

CHAPTER 7

PHARMACOLOGICAL PRINCIPLES

Psychopharmacology, one of the most active and developing areas of psychiatric research, is the use of psychotropic medication to treat psychiatric disorders. *Psychiatric-mental health nurse practitioners* (PMHNPs) must have a thorough understanding of the science and art of prescribing—of the pharmacokinetic and pharmacodynamic actions of a given drug, as well as the client's motivation to take the drug. The basic pharmacological principles are discussed in this chapter.

CONCEPTS IN PHARMACOLOGICAL MANAGEMENT

- ▶ *Pharmacology*: Study of what drugs do and how they do it
- ▶ *Pharmacokinetics*: Study of what the body does to drugs; includes absorption, distribution, metabolism, and excretion
- ▶ *Pharmacodynamics*: Study of what drugs do to the body; target sites for drug actions include receptors, ion channels, enzymes, and carrier proteins

Pharmacokinetics

- ▶ *Absorption*: Method and rate at which drugs leave the site of administration
 - ▷ With oral medications, absorption normally occurs in the small intestine and then in the liver.
- ▶ *Distribution*: Occurs after the drug leaves the systemic circulation and enters the interstitium and cells
 - ▷ Drugs are redistributed in organs according to their fat and protein content.
 - ▷ Most psychotropic medications are lipophilic and highly protein-bound. Only the unbound (free) portion of the drug is active. Therefore, people with low protein (albumin) levels, such as in malnutrition, wasting, or aging, can potentially experience toxicity (see below) from an increased amount of free drug. People with high fat-to-lean body mass ratio (as in older adults) will have erratic amounts of active drug in their system.

- ▶ *Metabolism*: Process by which the drug becomes chemically altered in the body
- ▶ *First-pass metabolism*: Process by which the drug is metabolized by cytochrome P450 (P450) enzymes in the intestines and liver prior to going to the systemic circulation
- ▶ *Elimination*: Process by which the drug is removed from the body
- ▶ *Half-life ($T_{1/2}$)*: Time needed to clear 50% of the drug from the plasma
 - ▷ The half-life also determines the dosing interval and the length of time to reach a steady state.
- ▶ *Steady state*: Point at which the amount of drug eliminated between doses is approximately equal to the dose administered.
 - ▷ Drugs usually are administered once every half-life to achieve a steady state.
 - ▷ It takes approximately five half-lives to achieve a steady state and five half-lives to completely eliminate a drug.
- ▶ Alterations in pharmacokinetics
 - ▷ Hepatic cytochrome P450 enzyme interactions can induce or inhibit the metabolism of certain drugs, thus changing their desired concentration levels (see Table 7–1).
 - ▷ Approximately 10% of Caucasians are poor metabolizers of the P450 2D6 enzyme.
 - ▷ Approximately 20% of Asians may have reduced activity of the P450 2C19 enzyme.
 - ▷ First-pass metabolism activity of P450 enzymes 2C9, 2C19, 2D6, and 3A4 in young children may exceed rates of adolescents and adults and give rise to underexposure to certain medications. Conversely, the ontogeny of the 1A2 pathway is delayed, possibly leading to toxic effects from drugs that are substrates of this pathway (e.g., some antipsychotics).
 - ▷ Enzyme inducers can decrease the serum level of other drugs that are substrates of that enzyme, thus possibly causing subtherapeutic drug levels.

TABLE 7–1.
CYTOCHROME P450 INHIBITORS AND INDUCERS

INHIBITORS	INDUCERS
Bupropion	Carbamazepine
Clomipramine	Hypericum (St. John's Wort)
Cimetidine	Phenytoin
Clarithromycin	Phenobarbital
Fluoroquinolones	Tobacco
Grapefruit and grapefruit juice	
Ketoconazole	
Nefazodone	
SSRIs	

- ▷ Enzyme inhibitors can increase the serum level of other drugs that are substrates of that enzyme, thus possibly causing toxic levels.
- ▷ Liver disease will affect liver enzyme activity and first-pass metabolism, possibly resulting in toxic plasma drug levels.
- ▷ Kidney disease or drugs that reduce renal clearance, such as nonsteroidal anti-inflammatory drugs (NSAIDs), may increase serum concentration of drugs that are excreted by the kidneys (such as lithium). Older adults are more sensitive to psychotropics because of their decreased intracellular water, protein binding, low muscle mass, decreased metabolism, and increased body fat concentration.
 - ▶ Most psychotropics are lipophilic and highly protein-bound. Thus, because older adults have more body fat and less protein, they are more likely to develop toxicity due to accumulation and erratic blood levels of drug.

Pharmacodynamics

- ▶ Target sites for drug actions include receptors. Several types of pharmacodynamics involve receptors:
 - ▷ *Agonist effect*: Drug binds to receptors and activates a biological response
 - ▷ *Inverse agonist effect*: Drug causes the opposite effect of agonist; does not bind to receptor
 - ▷ *Partial agonist effect*: Drug does not fully activate the receptors
 - ▷ *Antagonist effect*: Drug binds to the receptor but does not activate a biological response
- ▶ Another site for drug actions is ion channels, which exist for many ions such as sodium, potassium, chloride, and calcium and can be open at some times and closed at other times. Neurotransmitters or drugs may be excitatory or inhibitory depending on the type of ion channel they gate.
 - ▷ *Excitatory response*: Depolarization; involves the opening of sodium and calcium channels so these ions go into the cell
 - ▷ *Inhibitory response*: Repolarization; involves the opening of chloride channels so chloride goes into the cell, potassium leaves, or both
- ▶ Another site for drug actions are enzymes, which are important for drug metabolism and play an important role in the chemical alteration of the drug. Some drugs (e.g., monoamine oxidase inhibitors [MAOIs]) inhibit the action of a particular enzyme, thus increasing the availability of the neurotransmitter.
- ▶ Another site for drug actions is carrier proteins or reuptake pumps, which transport neurotransmitters out of the synapse and back into the presynaptic neuron to be recycled or reused. Some drugs, such as selective serotonin reuptake inhibitors (SSRIs), will inhibit reuptake pumps, thus increasing the synaptic availability of the neurotransmitter.

Other Terminology

- ▶ *Potency*: Relative dose required to achieve certain effects

- ▶ *Therapeutic index*: Relative measure of the toxicity or safety of a drug; ratio of the median toxic dose to the median effective dose
 - ▷ Drugs with a high therapeutic index (e.g., divalproex, 50–125 mcg/ml) have a high margin of safety; that is, the therapeutic dose and the toxic dose are far apart.
 - ▷ Drugs with a low therapeutic index (e.g., lithium, 0.5–1.2 mEQ/L) have a low margin of safety; that is, the therapeutic dose and the toxic dose are close together.
- ▶ *Tolerance*: The process of becoming less responsive to a particular drug over time
- ▶ *Tachyphylaxis*: An acute decrease in the therapeutic response

PMHNP PHARMACOLOGICAL MANAGEMENT ROLE

- ▶ Pharmacological management process:
 - ▷ Make a diagnosis and identify the target symptoms.
 - ▷ Consider the phase of illness (such as acute, relapse, recurrence).
 - ▷ Assess prior personal and family history of response to certain medications.
 - ▷ Assess the client's motivation for and any misgivings about treatment.
 - ▷ Identify potential interactions between the currently prescribed medications.
 - ▷ Identify cultural implications of certain drugs.
 - ▷ Discuss the risks and benefits of the treatment.
 - ▷ Document informed consent and the client's understanding of target symptoms, benefits, risks, and alternatives to treatment.
 - ▷ Monitor response and side effects.
- ▶ Follow-up and role of the PMHNP
 - ▷ Use of standards of care:
 - ▶ Assist in determining length of treatment.
 - ▶ Do relapse planning.
 - ▷ It is helpful and advised to use standardized clinical rating scales to establish the client's baseline and to monitor progress or decompensation over time. Screening tests also will aid in making a diagnosis and ruling out other disorders. (See corresponding chapters for a list of relevant screening tools.)
 - ▷ It is important to recognize the large body of evidence-based data supporting the combined use of pharmacological and nonpharmacological treatments as offering psychiatric clients the best possibility for significant clinical improvement.
 - ▷ Nonadherence is a common problem with all chronic illness, including psychiatric disorders, and should be a continuous focus of concern for the PMHNP.

- ▷ Common medications used in the clinical management of psychiatric disorders and usually prescribed by the PMHNP are identified in Table 7–2. See corresponding chapters for specific information on each medication.
- ▷ A Drug Enforcement Administration (DEA) number is required for prescription of controlled substances.
 - ▶ Schedule of controlled substances
 - ▷ Schedule I
 - ▶ Nonmedicinal substances

TABLE 7–2.
MEDICATIONS COMMONLY USED IN THE CLINICAL MANAGEMENT OF PSYCHIATRIC DISORDERS

MEDICATIONS USED TO TREAT SCHIZOPHRENIA AND OTHER PSYCHOTIC DISORDERS	
Typical Antipsychotics	Haloperidol (Haldol), haloperidol decanoate (Haldol Decanoate)
	Loxapine (Loxitane)
	Thioridazine (Mellaril)
	Thiothixene (Navane)
	Fluphenazine (Prolixin), fluphenazine decanoate (Prolixin Decanoate)
	Mesoridazine (Serentil)
	Trifluoperazine (Stelazine)
	Chlorpromazine (Thorazine)
	Perphenazine (Trilafon)
Second-Generation Antipsychotics	Clozapine (Clozaril)
	Ziprasidone (Geodon)
	Risperidone (Risperdal)
	Quetiapine (Seroquel)
	Olanzapine (Zyprexa)
	Aripiprazole (Abilify)
	Paliperidone (Invega)
	Iloperidone (Fanapt)
	Asenapine (Saphris)
Lurasidone (Latuda)	
MEDICATIONS USED TO TREAT MOOD DISORDERS AND BIPOLAR AFFECTIVE DISORDERS	
Mood Stabilizers	Valproic acid (Depakene)
	Divalproex sodium (Depakote)
	Lithium carbonate (Eskalith, Lithobid, Lithonate, Lithotabs)
	Lamotrigine (Lamictal)
	Carbamazepine (Tegretol)
	Carbamazepine ER (Equetro)
	Oxcarbazepine (Trileptal; off-label)

CONTINUED

MEDICATIONS USED TO TREAT MOOD DISORDERS, UNIPOLAR AFFECTIVE DISORDERS, AND DEPRESSIVE DISORDERS

Tricyclics (TCAs)	Clomipramine (Anafranil)
	Amoxapine (Asendin)
	Amitriptyline (Elavil)
	Desipramine (Norpramin)
	Nortriptyline (Pamelor)
	Doxepin (Sinequan)
	Trimipramine (Surmontil)
	Imipramine (Tofranil)
	Protriptyline (Vivactil)
Serotonin Selective Reuptake Inhibitors (SSRIs)	Citalopram (Celexa)
	Fluvoxamine (Luvox)
	Paroxetine (Paxil)
	Paroxetine mesylate (Pexeva)
	Fluoxetine (Prozac)
	Sertraline (Zoloft)
Monoamine Oxidase Inhibitors (MAOIs)	Escitalopram (Lexapro)
	Phenelzine (Nardil)
	Tranylcypromine sulfate (Parnate)
SNRIs and Other Agents	Selegiline transdermal (EMSAM)
	Trazodone (Desyrel)
	Venlafaxine (Effexor)
	Desvenlafaxine (Pristiq)
	Mirtazapine (Remeron)
	Nefazodone (Serzone)
	Bupropion (Wellbutrin, Forfivo, Aplenzin)
	Duloxetine (Cymbalta)
	Vilazodone (Viibryd)
	Vortioxetine (Brintellix)
Levomilnacipran (Fetzima)	

MEDICATIONS USED TO TREAT ANXIETY DISORDERS

Benzodiazepines (BNZs)	Lorazepam (Ativan)
	Clonazepam (Klonopin)
	Chlordiazepoxide (Librium)
	Oxazepam (Serax)
	Clorazepate (Tranxene)
	Alprazolam (Xanax)
Anxiolytics	Buspirone (BuSpar)
Other Agents	Propranolol (Inderal)
	Atenolol (Tenormin)

MEDICATIONS USED TO TREAT ATTENTION DEFICIT DISORDER AND ATTENTION DEFICIT HYPERACTIVITY DISORDER

Stimulants	Amphetamine/dextroamphetamine (Adderall)
	Dexmethylphenidate (Focalin)
	Dextroamphetamine (Dexedrine)
	Methylphenidate (Ritalin)
	Methylphenidate (Concerta)
	Lisdexamfetamine dimesylate (Vyvanse)
Other Agents	Guanfacine (Intuniv)
	Clonidine (Kapvay)
	Atomoxetine (Strattera)
	Antidepressants such as desipramine (Norpramin), venlafaxine (Effexor), and bupropion (Wellbutrin) are also used in the clinical management of ADHD.

- ▶ High abuse potential
- ▶ Used for research purposes only
- ▶ Not legally available by prescription
- ▶ Examples include heroin and marijuana
- ▷ Schedule II
 - ▶ Medicinal drugs in current use
 - ▶ High potential for abuse and dependency
 - ▶ Written prescription only
 - ▶ No telephone orders allowed
 - ▶ No refills allowed on prescription
 - ▶ Examples include morphine sulfate, codeine, fentanyl, methadone, hydromorphone (Dilaudid), oxycodone (OxyContin, Percocet), hydrocodone (Vicodin and others), amphetamine salts, methylphenidate
- ▷ Schedule III
 - ▶ Medicinal drugs with less abuse potential than Schedule II drugs
 - ▶ Still greater potential for abuse than Schedule IV drugs
 - ▶ Telephone orders if followed by written prescription
 - ▶ Prescription must be renewed every 6 months
 - ▶ Refills limited to five
 - ▶ Examples include appetite suppressants, butalbital, testosterone, buprenorphine/naloxone
- ▷ Schedule IV
 - ▶ Medicinal drugs with less abuse potential than Schedule III drugs

- ▶ Examples include dextropropoxyphene (Darvon), pentazocine (Talwin), benzodiazepines (such as alprazolam [Xanax], chlordiazepoxide [Librium], clonazepam [Klonopin], diazepam [Valium], clorazepate [Tranxene], and lorazepam [Ativan]), modafinil (Provigil), phenobarbital, zolpidem (Ambien), eszopiclone (Lunesta), temazepam (Restoril), armodafinil (Nuvigil)
- ▷ Schedule V
 - ▶ Medicinal drugs with the lowest abuse potential
 - ▶ Handled in manner similar to noncontrolled drugs
 - ▶ Examples include buprenorphine (Buprenex), cheratussin (Robitussin) with codeine, promethazine (Phenergan) with codeine, diphenoxylate/atropine (Lomotil)

Other Pharmacological Considerations

- ▶ It is vital to be aware of the teratogenic nature of many psychotropic agents. It is important to discuss the risks versus the benefits of medications during pregnancy.
 - ▷ Possible risks of psychotropic medications during pregnancy include:
 - ▶ Problems with appetite
 - ▶ Transient agitation or sedation
 - ▶ Premature labor
 - ▶ Drug discontinuation symptoms
 - ▶ Teratogenic effects of certain psychotropics
 - ▷ Possible risks of not taking psychotropic medications during pregnancy include
 - ▶ Recurrence of symptoms
 - ▶ Adverse effects on mother–infant bonding
 - ▶ Poor maternal self-care
- ▶ Federal Drug Administration (FDA) pregnancy ratings for medications
 - ▷ **A:** Controlled studies show no risk
 - ▷ **B:** No evidence of risk in humans
 - ▷ **C:** Risk cannot be ruled out
 - ▷ **D:** Positive evidence of risk
 - ▷ **X:** Absolutely contraindicated in pregnancy
- ▶ Teratogenic risks of common psychiatric medications
 - ▷ Benzodiazepines: Floppy baby syndrome, cleft palate
 - ▷ Carbamazepine (Tegretol): Neural tube defects
 - ▷ Lithium (Eskalith): Epstein anomaly
 - ▷ Divalproex sodium (Depakote): Neural tube defects, specifically spina bifida, atrial septal defect, cleft palate, and possible long-term developmental deficits

- ▶ Some common medications can induce depression or mania (see Table 7–3).
- ▶ Remember that some medications can *possibly* cause a false urinary drug screen result (see Table 7–4).

TABLE 7–3.
MEDICATIONS THAT INDUCE DEPRESSION OR MANIA

MEDICATIONS THAT INDUCE DEPRESSION	MEDICATIONS THAT INDUCE MANIA
<ul style="list-style-type: none"> • Beta blockers • Steroids • Interferon • Isotretinoin (Accutane) • Some retroviral drugs • Antineoplastic drugs • Benzodiazepines • Progesterone 	<ul style="list-style-type: none"> • Steroids • Disulfiram (Antabuse) • Isoniazid (INH) • Antidepressants in persons with bipolar disorder

TABLE 7–4.
MEDICATIONS THAT CAN CAUSE DRUG SCREEN FALSE POSITIVE RESULTS

FALSE POSITIVE FOR	DRUG RESPONSIBLE
Amphetamines	<ul style="list-style-type: none"> • Stimulants (i.e., amphetamine/dextroamphetamine [Adderall], methylphenidate [Ritalin]) • Bupropion (Wellbutrin) • Fluoxetine (Prozac) • Trazodone • Ranitidine • Nefazodone (Serzone) • Nasal decongestants • Pseudoephedrine
Alcohol	<ul style="list-style-type: none"> • Valium
Benzodiazepines	<ul style="list-style-type: none"> • Sertraline (Zoloft)
Cocaine	<ul style="list-style-type: none"> • Amoxicillin • Most antibiotics • NSAIDs
Heroin or morphine	<ul style="list-style-type: none"> • Quinolones • Rifampin • Codeine • Poppy seeds
Methadone or PCP	<ul style="list-style-type: none"> • Over-the-counter cough medicine (such as Nyquil) Dextromethorphan

CASE STUDY 1

Ms. J., a 74-year-old client whom the PHMNP has been seeing for depression, presented at her appointment with complaints of tremors, diaphoresis, headache, and nausea over the past week. She is currently being prescribed amitriptyline (50 mg q.h.s.), which was increased at her last visit, and sertraline (100 mg q.d.). She denies depression but admits to increased confusion and memory problems.

1. What is the biggest pharmacological concern with the combination of medication the client is being prescribed?
2. What would be the PHMNP's plan of action?
3. What pharmacokinetics should the PHMNP keep in mind when treating older adults?

CASE STUDY 2

Ms. M. is a 30-year-old married Chinese woman who is in the midst of a first major depressive episode. Ms. M. is employed as a grade school teacher but is currently on summer break. Despite participating in 6 months of cognitive behavioral therapy with an experienced therapist, her symptoms have not improved. Ms. M describes feeling sad and cries easily. She feels anxious and has trouble shutting her thoughts off, particularly when trying to fall asleep at night. She feels tired upon awakening, despite getting 7 to 8 hours of sleep, and she has trouble getting out of bed. Her energy remains low throughout the day. She notes a worsening in her motivation as well. Her weight and appetite are unchanged. She denies suicidal ideation. After careful evaluation, the PMHNP suggests a trial of fluoxetine and prescribes 20 mg p.o. q.a.m. with food.

Ms. M. calls the PMHNP before her scheduled follow-up appointment, requesting to come in sooner because she feels "worse." She describes more difficulty falling asleep, feels "revved up" much of the time, and is having mild nausea and headaches.

1. What are possible reasons for Ms. M. feeling "worse"?
2. What should the PMHNP suggest as the next intervention for Ms. M.?

CASE STUDY 3

Ms. S. is a 22-year-old woman who presents to the PMHNP with signs and symptoms of major depression. Ms. S. has a strong family history of major depression and both her mother and older sister have been treated with an antidepressant. Ms. S. herself has never been treated for depression before, and she says she is nervous about taking medication because she "gets side effects from everything."

1. How should the PMHNP respond to Ms. S.'s concerns about taking medication?
2. How should the PMHNP begin to think about medication management for Ms. S.?

Ms. S. is started on sertraline 50 mg. She calls within a few days of starting the drug and says that she is experiencing an upset stomach, headache, difficulty sleeping, and an overall feeling of being "edgy."

3. What is the most likely reason for Ms. S.'s reported side effects?
4. What is the most reasonable intervention by the PMHNP?
5. Other than potential side effects, what information should the PMHNP include in client teaching when starting a person on a new medication?

ANSWERS TO CASE STUDY DISCUSSION QUESTIONS

Case Study 1

1. The SSRI is potentially increasing the concentration of the TCA to toxic levels.
2. Check the blood level of amitriptyline and decrease the dose; consider tapering Ms. J. off the TCA.
3. Higher body fat content, decreased gastric acid secretion, and decreased hepatic and renal functioning all predispose an older adult to the potential toxic effects of medications. Anticholinergic effects and orthostasis are particularly common and problematic.

Case Study 2

1. Fluoxetine may cause uncomfortable activation in some clients. In addition, Ms. M. appears to be having multiple side effects. Fluoxetine is metabolized primarily by cytochrome P450 2D6. People who are deficient in 2D6 are considered “slow metabolizers,” and may need significantly lower doses of medications that are substrates of 2D6. Finally, all clients started on antidepressants must be monitored closely for a switch from depression to hypomania or mixed mania. While Ms. M.’s increase in insomnia and feeling “revved up” and “worse” are likely side effects from fluoxetine, this could signal beginning symptoms of a shift into a bipolar spectrum mood state.
2. Unless agitation is prominent, the first prudent intervention would be to lower the dose of the fluoxetine. If this is not helpful in diminishing side effects, prescribing a low dose of lorazepam or other benzodiazepine used as a “bridge” medication until the SSRI is effective may be prudent. If neither of these interventions proves helpful, the medication should be changed.

Case Study 3

1. The PMHNP should ask Ms. S. to tell her more about being anxious about taking medicine, and ask about the medications her immediate family members are taking, whether or not the family members have had problems with side effects, and finally, whether any medication has been particularly helpful to her family members.
2. A genetic polymorphism screening test to determine gene variants may be reasonable. Because mood and anxiety disorders have a genetic component, beginning with a medication that has been beneficial in the treatment of similar symptoms in a first-degree relative is a reasonable starting point of treatment.
3. The sertraline was started at too high a dose.
4. Lower the dose to 25 mg. Make sure Ms. S. is taking the medication with food. If not already doing so, switch the time of dosing to after breakfast.
5. During client teaching, the PMHNP should cover the usual course of treatment: typical time until benefit, typical therapeutic dosing, and expected length of treatment. The PMHNP should also emphasize that most side effects are transient and can usually be managed, such as by adjusting the dose.

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