation. Treatment response and the emergence of adverse effects must be monitored closely. The dosage of the drug must be adjusted accordingly, and appropriate treatments for emergent adverse effects must be instituted as quickly as possible.

Long-Term Maintenance Therapy. Persons with mood, anxiety, and schizophrenic disorders live with an increased risk for relapse into illness at virtually any phase of their lives. Although some patients discontinue treatment because drugs are ineffective or poorly tolerated, many patients stop their medication because they are feeling well. This might be the result of effective treatment or simply naturally occurring remission. Clinicians should anticipate and alert persons to the natural variations of psychiatric illnesses. For example, a person who has taken medication to treat an acute psychotic episode may soon thereafter experience a relatively symptom-free period and may then impulsively discontinue taking the medication without informing his or her physician.

Long-term data show that persons who stop their medications after resolution of an acute episode of mental illness markedly increase their risk of relapse during the subsequent year compared with persons who remain on maintenance drug therapy. The fact is, most psychiatric disorders are chronic or recurrent. With disorders such as bipolar disorder, schizophrenia, or depression associated with suicide attempts, the consequences of relapse can be severe.

Treating clinicians are obliged to provide continuous educational review and reinforcement of the importance of taking medication. By comparing psychiatric illnesses with common chronic medical conditions, such as hypertension and diabetes mellitus, clinicians can help patients to understand that psychotropic drugs do not cure the disorders but rather keep their manifestations from causing distress or disability.

Special Populations

Children. Other than attention-deficit/hyperactivity disorder (ADHD) and OCD, commonly used psychotropic drugs have no labeling for pediatric use. When
drugs are used to treat children and adolescents, results are extrapolated from adult studies. This should be done with caution. For example, the smaller volume of distribution suggests the use of lower dosages than in adults, but children’s higher rate of metabolism indicates that higher ratios of milligrams of drug to kilograms of body weight might be required.

In practice, it is best to begin with a small dose and to increase it until clinical effects are observed. However, the clinician may use adult doses in children if they are effective and the adverse effects are acceptable.

**Geriatric Patients.** Cardiac rhythm disturbances, hypotension, cognitive disturbances, and falls are major concerns when treating geriatric persons. Elderly people may also metabolize drugs slowly (Table 1–8) and thus require low doses of medication. Another concern is that geriatric persons often take other medications, thereby requiring clinicians to consider the possible drug interactions.

In practice, clinicians should begin treating geriatric persons with low doses, usually about one-half the usual dose. The dose should be raised in small amounts, more slowly than for middle-aged adults, until either a clinical benefit is achieved or unacceptable adverse effects appear. Although many geriatric persons require low doses of medication, many others require the usual adult dose.

**Pregnant and Nursing Women.** Physicians who are considering the use of psychotropic drugs during pregnancy should weigh known risks or the lack of available information against the risks of nontreatment (Table 1–9). The basic rule is to avoid administering any drug to a woman who is pregnant (particularly during the first trimester) or who is breastfeeding a child, unless the mother’s mental disorder is severe.

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<th>Phase</th>
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<tbody>
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<td>Gastric pH increases</td>
<td>Absorption is slowed but just as complete</td>
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<td></td>
<td>Decreased surface villi</td>
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<td></td>
<td>delayed gastric emptying</td>
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<tr>
<td></td>
<td>Intestinal perfusion decreases</td>
<td></td>
</tr>
<tr>
<td>Distribution</td>
<td>Total body water and lean body mass</td>
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<tr>
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<td>mass decrease</td>
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</tr>
<tr>
<td></td>
<td>Increased total body fat, more</td>
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<tr>
<td>Metabolism</td>
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<td></td>
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<tr>
<td></td>
<td>α acid glycoprotein unchanged</td>
<td>The free or unbound percentage of albumin-bound drugs</td>
</tr>
<tr>
<td></td>
<td>Renal: renal blood flow and</td>
<td>increases</td>
</tr>
<tr>
<td></td>
<td>glomerular filtration rates decrease</td>
<td>Decreased metabolism leads to prolonged half-lives, if Vd remains the same</td>
</tr>
<tr>
<td></td>
<td>Hepatic: decreased enzyme activity and</td>
<td></td>
</tr>
<tr>
<td></td>
<td>perfusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total body weight decreases</td>
<td>Think on a mg/kg basis</td>
</tr>
<tr>
<td></td>
<td>Receptor sensitivity May increase</td>
<td>Increased effect</td>
</tr>
</tbody>
</table>

Vd: volume of distribution.

If a drug associated with the risk of birth defects needs to be used during pregnancy, the risks and benefits of the treatment, as well as therapeutic abortion, should be discussed. The most teratogenic psychotropic drugs are valproate (Depakote, Depakene); carbamazepine; and, to a lesser degree, lithium. Valproate exposure is associated with significant risk of spina bifida and midline craniofacial abnormalities, and carbamazepine exposure causes similar midline defects. Prophylactic folic acid supplementation may reduce the risk of spina bifida. Lithium exposure during pregnancy is associated with a small risk of Ebstein’s anomaly, a serious abnormality in cardiac development.

The administration of psychotherapeutic drugs at or near delivery may cause neonatal sedation and respiratory depression, possibly requiring mechanical ventilatory support, or physical dependence on the drug, requiring detoxification and the treatment of a withdrawal syndrome.

Virtually all psychotropic drugs are secreted in the milk of nursing mothers. Persons with hepatic or renal Insufficiency. Persons with hepatocellular insufficiency of any cause, including cirrhosis, hepatitis, metabolic disorders, and bile duct obstruction, are at risk of accumulating elevated concentrations of hepatically metabolized drugs. Drugs that are excreted by the kidneys may accumulate to toxic concentrations in persons with renal insufficiency of any cause, including atherosclerosis, nephrosis, nephritis, infiltrative disorders, and outflow obstruction. The presence of hepatocellular or renal insufficiency requires administration of a reduced dosage, usually half of the recommended dosage for healthy persons. Clinicians should be particularly alert to signs and symptoms of adverse drug effects in persons with hepatic or renal disorders. If available, monitoring of plasma drug concentrations may help guide dosage adjustments.

Persons with Other Medical Illnesses. Medical disorders should be ruled out as the cause of psychiatric symptoms. Considerations in the use of psychotropic drugs in medically ill persons include a potentially increased sensitivity to the drug’s adverse effects, either increased or decreased metabolism and excretion of the drug, and interactions with other medications. As with children and geriatric persons, the most reasonable clinical practice is to begin with a low dose, increase it slowly, and

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**Table 1–9**

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).</td>
</tr>
<tr>
<td>B</td>
<td>Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.</td>
</tr>
<tr>
<td>C</td>
<td>Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.</td>
</tr>
<tr>
<td>D</td>
<td>There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.</td>
</tr>
<tr>
<td>X</td>
<td>Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.</td>
</tr>
</tbody>
</table>
watch for both clinical and adverse effects. Special caution is needed with potential
drug–disease interactions. Patients with diabetes, for example, should not be treated
with drugs such as mirtazapine or olanzapine, which risk causing weight gain, or
drugs such as olanzapine or valproate, which cause insulin resistance. Patients with
seizure disorders should not receive bupropion, maprotiline (Ludiomil), or clomi-
pramine (Anafranil), which lower the seizure threshold.

**Laboratory Monitoring**

For most commonly used psychotropic drugs, routine testing is not required. How-
ever, serious complications of treatment with certain drugs can be prevented through
laboratory monitoring of either plasma drug concentrations or laboratory indicators
of organ dysfunction. Apart from drugs that require monitoring, laboratory testing
and therapeutic blood monitoring should be based on clinical circumstances. Lith-
ium and clozapine treatment require ongoing monitoring. Given the increased use
of antidepressant and atypical antipsychotic drugs in combination it is prudent to
obtain baseline and follow-up electrocardiography EKG studies. Further informa-
tion on monitoring is found in the chapter in which each drug is discussed.