3 Concepts of Psychobiology

CORE CONCEPTS

Genetics

Neuroendocrinology

Psychobiology

Psychoneuroimmunology

Psychopharmacology

CHAPTER OUTLINE

Objectives
Homework Assignment
The Nervous System: An Anatomical Review
Neuroendocrinology
Genetics
Psychoneuroimmunology
Psychopharmacology and the Brain
Implications for Nursing
Summary and Key Points
Review Questions

KEY TERMS

axon
cell body
circadian rhythms
dendrites
genotype
limbic system
neuron
neurotransmitter
phenotype
receptor sites
synapse

OBJECTIVES

After reading this chapter, the student will be able to:

1. Identify gross anatomical structures of the brain and describe their functions.
2. Discuss the physiology of neurotransmission in the central nervous system.
3. Describe the role of neurotransmitters in human behavior.
4. Discuss the association of endocrine functioning to the development of psychiatric disorders.
5. Describe the role of genetics in the development of psychiatric disorders.
6. Discuss the correlation of altered brain function to various psychiatric disorders.
7. Identify diagnostic procedures used to detect alteration in biological functioning that may contribute to psychiatric disorders.
8. Discuss the influence of psychological factors on the immune system.
9. Describe the biological mechanisms of psychoactive drugs at neural synapses.
10. Recognize theorized influences in the development of psychiatric disorders, including brain physiology, genetics, endocrine function, immune system, and psychosocial and environmental factors.
11. Discuss the implications of psychobiological concepts for the practice of psychiatric-mental health nursing.

HOMEWORK ASSIGNMENT

Please read the chapter and answer the following questions:

1. A dramatic reduction in which neurotransmitter is most closely associated with Alzheimer's disease?
2. Anorexia nervosa has been associated with a primary dysfunction of which structure of the brain?
3. Many psychotropic medications work by blocking the reuptake of neurotransmitters. Describe the process of *reuptake.*
4. Which psychiatric disorder may be linked to chronic hypothyroidism?

In recent years, increased emphasis has been placed on the organic basis for psychiatric illness. This "neuroscientific revolution" studies the biological basis of behavior, and several mental illnesses are now considered physical disorders resulting from malfunctions or malformations of the brain. That some psychiatric illnesses and associated behaviors can be traced to biological factors does not imply that psychosocial and sociocultural influences are completely discounted. For example, there is evidence that *psychological* interventions influence brain activity in a way similar to that of psychopharmacological intervention (Collerton, 2013; Flor, 2014; Mason, 2017). Other evidence indicates that lifestyle choices, such as marijuana use, can precipitate mental illness (psychosis) in individuals with genetic vulnerability (National Institutes of Health, 2018). Ongoing research will build a better understanding of the complex interplay of neural activities within the brain and interaction with one's environment.

The systems of biology, psychology, and sociology are not mutually exclusive—they are interacting systems. This interaction is clearly indicated by the fact that individuals experience biological changes in response to environmental events. One or several of these systems may at various times explain behavioral phenomena.

This chapter focuses on the role of neurophysiological, neurochemical, genetic, and endocrine influences on psychiatric illness. An introduction to psychopharmacology is included (discussed in more detail in Chapter 4, "Psychopharmacology"), and various diagnostic procedures used to detect alteration in biological function that may contribute to psychiatric illness are identified. The implications for psychiatric-mental health nursing are discussed.

CORE CONCEPT

Psychobiology
The study of the biological foundations of cognitive, emotional, and behavioral processes.

The Nervous System: An Anatomical Review

The Brain

The brain has three major divisions, subdivided into six major parts:

1. Forebrain
   a. Cerebrum
   b. Diencephalon
2. Midbrain (Mesencephalon)
3. Hindbrain
   a. Pons
   b. Medulla
   c. Cerebellum

Each of these structures is discussed individually. A summary is presented in Table 3–1.

Cerebrum

The cerebrum consists of a right and left hemisphere and constitutes the largest part of the human brain. The two hemispheres are separated by a deep groove but remain connected to each other by a band of 200 million axons (nerve fibers) called the *corpus callosum*. Because each hemisphere controls different functions, information is processed through the corpus callosum so that each hemisphere is aware of the activity of the other.

TABLE 3–1 **Structure and Function of the Brain**

STRUCTURE	PRIMARY FUNCTION
I. FOREBRAIN	
A. Cerebrum	Composed of two hemispheres connected by a band of nerve tissue that houses a band of 200 million axons called the *corpus callosum.* The outer layer is called the *cerebral cortex.* It is extensively folded and consists of billions of neurons. The left hemisphere appears to deal with logic and solving problems. The right hemisphere may be called the "creative" brain and is associated with affect, behavior, and spatial-perceptual functions. Each hemisphere is divided into four lobes.
1. Frontal lobes	Voluntary body movement, including movements that permit speaking, thinking and judgment formation, and expression of feelings
2. Parietal lobes	Perception and interpretation of most sensory information (including touch, pain, taste, and body position)
3. Temporal lobes	Hearing, short-term memory, and sense of smell; expression of emotions through connection with limbic system
4. Occipital lobes	Visual reception and interpretation
B. Diencephalon 1. Thalamus	Connects cerebrum with lower brain structures Integrates all sensory input (except smell) on way to cortex; some involvement with emotions and mood
2. Hypothalamus	Regulates anterior and posterior lobes of pituitary gland; exerts control over actions of the autonomic nervous system; regulates appetite and temperature; regulates visceral responses to emotional situations and body rhythms such as mood changes and sleep-wakefulness cycles
3. Limbic system*	
II. MIDBRAIN	
(Mesencephalon)	Responsible for visual, auditory, and balance ("righting") reflexes
III. HINDBRAIN	
A. Pons	Regulation of respiration and skeletal muscle tone; ascending and descending tracts connect brainstem with cerebellum and cortex
B. Medulla	Pathway for all ascending and descending fiber tracts; contains vital centers that regulate heart rate, blood pressure, and respiration; reflex centers for swallowing, sneezing, coughing, and vomiting
C. Cerebellum	Regulates muscle tone and coordination and maintains

*The limbic system consists of medially placed cortical and subcortical structures and the fiber tracts connecting them with one another and with the hypothalamus. It is sometimes called the “emotional brain”—associated with feelings of fear and anxiety; anger and aggression; love, joy, and hope; and with sexuality and social behavior. As research has advanced our understanding of the connectivity in brain structures, it has become difficult to define the boundaries of the limbic system.

The surface of the cerebrum consists of gray matter and is called the *cerebral cortex.* The gray matter is composed of neuron cell bodies that appear gray to the eye. These cell bodies are thought to be the actual “thinking” structures of the brain. The *basal ganglia,* four subcortical nuclei of gray matter (the striatum, the pallidum, the substantia nigra, and the subthalamic nucleus), are found deep within the cerebral hemispheres. They are responsible for certain subconscious aspects of voluntary movements, such as swinging the arms when walking, gesturing while speaking, and regulating muscle tone (Scanlon & Sanders, 2018).

The cerebral cortex is identified by numerous folds called *gyri* and deep grooves between the folds called *sulci.* This extensive folding extends the surface area of the cerebral cortex to permit the presence of millions more neurons than could be accommodated without the folds (as is the case in the brains of some animals, such as dogs and cats). Each hemisphere of the cerebral cortex is divided into the frontal lobe, parietal lobe, temporal lobe, and occipital lobe. These lobes, which are named for the overlying bones in the cranium, are identified in Figure 3-1.

The Frontal Lobes

Voluntary body movement is controlled by impulses through the frontal lobes. The right frontal lobe controls motor activity on the left side of the body, and the left frontal lobe controls motor activity on the right side of the body. The frontal lobe may also play a role in emotional experiences, as evidenced by changes in mood and character after damage to this area. The prefrontal cortex (the front part of the frontal lobe) plays an essential role in the regulation and adaptation of our emotions to new situations and may have implications for moral and spiritual responses (Sadock, Sadock, & Ruiz, 2015). Neuroimaging tests suggest there may be decreased activity in the frontal lobes (as well as temporal, parietal, and subcortical structures) in people with chronic schizophrenia (Lyall, Kubicki, & Shenton, 2017).

The Parietal Lobes

The parietal lobes manage somatosensory input, including touch, pain, pressure, taste, temperature, perception of joint and body position, and visceral sensations. The parietal lobes also contain association fibers linked to

the primary sensory areas through which interpretation of sensory-perceptual information is made. Language interpretation is associated with the left hemisphere of the parietal lobe.

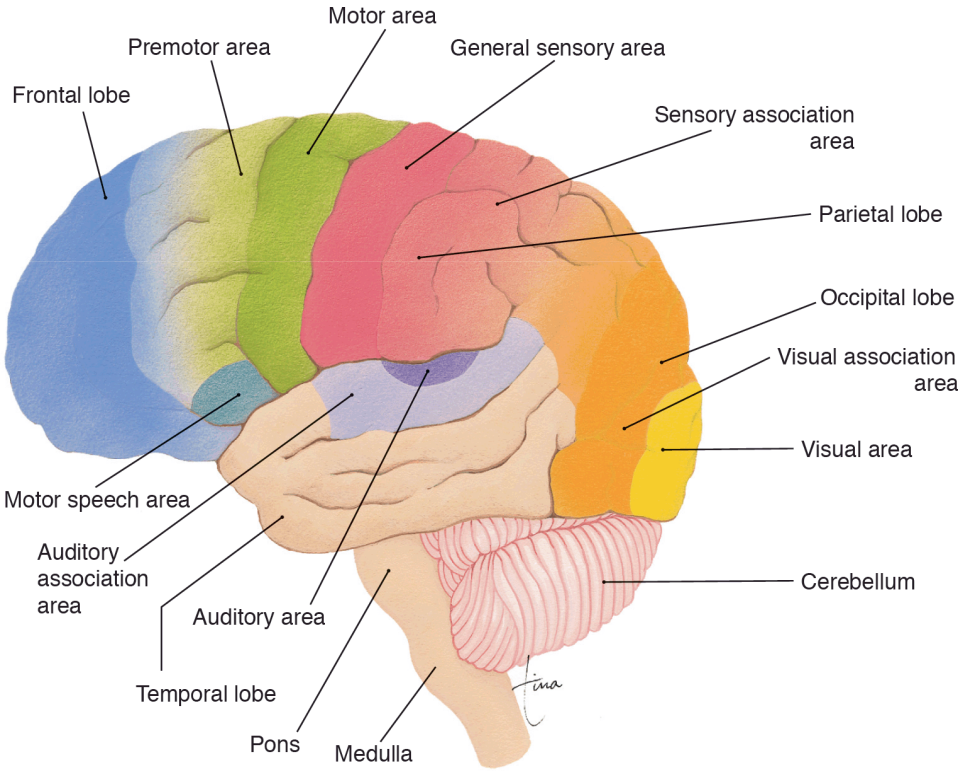


FIGURE 3-1 Left cerebral hemisphere showing some of the functional areas that have been mapped. (From Scanlon, V.C., & Sanders, T. [2018]. *Essentials of anatomy and physiology* [8th ed.]. Philadelphia: F.A. Davis Company, with permission.)

The Temporal Lobes

The upper anterior temporal lobe is concerned with auditory functions, and the lower part is dedicated to short-term memory. The sense of smell has a connection to the temporal lobes, as the impulses carried by the olfactory nerves end in this area of the brain. The temporal lobes also play a role in the expression of emotions through an interconnection with the limbic system. The left temporal lobe (along with the left parietal lobe) is involved in language interpretation.

The Occipital Lobes

The occipital lobes are the primary area of visual reception and interpretation. Visual perception, the ability to judge spatial relationships such as distance and to see in three dimensions, is also processed in this area. Language

interpretation is affected by the visual processing that occurs in the occipital lobes.

Diencephalon

The second part of the forebrain is the diencephalon, which connects the cerebrum with lower structures of the brain. The major components of the diencephalon include the thalamus and the hypothalamus, which are part of a neuroanatomical loop of structures known as the **limbic system** (sometimes called the emotional brain because these structures are associated with regulation of emotions). Commonly associated structures are identified in Figure 3-2.

Thalamus

The thalamus integrates all sensory input (except smell) on its way to the cortex. This integration allows for rapid interpretation of the whole rather than individual perception of each sensation. The thalamus is also involved in temporarily blocking minor sensations so that an individual can concentrate on one important event when necessary. For example, an individual who is studying for an examination may be unaware of the clock ticking in the room or another person entering because the thalamus has temporarily blocked these incoming sensations from the cortex. The impact of dopamine in the thalamus is associated with several neuropsychiatric disorders.

Hypothalamus

The hypothalamus is located just below the thalamus and just above the pituitary gland and has the following diverse functions:

1. **Regulation of the pituitary gland:** The pituitary gland consists of two lobes—the posterior lobe and the anterior lobe.
   a. The *posterior lobe* of the pituitary gland is actually extended tissue from the hypothalamus. The posterior lobe stores antidiuretic hormone (ADH), which helps to maintain blood pressure through regulation of water retention, and oxytocin, the hormone responsible for stimulation of the uterus during labor and the release of milk (along with prolactin) from the mammary glands. Both ADH and oxytocin are produced in the hypothalamus. When the hypothalamus detects the body's need for these hormones, it sends nerve impulses to the posterior pituitary for their release.
   b. The *anterior lobe* of the pituitary gland consists of glandular tissue that produces several hormones used by the body. These hormones are regulated by *releasing factors* from the hypothalamus. When the hormones are required by the body, the releasing factors stimulate the

release of the hormone from the anterior pituitary, and the hormone in turn stimulates its target organ to carry out its specific functions.

2. **Direct neural control over the actions of the autonomic nervous system:** The hypothalamus regulates the appropriate visceral responses during various emotional states. The actions of the autonomic nervous system are described later in this chapter.
3. **Regulation of appetite, temperature, and thirst:** Appetite may be triggered or inhibited depending on which networks in the hypothalamus are stimulated. Temperature is regulated through the hypothalamus as it senses internal and external temperature changes on the skin and in the blood. It then responds by triggering shivering or sweating to help maintain body temperature within the normal range. Thirst centers in the hypothalamus are stimulated by dry mouth or dehydration.
4. **Regulation of blood pressure:** Recent research has clarified the role of the hypothalamus in blood pressure regulation (Carmichael & Wainford, 2015). The hypothalamus, which acts as an interface between the endocrine and nervous systems, coordinating signal transduction from central and peripheral stimuli, has been identified as a key component in the development of hypertension when activated. A wide variety of functional changes in the hypothalamus are associated with multiple forms of hypertension.
5. **Circadian rhythms (sleep and wakefulness cycles):** The output of the suprachiasmatic nucleus (SNC) of the hypothalamus promotes a state of arousal; as the output decreases, the onset of sleep is facilitated in a complex process that drives the homeostatic need for sleep. This process includes an intrinsic 24-hour timing system and response to light or darkness. SNC neurons along with other peptides also produce gamma-Aminobutyric acid (GABA) (Moore, 2019).

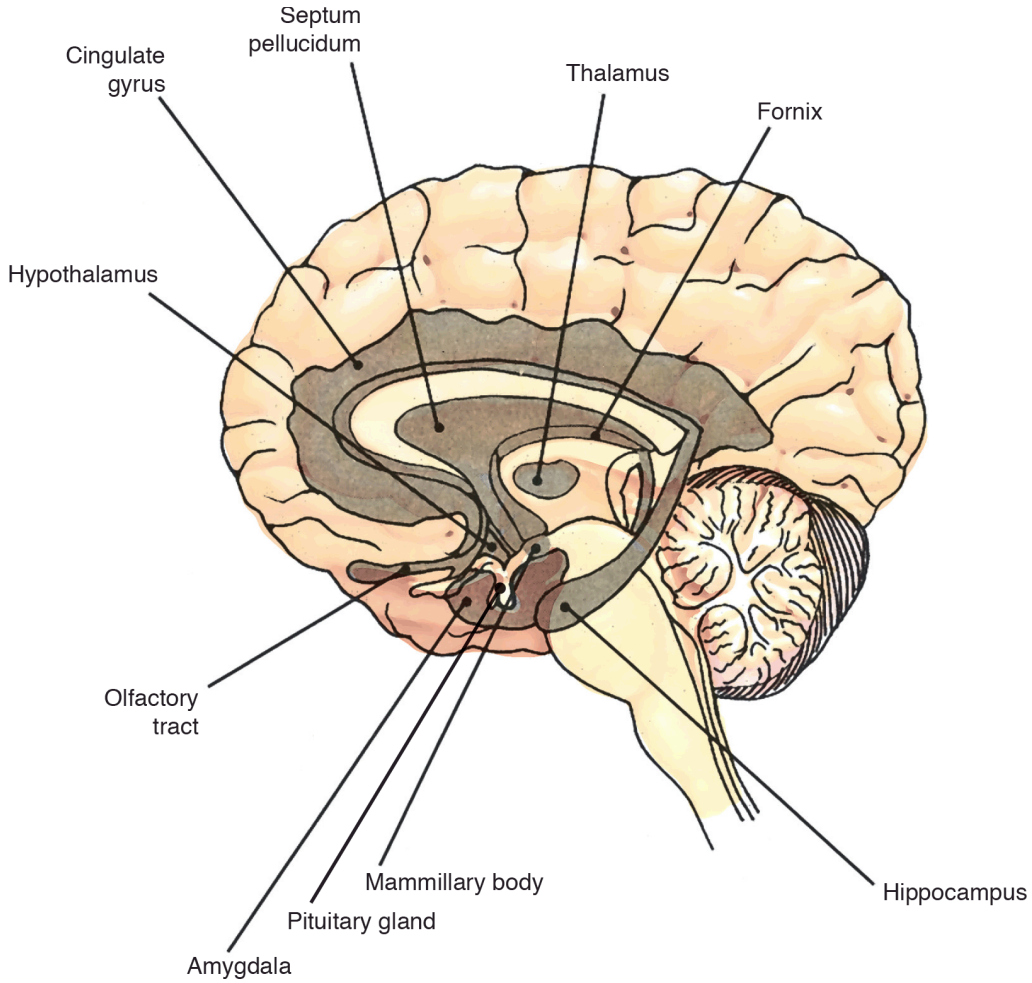


FIGURE 3-2 Structures of the limbic system. (From Scanlon, V.C., & Sanders, T. [2011]. *Essentials of anatomy and physiology* [6th ed.]. Philadelphia: F.A. Davis Company, with permission.)

Limbic System

The limbic system is a group of structures typically identified as including the amygdala, mammillary body, olfactory tract, hypothalamus, cingulate gyrus, septum pellucidum, thalamus, hippocampus, and fornix, which, through communication with the hypothalamus, control several autonomic, endocrine, and somatic functions. This system has been called the “emotional brain” because of its association with feelings of fear and anxiety; anger, rage, and aggression; love, joy, and hope; and with sexuality and social behavior. The amygdala seems to be a primary gateway for processing novel and ambiguous emotional stimuli, particularly related to fear, anxiety, and panic. As our knowledge of the complex interconnections within the brain has advanced, it has become more difficult to identify clear boundaries for the limbic system.

Mesencephalon (Midbrain)

Structures of major importance in the mesencephalon, or midbrain, include nuclei and fiber tracts. The mesencephalon extends from the pons to the hypothalamus and is responsible for integration of various reflexes, including visual reflexes (e.g., automatically turning away from a dangerous object when it comes into view), auditory reflexes (e.g., automatically turning toward a sound that is heard), and righting reflexes (e.g., automatically keeping the head upright and maintaining balance).

Pons

The pons is a bulbous structure that lies between the midbrain and the medulla as part of the brainstem (Fig. 3–1). It is composed of large bundles of fibers and forms a major connection between the cerebellum and the brainstem. The pons is a relay station that transmits messages between various parts of the nervous system, including the cerebrum and cerebellum. It contains the central connections of cranial nerves V through VIII and centers for respiration and skeletal muscle tone. The pons is also associated with sleep and dreaming.

Medulla

The medulla is the connecting structure between the spinal cord and the pons, and all of the ascending and descending fiber tracts pass through it. The vital centers are contained in the medulla, and its functions include regulation of heart rate, blood pressure, and respiration. The medulla contains reflex centers for swallowing, sneezing, coughing, and vomiting, as well as nuclei for cranial nerves IX through XII. The medulla, pons, and midbrain form the structure known as the *brainstem.*

Cerebellum

The cerebellum is separated from the brainstem by the fourth ventricle but is connected to it through bundles of fiber tracts (Fig. 3–1). The cerebellum is associated with involuntary aspects of movement such as coordination, muscle tone, and the maintenance of posture and equilibrium.

Nerve Tissue

The tissue of the central nervous system (CNS) consists of nerve cells called *neurons* that generate and transmit electrochemical impulses. The structure of a neuron is composed of a cell body, an axon, and dendrites. The **cell body** contains the nucleus and is essential for the continued life of the neuron. The **dendrites** are processes that transmit impulses toward the cell body, and the **axon** transmits impulses away from the cell body. The axons and dendrites are covered by layers of cells called *neuroglia* that form a coating, or “sheath,” of myelin. *Myelin* is a phospholipid that provides insulation against short-circuiting of the neurons during their electrical activity and increases the velocity of the

impulse. The white matter of the brain and spinal cord is so called because of the whitish appearance of the myelin sheath covering the axons and dendrites. The gray matter is composed of cell bodies that contain no myelin.

Classes of Neurons

The three classes of neurons are afferent (sensory) neurons, efferent (motor) neurons, and interneurons. The *afferent neurons* carry impulses from receptors in the internal and external periphery to the CNS, where they are then interpreted into various sensations. The *efferent neurons* carry impulses from the CNS to *effectors* in the periphery, such as muscles (that respond by contracting) and glands (that respond by secreting).

Interneurons exist entirely within the CNS, and 99% of all nerve cells belong to this group. They may carry only sensory or motor impulses, or they may serve as integrators in the pathways between afferent and efferent neurons. They account in large part for thinking, feelings, learning, language, and memory.

Synapses

Information is transmitted through the body from one neuron to another. Some messages may be processed through only a few neurons, whereas others may require thousands of neuronal connections. The neurons that transmit the impulses do not actually touch each other. The junction between two neurons is called a **synapse.** The small space between the axon terminals of one neuron and the cell body or dendrites of another is called the *synaptic cleft.* Neurons conducting impulses toward the synapse are called *presynaptic neurons,* and those conducting impulses away are called *postsynaptic neurons.*

Chemicals that act as **neurotransmitters** are stored in the axon terminals of the presynaptic neuron. An electrical impulse through the neuron causes the release of this neurotransmitter into the synaptic cleft. The neurotransmitter then diffuses across the synaptic cleft and combines with **receptor sites** that are situated on the cell membrane of the postsynaptic neuron. The type of combination determines whether or not another electrical impulse is generated. If an electrical impulse is generated, the result is called an *excitatory response,* and the electrical impulse moves on to the next synapse, where the same process recurs. If an electrical impulse is not generated by the neurotransmitter–receptor site combination, the result is called an *inhibitory response,* and synaptic transmission is terminated. Activity at the neural synapse is relevant in the study of psychiatric disorders because excessive or deficient activity of neurotransmitters influences a variety of cognitive and

emotional symptoms. The synapse is also believed to be the primary site of activity for psychotropic drugs.

The cell body of the postsynaptic neuron also contains a chemical *inactivator* that is specific to the neurotransmitter released by the presynaptic neuron. When the synaptic transmission has been completed, the chemical inactivator quickly inactivates the neurotransmitter to prevent unwanted, continuous impulses until a new impulse from the presynaptic neuron releases more of the neurotransmitter. Continuous impulses can result in excessive activity of neurotransmitters such as dopamine, which is believed to be responsible for symptoms such as hallucinations and delusions seen in people with schizophrenia. A schematic representation of a synapse is presented in Figure 3-3.

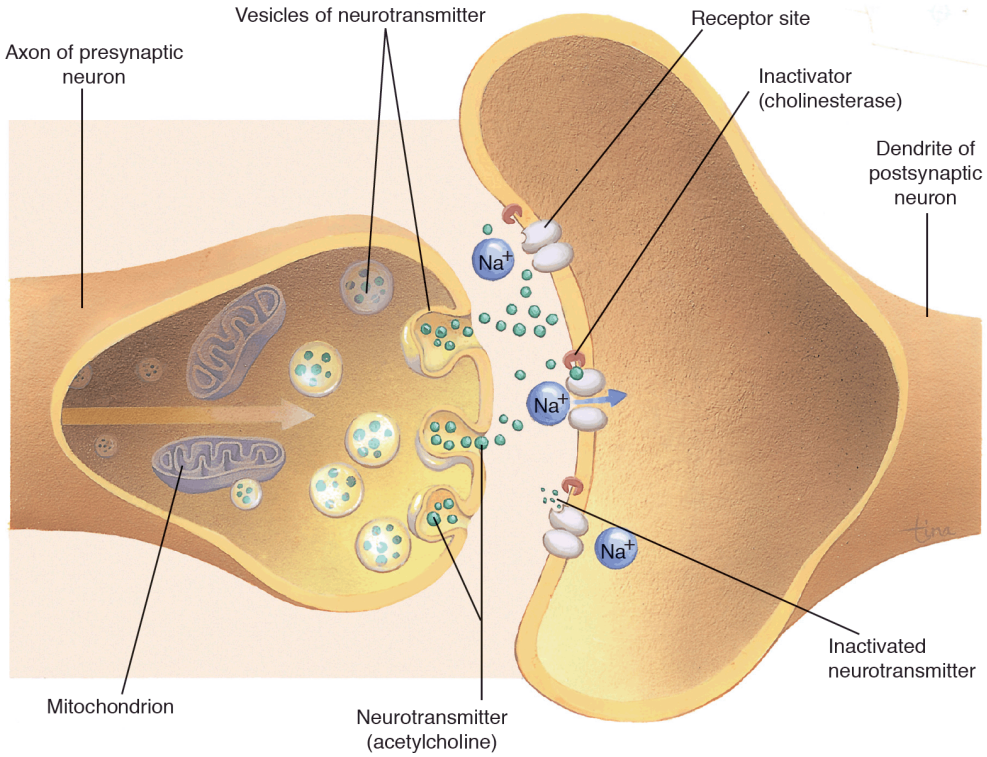


FIGURE 3-3 Impulse transmission at a synapse. The arrow indicates the direction of electrical impulses. (From Scanlon, V.C., & Sanders, T. [2018]. *Essentials of anatomy and physiology* [8th ed.]. Philadelphia: F.A. Davis Company, with permission.)

Autonomic Nervous System

The autonomic nervous system (ANS) is considered part of the peripheral nervous system. Its regulation is modulated by the hypothalamus, and emotions exert a great deal of influence over its functioning. For this reason,

the ANS has been implicated in the etiology of a number of psychophysiological disorders.

The ANS has two divisions: the sympathetic and the parasympathetic. The sympathetic division is dominant in stressful situations and prepares the body for the fight-or-flight response (discussed in Chapter 1, “The Concept of Stress Adaptation”). The neuronal cell bodies of the sympathetic division originate in the thoracolumbar region of the spinal cord. Their axons extend to the chains of sympathetic ganglia where they synapse with other neurons that subsequently innervate the visceral effectors, resulting in an increase in heart rate and respiration and a decrease in digestive secretions and peristalsis. Blood is shunted to the vital organs and skeletal muscles to ensure adequate oxygenation.

The neuronal cell bodies of the parasympathetic division originate in the brainstem and the sacral segments of the spinal cord and extend to the parasympathetic ganglia where the synapse occurs either very close to or actually in the visceral organ being innervated. In this way, a localized response is possible. The parasympathetic division dominates when an individual is in a relaxed, nonstressful condition. The heart and respirations are maintained at a normal rate, and secretions and peristalsis increase for normal digestion. Elimination functions are promoted. A schematic representation of the ANS is presented in Figure 3-4.

Neurotransmitters

Although neurotransmitters were described during the explanation of synaptic activity, they are discussed here separately and in detail because of their essential roles in human emotion and behavior. Neurotransmitters are also central to the therapeutic action of many psychotropic medications.

Neurotransmitters are chemicals that convey information across synaptic clefts to neighboring target cells. They are stored in small vesicles in the axon terminals of neurons. When the action potential, or electrical impulse, reaches this point, the neurotransmitters are released from the vesicles. They cross the synaptic cleft and bind with receptor sites on the cell body or dendrites of the adjacent neuron to allow the impulse to continue its course or to prevent the impulse from continuing. After the neurotransmitter has performed its function in the synapse, it either returns to the vesicles to be stored and used again or is inactivated and dissolved by enzymes. The process of being stored for reuse is called *reuptake,* a function that holds significance for understanding the mechanism of action of certain psychotropic medications.

Many neurotransmitters exist in the central and peripheral nervous systems, but only a limited number have implications for psychiatry. Major categories include cholinergic neurotransmitters, monoamines, amino acids, and

neuropeptides. Each of these is discussed separately and summarized in Table 3–2.

Cholinergic Neurotransmitters

Acetylcholine

Location: Acetylcholine was the first chemical to be identified as and proven to be a neurotransmitter. It is a major effector chemical in the ANS, producing activity at all sympathetic and parasympathetic presynaptic nerve terminals and all parasympathetic postsynaptic nerve terminals. It is highly significant in the neurotransmission that occurs at the junctions of nerves and muscles. Acetylcholinesterase is the enzyme that destroys acetylcholine or inhibits its activity.

In the CNS, acetylcholine neurons innervate the cerebral cortex, hippocampus, and limbic structures. The pathways are especially dense through the area of the basal ganglia in the brain.

Functions: Functions of acetylcholine are manifold and include sleep, arousal, pain perception, the modulation and coordination of movement, and memory acquisition and retention.

Possible Implications in Mental Illness: Cholinergic mechanisms may have some role in certain disorders of motor behavior and memory, such as Parkinson's disease, Huntington's disease, and Alzheimer's disease.

Monoamines

Norepinephrine

Location: Norepinephrine is the neurotransmitter that produces activity at the sympathetic postsynaptic nerve terminals in the ANS, resulting in fight-or-flight responses in the effector organs. In the CNS, norepinephrine pathways originate in the pons and medulla and innervate the thalamus, dorsal hypothalamus, limbic system, hippocampus, cerebellum, and cerebral cortex. When norepinephrine is not returned for storage in the vesicles of the axon terminals, it is metabolized and inactivated by the enzymes monoamine oxidase (MAO) and catechol-O-methyl-transferase (COMT).

Functions: The functions of norepinephrine include the regulation of mood, cognition, perception, locomotion, cardiovascular functioning, and sleep and arousal.

Possible Implications in Mental Illness: The activity of norepinephrine also has been implicated in certain mood disorders such as depression and mania, anxiety states, and schizophrenia (Sadock et al., 2015).

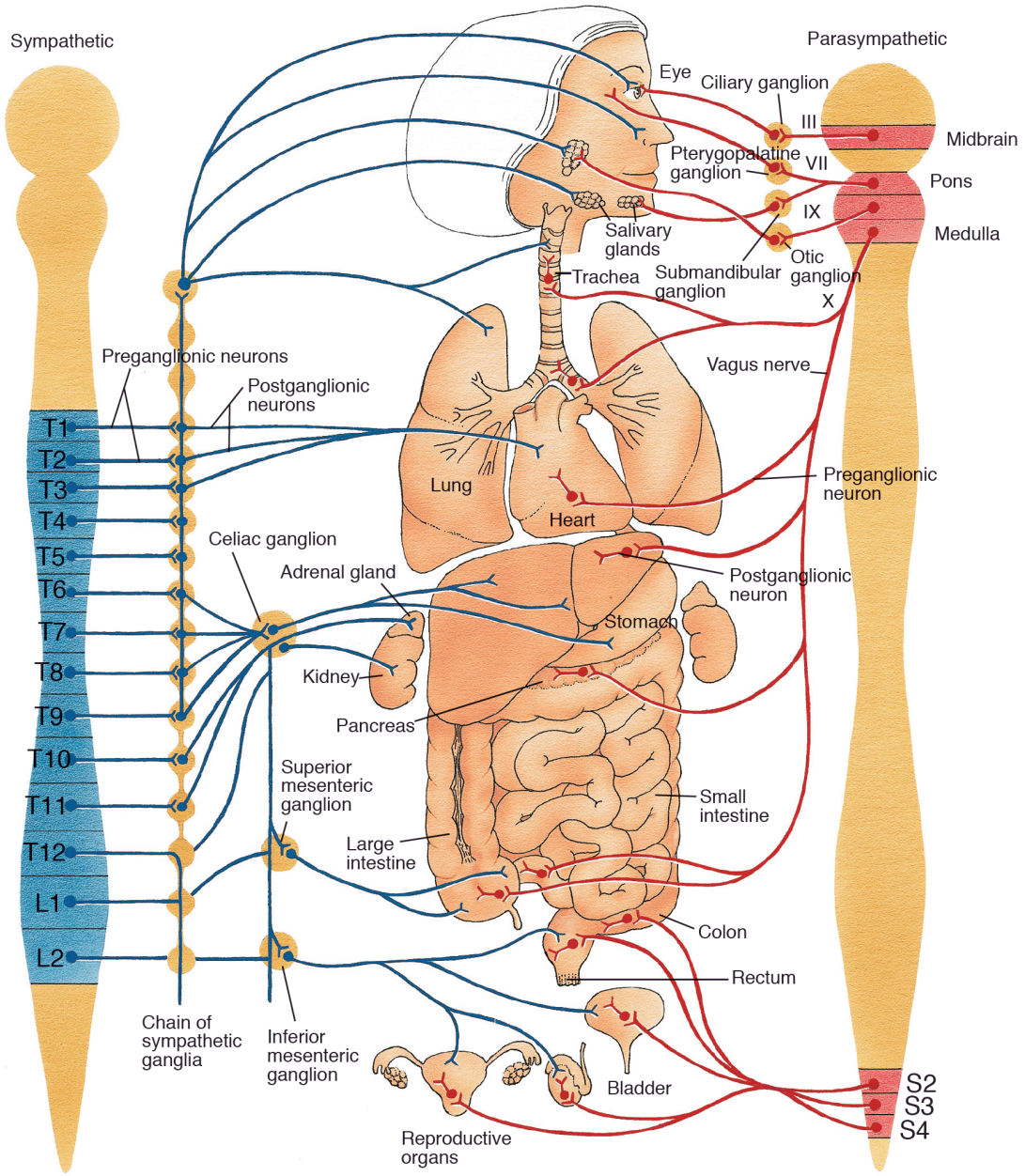


FIGURE 3-4 The autonomic nervous system. The sympathetic division is shown on the left, and the parasympathetic division is shown on the right (both divisions are bilateral). (From Scanlon, V.C., & Sanders, T. [2018]. *Essentials of anatomy and physiology* [8th ed.]. Philadelphia: F.A. Davis Company, with permission.)

Dopamine

Location: Dopamine pathways arise from the midbrain and hypothalamus and terminate in the frontal cortex, limbic system, basal ganglia, and thalamus. As

with norepinephrine, the inactivating enzymes for dopamine are MAO and COMT.

Functions: Dopamine functions include regulation of movements and coordination, emotions, and voluntary decision-making ability, and because of its influence on the pituitary gland, it inhibits the release of prolactin (Sadock et al., 2015).

Possible Implications in Mental Illness: Increased levels of dopamine are associated with mania and schizophrenia. Decreased levels of dopamine have been associated with Parkinson's disease and depression. Dopamine may contribute to addictions.

TABLE 3–2 **Neurotransmitters in the Central Nervous System**

NEUROTRANSMITTER	LOCATION AND FUNCTION	POSSIBLE IMPLICATIONS FOR MENTAL ILLNESS
I. CHOLINERGICS		
A. Acetylcholine	*ANS:* Sympathetic and parasympathetic presynaptic nerve terminals; parasympathetic postsynaptic nerve terminals *CNS:* Cerebral cortex, hippocampus, limbic structures, and basal ganglia *Functions:* Sleep, arousal, pain perception, movement, memory	*Decreased levels:* Alzheimer's disease, *Huntington's* disease, Parkinson's disease *Increased levels:* Depression
II. MONOAMINES		
A. Norepinephrine	*ANS:* Sympathetic postsynaptic nerve terminals *CNS:* Thalamus, hypothalamus, limbic system, hippocampus, cerebellum, cerebral cortex *Functions:* Mood, cognition, perception, locomotion, cardiovascular functioning, and sleep and arousal	*Decreased levels:* Depression *Increased levels:* Mania, anxiety states, schizophrenia
B. Dopamine	Frontal cortex, limbic system, basal ganglia, thalamus, posterior pituitary, spinal cord *Functions:* Movement and coordination, emotions, voluntary judgment, release of prolactin	*Decreased levels:* Parkinson's disease and depression *Increased levels:* Mania and schizophrenia
C. Serotonin	Hypothalamus, thalamus, limbic system, cerebral cortex, cerebellum, spinal cord *Functions:* Sleep and arousal, libido, appetite, mood, aggression, pain perception, coordination, judgment	*Decreased levels:* Depression *Increased levels:* Anxiety states (there are seven different types of serotonin receptors, increased levels of some serotonin subtypes [5HT1A] have an antianxiety effect, and increased levels of others [5HT3] may increase anxiety

		[Elsworth & Roth, 2017])
D. Histamine	Hypothalamus, hippocampus, cortex, cerebellum, basal ganglia, spinal cord, retina *Functions:* Wakefulness; pain sensation and inflammatory response	*Decreased levels:* Depression *Increased levels:* Sleep disorders, anxiety, Alzheimer's disease, psychosis
III. AMINO ACIDS		
A. Gamma-aminobutyric acid	Hypothalamus *Functions:* Slowing of body activity	*Decreased levels:* Huntington's disease, anxiety disorders, schizophrenia, and various forms of epilepsy
B. Glycine	Spinal cord, brainstem *Functions:* Recurrent inhibition of motor neurons	*Toxic levels:* Glycine encephalopathy *Decreased levels:* Correlated with spastic motor movements
C. Glutamate and aspartate	Pyramidal cells of the cortex, cerebellum, and the primary sensory afferent systems; hippocampus, thalamus, hypothalamus, spinal cord *Functions:* Relay of sensory information and regulation of various motor and spinal reflexes; glutamate also has a role in memory and learning	*Decreased levels:* Schizophrenia *Increased levels:* Huntington's disease, temporal lobe epilepsy, spinal cerebellar degeneration, anxiety disorders, depressive disorders
D. D-Serine	Cerebral cortex, forebrain, hippocampus, cerebellum striatum, thalamus *Functions:* Binds at NMDA receptors and, with glutamate, is a coagonist whose functions include mediating NMDA receptor transmission, synaptic plasticity, neurotoxicity	*Decreased levels:* Schizophrenia
IV. NEUROPEPTIDES		
A. Endorphins and enkephalins	Hypothalamus, thalamus, limbic structures, midbrain, brainstem; enkephalins are also found in the gastrointestinal tract	*Modulation* of dopamine activity by opioid peptides may indicate some link to the

	Functions: Modulation of pain and reduced peristalsis (enkephalins)	symptoms of schizophrenia
B. Substance P	Hypothalamus, limbic structures, midbrain, brainstem, thalamus, basal ganglia, spinal cord; also found in gastrointestinal tract and salivary glands *Function:* Regulation of pain	*Decreased levels:* Huntington's disease, Alzheimer's disease *Increased levels:* Depression
C. Somatostatin	Cerebral cortex, hippocampus, thalamus, basal ganglia, brainstem, spinal cord *Function:* Depending on part of the brain affected, stimulates release of dopamine, serotonin, norepinephrine, and acetylcholine and inhibits release of norepinephrine, histamine, and glutamate; also acts as a neuromodulator for serotonin in the hypothalamus	*Decreased levels:* Alzheimer's disease *Increased levels:* Huntington's disease

ANS, autonomic nervous system; CNS, central nervous system; NMDA, *N*-methyl D-aspartate.

Serotonin

Location: Serotonin pathways originate from cell bodies located in the pons and medulla and project to areas including the hypothalamus, thalamus, limbic system, cerebral cortex, cerebellum, and spinal cord. Serotonin that is not returned to be stored in the axon terminal vesicles is catabolized by the enzyme MAO.

Functions: Serotonin may play a role in sleep and arousal, libido, appetite, mood, aggression, and pain perception. The fact that both too much and too little serotonin have been associated with anxiety has led to the hypothesis that serotonin may modulate intense emotional states rather than influencing one kind of mood disruption. Further, there are seven different subgroups of serotonin receptors, which when activated result in different effects (Elsworth & Roth, 2017).

Possible Implications in Mental Illness: The serotoninergic (or serotonergic) system has been implicated in the etiology of certain psychopathological conditions including anxiety states, mood disorders, and schizophrenia (Sadock et al., 2015).

Histamine

Location: The role of histamine in mediating allergic and inflammatory reactions has been well documented. Its role in the CNS as a neurotransmitter has only recently been confirmed, and the availability of information on this function is limited. The highest concentrations of histamine are found within various regions of the hypothalamus.

Functions: Brain histamine regulates many physiological functions: neuroendocrine, circadian rhythms, the sleep–wake cycle, psychomotor activity, mood, learning, cognition, appetite, and eating behavior (Cacabelos, Torrellas, Fernández-Novoa, & López-Muñoz, 2016). The enzyme that catabolizes histamine is MAO.

Possible Implications in Mental Illness: Alterations in brain histamine are associated with several pathological conditions, such as epilepsy, stroke, anxiety, depression, psychosis, neurodegeneration, and neuroinflammatory processes (Cacabelos et al., 2016).

Amino Acids

Inhibitory Amino Acids

Gamma-Aminobutyric Acid

Location: Gamma-aminobutyric acid (GABA) has a widespread distribution in the CNS, with high concentrations in the hypothalamus, hippocampus, cortex, cerebellum, and basal ganglia of the brain; in the gray matter of the dorsal horn of the spinal cord; and in the retina. GABA is catabolized by the enzyme GABA transaminase.

Functions: Inhibitory neurotransmitters such as GABA prevent postsynaptic excitation, interrupting the progression of the electrical impulse at the synaptic junction. This function is significant when slowdown of body activity is advantageous. Enhancement of the GABA system is the mechanism of action by which the benzodiazepines produce their calming effect.

Possible Implications in Mental Illness: Alterations in the GABA system have been implicated in the etiology of anxiety disorders, movement disorders (e.g., Huntington's disease), and various forms of epilepsy. GABA levels, in a complex interaction with other neurotransmitters such as dopamine, have also been implicated in substance use disorders and addiction.

Glycine

Location: The highest concentrations of glycine in the CNS are found in the spinal cord and brainstem. Little is known about the possible enzymatic metabolism of glycine.

Functions: Glycine appears to be the neurotransmitter of recurrent inhibition of motor neurons within the spinal cord and is possibly involved in the regulation of spinal and brainstem reflexes.

Possible Implications in Mental Illness: Glycine has been implicated in the pathogenesis of certain types of spastic disorders and in *glycine encephalopathy,* which is known to occur with toxic accumulation of the neurotransmitter in the brain and cerebrospinal fluid (Van Hove, Coughlin, & Sharer, 2013).

Excitatory Amino Acids

Glutamate and Aspartate

Location: Glutamate and aspartate appear to be primary excitatory neurotransmitters in the pyramidal cells of the cortex, the cerebellum, and the primary sensory afferent systems. They are also found in the hippocampus, thalamus, hypothalamus, and spinal cord. Glutamate and aspartate are inactivated by uptake into the tissues and through assimilation in various metabolic pathways.

Functions: Glutamate and aspartate function in the relay of sensory information and regulation of various motor and spinal reflexes. Glutamate also plays a role in memory and learning.

Possible Implications in Mental Illness: Alteration in these systems has been implicated in the etiology of certain neurodegenerative disorders, such as Huntington's disease, temporal lobe epilepsy, and spinal cerebellar degeneration. Increases in glutamate have been associated with neuron degeneration in Alzheimer's disease (Coyle, 2017). Problems in making or using glutamate have been linked to many mental disorders, including autism, obsessive-compulsive disorder (OCD), schizophrenia, and depression (National Institute of Mental Health [NIMH], no date).

Neuropeptides

Neuropeptides act as signaling molecules in the CNS. Their activities include regulating processes related to sex, sleep, stress and pain, emotion, and social cognition. They may contribute to symptoms and behaviors associated with psychosis, mood disorders, dementia, and autism spectrum disorders (Sadock et al., 2015). Opioid peptides, substance P, and somatostatin are discussed here. Hormonal neuropeptides are discussed in the section of this chapter on neuroendocrinology.

Opioid Peptides

Location: Opioid peptides, which include the endorphins and enkephalins, have been widely studied. They are found in various concentrations in the hypothalamus, thalamus, limbic structures, midbrain, and brainstem. Enkephalins are also found in the gastrointestinal tract.

Functions: With their natural morphine-like properties, opioid peptides are thought to have a role in pain modulation. Released in response to painful stimuli, they may be responsible for producing the analgesic effect that results from acupuncture. Opioid peptides alter the release of dopamine and affect the spontaneous activity of the dopaminergic neurons.

Possible Implications in Mental Illness: Modulation of dopamine activity by opioid peptides may be associated with addiction and some symptoms of schizophrenia.

Substance P

Location: Substance P, the first neuropeptide to be discovered, is present in high concentrations in the hypothalamus, limbic structures, midbrain, and brainstem. It is also found in the thalamus, basal ganglia, and spinal cord.

Functions: Substance P plays a role in sensory transmission, particularly in the regulation of pain.

Possible Implications in Mental Illness: Studies demonstrated that people with depression and posttraumatic stress disorder (PTSD) had elevated levels of substance P in cerebrospinal fluid (Sadock et al., 2015).

Somatostatin

Location: Somatostatin (also called *growth hormone–inhibiting hormone [GHIH]*) is found in the cerebral cortex, hippocampus, thalamus, basal ganglia, brainstem, and spinal cord.

Functions: In its function as a neurotransmitter, somatostatin exerts both stimulatory and inhibitory effects depending on the part of the brain affected. It has been shown to stimulate dopamine, serotonin, norepinephrine, and acetylcholine and to inhibit norepinephrine, histamine, and glutamate. It also acts as a neuromodulator for serotonin in the hypothalamus, thereby regulating its release (i.e., controlling whether it is stimulated or inhibited). Somatostatin may serve this function for other neurotransmitters as well.

Possible Implications in Mental Illness: High concentrations of somatostatin have been reported in brain specimens of clients with Huntington's disease, and low concentrations have been found in those with Alzheimer's disease.

CORE CONCEPTS

Neuroendocrinology
The study of the interaction between the nervous system and the endocrine system and the effects of various hormones on cognitive, emotional, and behavioral functioning.

Neuroendocrinology

Human endocrine functioning has a strong foundation in the CNS under the direction of the hypothalamus, which has direct control over the pituitary gland. The pituitary gland has two major lobes—the anterior lobe (also called the *adenohypophysis*) and the posterior lobe (also called the *neurohypophysis*). The pituitary gland is only about the size of a pea, but despite its size and because of the powerful control it exerts over endocrine functioning in humans, it is sometimes called the "master gland." Figure 3-5 shows the hormones of the pituitary gland and their target organs. Many of the hormones subject to hypothalamus-pituitary regulation may have implications for behavioral functioning. Discussion of these hormones is summarized in Table 3–3.

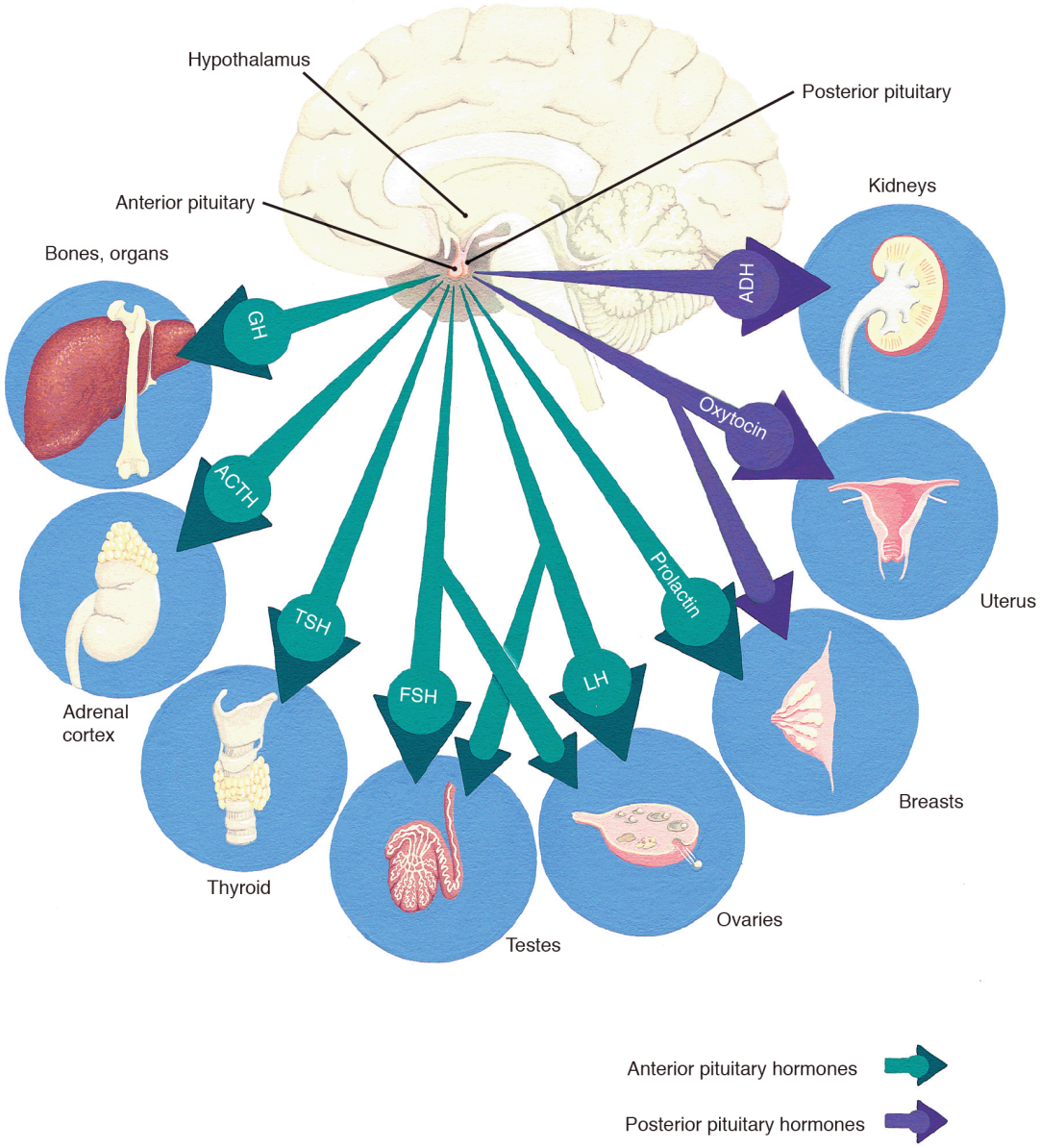


FIGURE 3-5 Hormones of the pituitary gland and their target organs. (From Scanlon, V.C., & Sanders, T. [2018]. *Essentials of anatomy and physiology* [8th ed.]. Philadelphia: F.A. Davis Company, with permission.)

Pituitary Gland

The Posterior Pituitary (Neurohypophysis)

The hypothalamus has direct control over the posterior pituitary through efferent neural pathways. Two hormones are found in the posterior pituitary: vasopressin (antidiuretic hormone) and oxytocin. They are actually produced by the hypothalamus and stored in the posterior pituitary. Their release is mediated by neural impulses from the hypothalamus (Fig. 3–6).

Antidiuretic Hormone

The main function of antidiuretic hormone (ADH) is to conserve body water and maintain normal blood pressure. The release of ADH is stimulated by pain, emotional stress, dehydration, increased plasma concentration, and decreases in blood volume. An alteration in the secretion of this hormone is related to the polydipsia seen in patients with diabetes. ADH alterations also may be one of many factors contributing to the polydipsia and water intoxication (a state of hyper-hydration related to excessive consumption of water) observed in 10% to 20% of patients with severe mental illness, particularly those with schizophrenia. Other factors correlated with this behavior include adverse effects of psychotropic medications and features of the behavioral disorder itself. It is important to note that severe polydipsia can result in electrolyte imbalance and death (Gill & McCauley, 2015). ADH also may play a role in learning and memory, alteration of the pain response, and modification of sleep patterns.

TABLE 3–3 **Hormones of the Neuroendocrine System**

HORMONE	LOCATION AND STIMULATION OF RELEASE	TARGET ORGAN	FUNCTION	POSSIBLE BEHAVIORAL CORRELATION TO ALTERED SECRETION
Antidiuretic hormone (ADH)	Posterior pituitary; release stimulated by dehydration, pain, stress	Kidney (causes increased reabsorption)	Conservation of body water; maintenance of blood pressure	Polydipsia; altered pain response; modified sleep pattern
Oxytocin	Posterior pituitary; release stimulated by end of pregnancy; stress; during sexual arousal	Uterus; breasts	Contraction of the uterus for labor; release of breast milk	May perform role in stress response by stimulation of ACTH
Growth hormone (GH)	Anterior pituitary; release stimulated by growth hormone-releasing hormone from hypothalamus	Bones and tissues	Growth in children; protein synthesis in adults	Anorexia nervosa
Thyroid-stimulating hormone (TSH)	Anterior pituitary; release stimulated by thyrotropin-releasing hormone from hypothalamus	Thyroid gland	Stimulation of secretion of needed thyroid hormones for metabolism of food and regulation of temperature	*Increased levels of thyroid hormones (decreased secretion of TSH):* Insomnia, anxiety, emotional lability *Decreased levels of thyroid hormones (increased secretion of TSH):* Fatigue, depression

Adrenocorticotropic hormone (ACTH)	Anterior pituitary; release stimulated by corticotropin-releasing hormone from hypothalamus	Adrenal cortex	Stimulation of secretion of cortisol, which performs a role in response to stress	*Increased levels:* Mood disorders, psychosis *Decreased levels:* Depression, apathy, fatigue
Prolactin	Anterior pituitary; release stimulated by prolactin-releasing hormone from hypothalamus	Breasts	Stimulation of milk production	*Increased levels:* Depression, anxiety, decreased libido, irritability
Gonadotropic hormones	Anterior pituitary; release stimulated by gonadotropin-releasing hormone from hypothalamus	Ovaries and testes	Stimulation of secretion of estrogen, progesterone, and testosterone; role in ovulation and sperm production	*Decreased levels:* Depression, anorexia nervosa *Increased testosterone:* Increased sexual behavior and aggressiveness
Melanocyte-stimulating hormone (MSH)	Anterior pituitary; release stimulated by onset of darkness	Pineal gland	Stimulation of secretion of melatonin	*Increased levels:* Depression

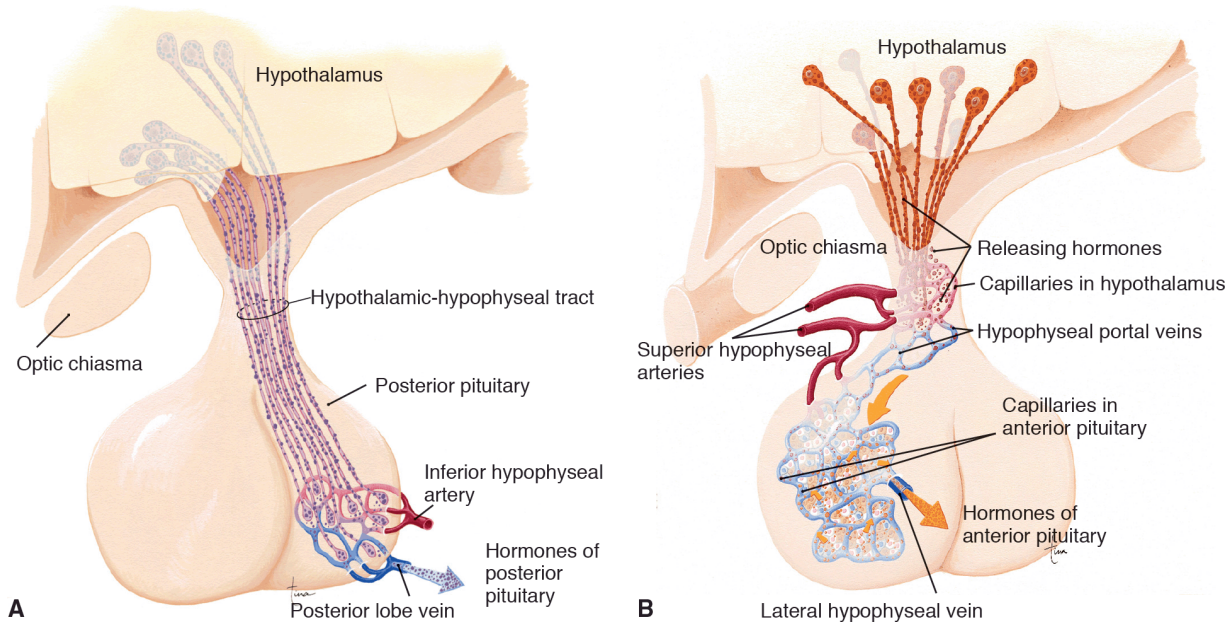


FIGURE 3-6 Structural relationships of hypothalamus and pituitary gland. (A) Posterior pituitary stores hormones produced in the hypothalamus. (B) Releasing hormones of the hypothalamus circulate directly to the anterior pituitary and influence its secretions. Notice the two networks of capillaries. (From Scanlon, V.C., & Sanders, T. [2018]. *Essentials of anatomy and physiology* [8th ed.]. Philadelphia: F.A. Davis Company, with permission.)

Oxytocin

Oxytocin causes contraction of the uterus during labor and stimulates release of milk from the mammary glands (Scanlon & Sanders, 2018). It is also released in response to stress and during sexual arousal. Oxytocin may promote social bonding and has been used experimentally with autistic children to increase socialization (Sadock et al., 2015). Increases in oxytocin demonstrate antianxiety effects (in interaction with adrenocorticotrophic hormone [ACTH]) and may facilitate the development of substance use disorders, especially with "party drugs" (e.g., 3,4-methylenedioxy-methamphetamine [MDMA] and gamma hydroxybutyrate [GBH]) that are often used to facilitate social interaction (Harris, Wolkowitz, & Reus, 2017). Decreased levels have been reported in patients with autism and anorexia.

The Anterior Pituitary (Adenohypophysis)

The hypothalamus produces releasing hormones that pass through capillaries and veins of the hypophyseal portal system to capillaries in the anterior pituitary, where they stimulate secretion of specialized hormones. The hormones of the anterior pituitary gland regulate multiple body functions and include growth hormone, thyroid-stimulating hormone, ACTH, prolactin,

gonadotropin-stimulating hormone, and melanocyte-stimulating hormone. Most of these hormones are regulated by a *negative feedback mechanism.* Once the hormone has exerted its effects, the information is “fed back” to the anterior pituitary, which inhibits the release and ultimately decreases the effects of the stimulating hormones.

Growth Hormone

The release of growth hormone (GH), also called *somatotropin,* is stimulated by growth hormone–releasing hormone (GHRH) from the hypothalamus. Its release is inhibited by GHIH, or somatostatin, also from the hypothalamus. It is responsible for growth in children and continued protein synthesis throughout life. During periods of fasting, it stimulates the release of fat from the adipose tissue to increase energy. The release of GHIH is stimulated in response to periods of hyperglycemia. GHRH is stimulated in response to hypoglycemia and stressful situations. During prolonged stress, GH has a direct effect on protein, carbohydrate, and lipid metabolism, resulting in increased serum glucose and free fatty acids to be used for increased energy. GH deficiency has been noted in many patients with major depressive disorder, and several GH abnormalities have been noted in patients with anorexia nervosa.

Thyroid-Stimulating Hormone

Thyrotropin-releasing hormone (TRH) from the hypothalamus stimulates the release of thyroid-stimulating hormone (TSH), or thyrotropin, from the anterior pituitary. TSH stimulates the thyroid gland to secrete triiodothyronine (T_3) and thyroxine (T_4). Thyroid hormones are integral to the metabolism of food and the regulation of temperature.

A correlation between thyroid dysfunction and altered behavioral functioning has been well documented. Common symptoms of hyperthyroidism include irritability, insomnia, anxiety, restlessness, weight loss, and emotional lability, in some instances progressing to delirium or psychosis. Symptoms of fatigue, decreased libido, memory impairment, depression, and suicidal ideation have been associated with chronic hypothyroidism. Studies have correlated various forms of thyroid dysfunction with mood disorders, anxiety, eating disorders, schizophrenia, and dementia.

Adrenocorticotropic Hormone

Corticotropin-releasing hormone (CRH) from the hypothalamus stimulates the release of ACTH from the anterior pituitary. ACTH stimulates the adrenal cortex to secrete cortisol. CRH, ACTH, and cortisol levels all increase in response to stress. Disorders of the adrenal cortex have been associated with mood disorders, PTSD, Alzheimer’s dementia, and substance use disorders.

Addison's disease is the result of hyposecretion of the hormones of the adrenal cortex. Behavioral symptoms of hyposecretion include mood changes with apathy, social withdrawal, impaired sleep, decreased concentration, and fatigue. Hypersecretion of cortisol results in Cushing's disease and is associated with behaviors that include depression, mania, psychosis, and suicidal ideation. Cognitive impairments also have been observed.

Prolactin

Prolactin is mainly involved in reproductive functions and milk production in the mammary glands during and after pregnancy. First generation antipsychotic medications increase prolactin levels and may be responsible for the undesired side effect of lactation. High prolactin levels are also associated with depression, decreased libido, anxiety, irritability, and the negative symptoms of schizophrenia. Prolactin levels in psychotic patients have been positively correlated with severity of tardive dyskinesia (Sadock et al., 2015).

Gonadotropic Hormones

The gonadotropic hormones are so called because they produce an effect on the gonads—the ovaries and the testes. The gonadotropins include follicle-stimulating hormone (FSH) and luteinizing hormone (LH). In women, FSH initiates maturation of ovarian follicles into ova and stimulates secretion of estrogen from follicular granulosa cells. LH is responsible for ovulation and the secretion of progesterone from the corpus luteum. In men, FSH initiates sperm production in the testes, and LH increases secretion of testosterone by the interstitial cells of the testes (Scanlon & Sanders, 2018).

Limited evidence exists to correlate gonadotropins to behavioral functioning, although some observations warrant hypothetical consideration. Studies have indicated decreased levels of testosterone, LH, and FSH in men who have depression. Increased sexual behavior and aggression have been linked to elevated testosterone levels in both men and women. Decreased plasma levels of LH and FSH commonly occur in patients with anorexia nervosa. Supplemental estrogen therapy has resulted in improved mentation and mood in some depressed women.

Melanocyte-Stimulating Hormone

Melanocyte-stimulating hormone (MSH) from the hypothalamus stimulates the pineal gland to secrete melatonin. The release of melatonin appears to depend on the onset of darkness and is suppressed by light. Studies of this hormone have indicated that environmental light can affect neuronal activity and influence circadian rhythms. Correlation between abnormal secretion of melatonin and symptoms of depression has led to the implication of melatonin

in the etiology of seasonal affective disorder, in which individuals become depressed only during the fall and winter months when the amount of daylight decreases.

Circadian Rhythms

Human biological rhythms are largely determined by genetic coding, with input from the external environment influencing the cyclic effects. **Circadian rhythms** in humans follow a near-24-hour cycle and may influence a variety of regulatory functions, including the sleep–wakefulness cycle, body temperature regulation, patterns of activity such as eating and drinking, and hormone secretion. The 24-hour rhythms in humans are affected to a large degree by the cycles of lightness and darkness. These rhythms occur because of a "pacemaker" in the brain that sends messages to other systems in the body and maintains the 24-hour rhythm. This endogenous pacemaker appears to be the suprachiasmatic nuclei of the hypothalamus. These nuclei receive projections of light through the retina and in turn stimulate electrical impulses to various other systems in the body, mediating the release of neurotransmitters or hormones that regulate bodily functioning.

Most of the biological rhythms of the body operate for approximately 24 hours, but cycles of longer lengths have been studied. For example, women of menstruating age have monthly cycles of variable progesterone levels.

Some rhythms may even last as long as a year. These circannual rhythms may influence the accuracy of some laboratory tests results and the effectiveness of some medications. Clinical studies have shown that administration of chemotherapy during the appropriate circadian phase and at the appropriate time of day can significantly increase the efficacy and decrease the toxic effects of certain cytotoxic agents (Garlapow, 2016; Lis et al., 2003).

The Role of Circadian Rhythms in Psychopathology

Circadian rhythms may play a role in psychopathology. Abnormal circadian rhythms have been associated with a variety of mental illnesses including depression, bipolar disorder, and seasonal affective disorder. Because many hormones have been implicated in behavioral functioning, it is reasonable to believe that peak secretion times could be influential in predicting certain behaviors. The association of depression with increased secretion of melatonin during darkness hours has already been discussed. External manipulation of the light–dark cycle and removal of external time cues often have beneficial effects on mood disorders.

Symptoms that occur premenstrually have been linked to disruptions in biological rhythms. A number of the symptoms associated with premenstrual

dysphoric disorder (PMDD) strongly resemble those attributed to depression, and hormonal changes have been implicated in the etiology. Some of these changes include progesterone–estrogen imbalance, increase in prolactin and mineralocorticoids, high level of prostaglandins, decrease in endogenous opiates, changes in metabolism of biogenic amines (serotonin, dopamine, norepinephrine, acetylcholine), and variations in secretion of glucocorticoids or melatonin.

The sleep–wakefulness cycle is probably the most fundamental of biological rhythms, and sleep disturbances are common in both depression and PMDD. Neurochemicals such as serotonin and norepinephrine appear to be most active during non–rapid eye movement (NREM) sleep, whereas the neurotransmitter acetylcholine is activated during REM sleep (Skudaev, 2019). Several studies have revealed information about the sleep-inducing characteristics of serotonin. L-tryptophan, the amino acid precursor to serotonin, has been used for many years as an effective sedative-hypnotic to induce sleep in individuals with sleep-onset disorder. A representation of bodily functions affected by 24-hour biological rhythms is presented in Figure 3-7.

Sleep

The sleep–wakefulness cycle is genetically determined rather than learned and is established after birth. Even when environmental cues, such as the ability to detect light and darkness, are removed, the human sleep–wakefulness cycle generally develops a periodicity of approximately 25 hours, which is close to the 24-hour normal circadian rhythm.

Sleep can be measured by the types of brain waves that occur during various stages of sleep activity. Dreaming episodes occur during REM sleep. The sleep–wakefulness cycle is represented by six distinct stages:

Stage 0—Alpha rhythm: This stage of the sleep–wakefulness cycle is characterized by a relaxed, waking state with eyes closed. The alpha brain wave rhythm has a frequency of 8 to 12 cycles per second.

Stage 1—Beta rhythm: Stage 1 characterizes the transition into sleep, a period of dozing in which thoughts wander and the person drifts in and out of sleep. Beta brain wave rhythm has a frequency of 18 to 25 cycles per second.

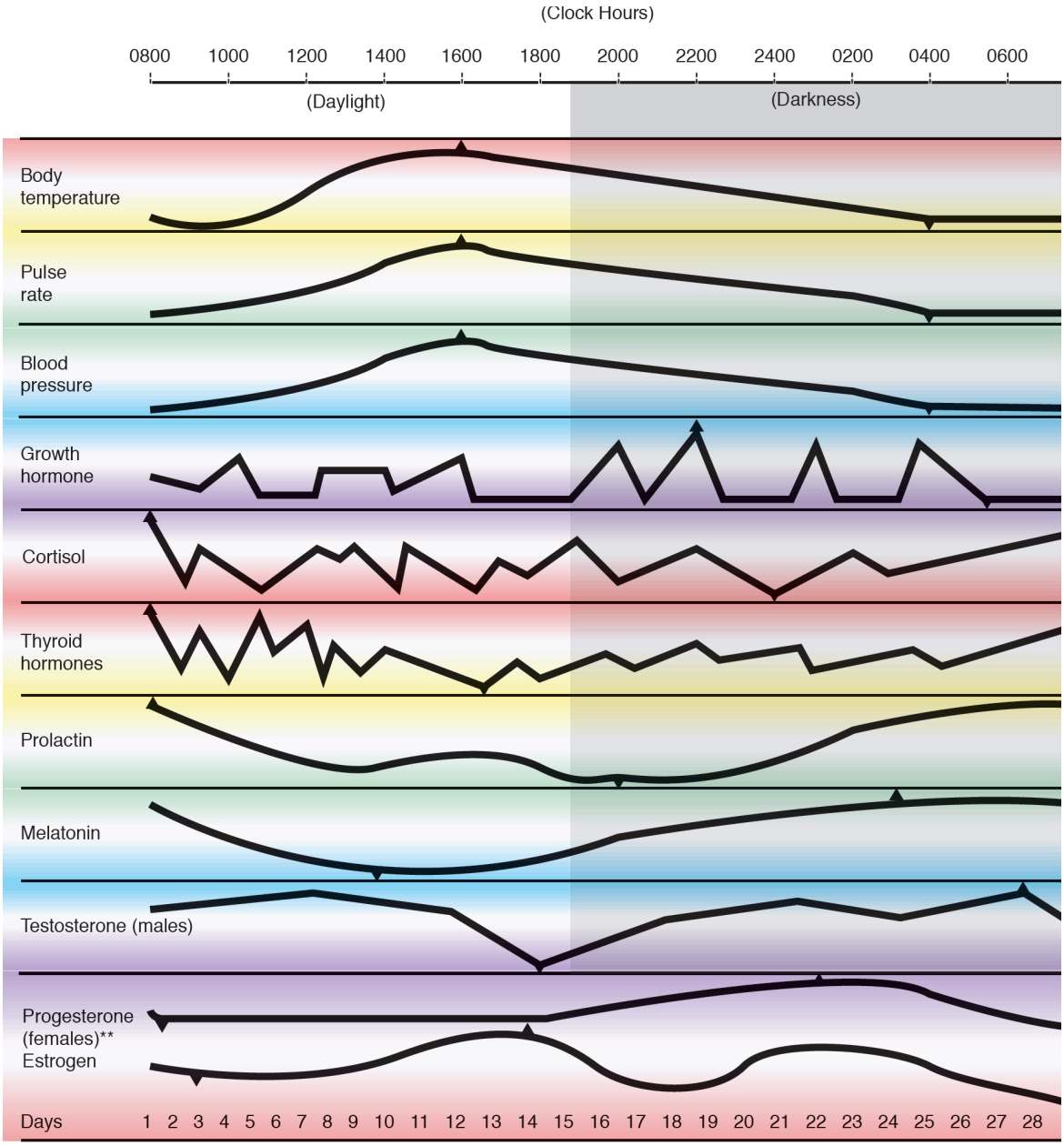
Stage 2—Theta rhythm: This stage comprises about one half of the time spent sleeping. Eye movement and muscular activity are minimal. Theta brain wave rhythm has a frequency of 4 to 7 cycles per second.

Stage 3—Delta rhythm: This is a period of deep and restful sleep. Muscles are relaxed, heart rate and blood pressure fall, and breathing slows. No eye

movement occurs. Delta brain wave rhythm has a frequency of 1.5 to 3 cycles per second.

Stage 4—Delta rhythm: This is the stage of deepest sleep. Individuals with insomnia or other sleep disorders often do not experience this stage of sleep. Eye movement and muscular activity are minimal. Delta waves predominate.

REM sleep—Beta rhythm: The dream cycle occurs during REM sleep. Eyes dart about beneath closed eyelids, moving more rapidly than when awake. The brain wave pattern is similar to that of stage 1 sleep. Heart and respiration rates increase, and blood pressure may increase or decrease. Muscles are hypotonic during REM sleep.



* ▼ indicates low point and ▲ indicates peak time of these biological factors within a 24-hour circadian rhythm.
** The female hormones are presented on a monthly rhythm because of their influence on the reproductive cycle. Daily rhythms of female gonadotropins are difficult to assay and are probably less significant than monthly.

FIGURE 3-7 Circadian biological rhythms.

Stages 2 through REM repeat throughout the cycle of sleep. One is more likely to experience longer periods of stages 3 and 4 sleep early in the cycle and longer periods of REM sleep later in the sleep cycle. Most people experience REM sleep about four to five times during the night. The amount of time spent in REM sleep and deep sleep decreases with age, and the time spent in drowsy wakefulness and dozing increases.

Neurochemical Influences

A number of neurochemicals have been shown to influence the sleep–wakefulness cycle. As noted previously, several studies have revealed information about the sleep-inducing characteristics of serotonin. L-Tryptophan, the amino acid precursor to serotonin, has been used for many years as an effective sedative-hypnotic to induce sleep in individuals with sleep-onset disorder. Serotonin and norepinephrine both appear to be most active during non-REM sleep, whereas the neurotransmitter acetylcholine is activated during REM sleep (Skudaev, 2019). The exact role of GABA in sleep facilitation is unclear, although the sedative effects of drugs that enhance GABA transmission, such as benzodiazepines, suggest that this neurotransmitter plays an important role in the regulation of sleep and arousal. Some studies have suggested that acetylcholine induces and prolongs REM sleep, whereas histamine appears to have an inhibitory effect.

CORE CONCEPT

Genetics
The study of the biological transmission of certain physical or behavioral characteristics from parent to offspring.

Genetics

Human behavioral genetics seeks to understand both the genetic and environmental contributions to individual variations in human behavior. This type of study is complicated by the fact that behaviors, like all complex traits, involve *multiple genes.*

The term **genotype** refers to the complete set of genes present in an individual and coded in the DNA at the time of conception. The physical manifestations of a particular genotype are designated by characteristics that specify a **phenotype.** Examples of phenotypes include eye color, height, blood type, the characteristics of one's voice, and hair type. As evident by the examples presented, phenotypes are not *only* genetic but may also be acquired (i.e., influenced by the environment) or a combination of both. It is likely that many psychiatric disorders are the result of a combination of genetics and environmental influences.

Investigators who study the causes and contributing factors for psychiatric illness explore several risk factors. Studies to determine whether an illness is *familial* compare the percentage of family members with the illness to those in the general population or within a control group of unrelated individuals. These

studies estimate the prevalence of psychopathology among relatives and predict predisposition to an illness based on familial risk factors. Schizophrenia, bipolar disorder, major depressive disorder, anorexia nervosa, panic disorder, somatic symptom disorder, antisocial personality disorder, and alcoholism are examples of psychiatric illnesses in which familial tendencies have been indicated.

Studies that focus only on genetics search for a specific gene that causes a particular illness. A number of disorders exist in which the mutation of a specific gene or change in the number or structure of chromosomes are associated with the etiology. Examples include Huntington's disease, cystic fibrosis, phenylketonuria, Duchenne's muscular dystrophy, and Down's syndrome.

The search for genetic links to certain psychiatric disorders continues. Risk factors for early-onset Alzheimer's disease have been linked to mutations on chromosomes 21, 14, and 1 (National Institute on Aging, 2015). Other studies have linked a gene in the region of chromosome 19 that produces apolipoprotein E (ApoE) with late-onset Alzheimer's disease. One large study (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013) found similar genetic variations in patients with five mental disorders that were previously considered completely distinct. Autism, attention deficit-hyperactivity disorder (ADHD), bipolar disorder, major depression, and schizophrenia all showed some common gene variations, including differences in two genes that regulate the flow of calcium into cells. Although these findings are intriguing, they do not clearly explain all the genetic risks for mental illness, the nongenetic risks, or the interaction between the two. Future research will continue to search for answers with the ultimate goal of improving diagnosis and treatment and perhaps uncovering keys to prevention of mental illness. In addition to familial and purely genetic investigations, other types of studies have been conducted to estimate the existence and degree of genetic and environmental contributions to the etiology of certain psychiatric disorders. Twin studies and adoption studies have been successfully employed for this purpose.

Twin studies examine the frequency of a disorder in monozygotic (genetically identical) and dizygotic (not genetically identical) twins. Twins are called *concordant* when both members have the disorder in question. Concordance in monozygotic twins is considered stronger evidence of genetic involvement than it is in dizygotic (fraternal) twins. Twin studies have supported genetic vulnerability in the etiology of several mental illnesses, including adjustment disorders, PTSD, substance abuse, schizophrenia, bipolar disorder, major depression, obsessive-compulsive disorder, suicidal ideation, and others (Sadock et al., 2015).

Adoption studies allow researchers to compare the influence of genetics versus environment on the development of a psychiatric disorder. Adoption studies include the following four types:

1. Adopted children whose biological parent(s) had a psychiatric disorder but whose adoptive parent(s) did not.
2. Adopted children whose adoptive parent(s) had a psychiatric disorder but whose biological parent(s) did not.
3. Adoptive and biological relatives of adopted children who developed a psychiatric disorder.
4. Monozygotic twins reared apart by different adoptive parents.

Disorders in which adoption studies have suggested a possible genetic link include alcoholism, schizophrenia, major depression, bipolar disorder, suicidality, ADHD, and antisocial personality disorder (Sadock et al., 2015).

Various psychiatric disorders and the possible biological influences discussed in this chapter are presented in Table 3–4. Diagnostic procedures used to detect alteration in biological functioning that may contribute to psychiatric disorders are presented in Table 3–5.

CORE CONCEPT

Psychoneuroimmunology
The study of the relationship between the immune system, the nervous system, and psychological processes such as thinking and behavior.

Psychoneuroimmunology

Normal Immune Response

Cells responsible for *nonspecific* immune reactions include neutrophils, monocytes, and macrophages. They work to destroy invasive organisms and initiate and facilitate the healing of damaged tissue. If these cells do not accomplish a satisfactory healing response, *specific* immune mechanisms take over.

Cytokines are one such mechanism. These molecules, which regulate immune and inflammatory responses, become active when an individual is fighting an infection or any other condition that creates inflammation in the body. Recent research has also demonstrated that cytokines are active in mood disorders such as depression and bipolar disorder. Current research focuses on the impact of cytokines as part of an essential and complex system of responses that are crucial for reducing inflammation and bolstering the immune response. Studies are also attempting to identify what happens when

inflammation is not resolved and cytokines remain active or cross the blood–brain barrier. There is evidence that these maladaptations may be implicated in a multitude of illnesses (Ratnayake et al., 2013).

TABLE 3–4 **Biological Implications of Psychiatric Disorders**

ANATOMICAL BRAIN STRUCTURES INVOLVED	NEUROTRANSMITTER HYPOTHESIS	POSSIBLE ENDOCRINE CORRELATION	IMPLICATIONS OF CIRCADIAN RHYTHMS	POSSIBLE GENETIC LINK
SCHIZOPHRENIA				
Frontal cortex, temporal lobes, limbic system	Dopamine hyperactivity; decreased glutamate	Decreased prolactin levels	May correlate antipsychotic medication administration to times of lowest level	Twin, familial, and adoption studies suggest genetic link
DEPRESSIVE DISORDERS				
Frontal lobes, limbic system, temporal lobes	Decreased levels of norepinephrine, dopamine, and serotonin; increased glutamate	Increased cortisol levels; thyroid hormone hyposecretion; increased melatonin	DST* used to predict effectiveness of antidepressants; melatonin linked to depression during periods of darkness	Twin, familial, and adoption studies suggest a genetic link
BIPOLAR				
DISORDER Frontal lobes, limbic system, temporal lobes	Increased levels of norepinephrine and dopamine in acute mania	Some indication of elevated thyroid hormones in acute mania	Abnormal circadian rhythms have been associated with bipolar disorder	Twin, familial, and adoption studies suggest a genetic link
PANIC DISORDER				
Limbic system, midbrain	Increased levels of norepinephrine; decreased GABA activity	Elevated levels of thyroid hormones	May have some application for times of medication administration	Twin and familial studies suggest a genetic link
ANOREXIA NERVOSA				
Limbic system, particularly the hypothalamus	Decreased levels of norepinephrine, serotonin, and dopamine	Decreased levels of gonadotropins and growth hormone; increased cortisol levels	DST often shows same results as in depression	Twin and familial studies suggest a genetic link
OBSESSIVE-COMPULSIVE DISORDER				
Limbic system,	Decreased levels of	Increased	DST often	Twin studies

basal ganglia (specifically caudate nucleus)	serotonin	cortisol levels	shows same results as in depression	suggest a possible genetic link
ALZHEIMER'S DISEASE				
Temporal, parietal, and occipital regions of cerebral cortex; hippocampus	Decreased levels of acetylcholine, norepinephrine, serotonin, and somatostatin	Decreased corticotropin-releasing hormone	Decreased levels of acetylcholine and serotonin may inhibit hypothalamic-pituitary axis and interfere with hormonal releasing factors	Familial studies suggest a genetic predisposition; late-onset disorder linked to marker on chromosome 19; early-onset disorder linked to chromosomes 21, 14, and 1

*DST, dexamethasone suppression test. Dexamethasone is a synthetic glucocorticoid that suppresses cortisol secretion via the feedback mechanism. In this test, 1 mg of dexamethasone is administered at 11:30 p.m., and blood samples are drawn at 8:00 a.m., 4:00 p.m., and 11:00 p.m. on the following day. A plasma value greater than 5 mcg/dL suggests that the individual is not suppressing cortisol in response to the dose of dexamethasone. This is a positive result for depression and may have implications for other disorders as well. GABA, gamma-Aminobutyric acid.

TABLE 3–5 Diagnostic Procedures Used to Detect Altered Brain Functioning

EXAMINATION	TECHNIQUE USED	PURPOSE AND POSSIBLE FINDINGS
Electroencephalography (EEG)	Electrodes are placed on the scalp in a standardized position. Amplitude and frequency of beta, alpha, theta, and delta brain waves are graphically recorded on paper by ink markers for multiple areas of the brain surface.	Measures brain electrical activity; identifies dysrhythmias, asymmetries, or suppression of brain rhythms; used in the diagnosis of epilepsy, neoplasm, stroke, metabolic, or degenerative disease.
Computerized EEG mapping	EEG tracings are summarized by computer-assisted systems in which various regions of the brain are identified and functioning is interpreted by color coding or gray shading.	Measures brain electrical activity; used largely in research to represent statistical relationships between individuals and groups or between two populations of subjects (e.g., patients with schizophrenia vs. control subjects).
Computed tomography (CT) scan	CT scan may be used with or without contrast medium. X-rays are taken of various transverse planes of the brain while a computerized analysis produces a precise reconstructed image of each segment.	Measures accuracy of brain structure to detect possible lesions, abscesses, areas of infarction, or aneurysm. CT has also identified various anatomical differences in patients with schizophrenia, organic mental disorders, and bipolar disorder.
Magnetic resonance imaging (MRI)	Within a strong magnetic field, the nuclei of hydrogen atoms absorb and reemit electromagnetic energy that is computerized and transformed into image information. No radiation or contrast medium is used.	Measures anatomical and biochemical status of various segments of the brain; detects brain edema, ischemia, infection, neoplasm, trauma, and other changes such as demyelination. Morphological differences have been noted in brains of patients with schizophrenia compared with control subjects.
Positron emission tomography (PET)	The patient receives an intravenous (IV) injection of a radioactive substance (type depends on brain activity to	Measures specific brain functioning, such as glucose metabolism, oxygen utilization, blood flow, and, of

	be visualized). The head is surrounded by detectors that relay data to a computer that interprets the signals and produces the image.	particular interest in psychiatry, neurotransmitter-receptor interaction.
Single-photon emission computed tomography (SPECT)	The technique is similar to PET, but longer-acting radioactive substance must be used to allow time for a gamma-camera to rotate about the head and gather the data, which are then computer assembled into a brain image.	Measures various aspects of brain functioning, as with PET; has also been used to image activity of cerebrospinal fluid circulation.

Implications of the Immune System in Psychiatric Illness

Studies of the biological response to stress have hypothesized that individuals become more susceptible to physical illness following exposure to a stressful stimulus or life event (see Chapter 1, “The Concept of Stress Adaptation”). This response is thought to be caused by increased glucocorticoid release from the adrenal cortex following stimulation from the hypothalamic-pituitary-adrenal axis during stressful situations (“axis” refers to the complex interactions between these three glands). The result is suppression of lymphocyte proliferation and function.

Studies have shown that nerve endings exist in tissues of the immune system. The CNS has connections in both bone marrow and the thymus, where immune system cells are produced, and in the spleen and lymph nodes, where those cells are stored.

GH, which may be released in response to certain stressors, may enhance immune functioning, whereas testosterone is thought to inhibit immune functioning. Increased production of epinephrine and norepinephrine occurs in response to stress and may decrease immunity. Serotonin has been described as an immunomodulator because it has demonstrated both stimulatory and inhibitory effects on inflammation and immunity (Arreola et al., 2015).

Studies have correlated a decrease in lymphocyte function with periods of grief, bereavement, and depression, associating the degree of altered immunity with the severity of depression. Several research studies have attempted to correlate the onset of schizophrenia with abnormalities of the immune system. These studies have considered autoimmune responses, viral infections, and immunogenetics (Sadock et al., 2015). A link has been identified between toxoplasmosis and psychiatric disorders such as

schizophrenia, bipolar disorder, and suicidal/aggressive behaviors (Del Grande et al., 2017). *Toxoplasma gondii,* the parasite responsible for toxoplasmosis, has an affinity for brain tissue where it causes brain inflammation and may affect neurotransmitters such as dopamine. Immunological abnormalities have also been investigated in other psychiatric illnesses, including alcoholism, autism spectrum disorder, and neurocognitive disorder.

Evidence exists to support a correlation between psychosocial stress and the onset of illness. More research is needed to determine the specific processes involved in stress-induced modulation of the immune system.

Psychopharmacology and the Brain

Understanding the brain and the biological processes involved in thoughts, feelings, and behavior has positive ramifications beyond better understanding of psychopharmacological treatment options. As mentioned earlier, future research may continue to demonstrate the impact of psychological interventions on brain activity and neurotransmitters, which would open opportunities to hone psychological treatments and avoid the troubling side effects that accompany many medications. Furthermore, continued research in areas such as psychoneuroimmunology may reveal causes of mental illness, which would provide the opportunity for primary prevention.

In spite of these opportunities, psychopharmacology remains a primary treatment modality for mental disorders. Current evidence suggests that early medication treatment of schizophrenia at the first signs of psychosis may prevent the damaging effects of multiple psychotic episodes on the brain (Nasrallah, 2018). Understanding, as best we can with current evidence, the biological mechanisms at work in psychoactive drugs is essential to nursing practice. Figure 3-8 shows the biological mechanism of psychoactive drugs at the neural synapse. Psychopharmacology, the classes of psychoactive drugs, and relevant nursing implications are discussed in detail in Chapter 4, “Psychopharmacology.”

Implications for Nursing

Psychiatric nurses must integrate knowledge of the biological sciences into their practices if they are to ensure safe and effective care to people with mental illness. Much progress has been made in understanding the biochemical, neuroanatomical, and genetic influences in mental illness, but much remains theoretical. Further, there is evidence that psychosocial influences, particularly a history of trauma such as abuse and neglect, interact

significantly with an individual's biological vulnerabilities in the development of these illnesses.

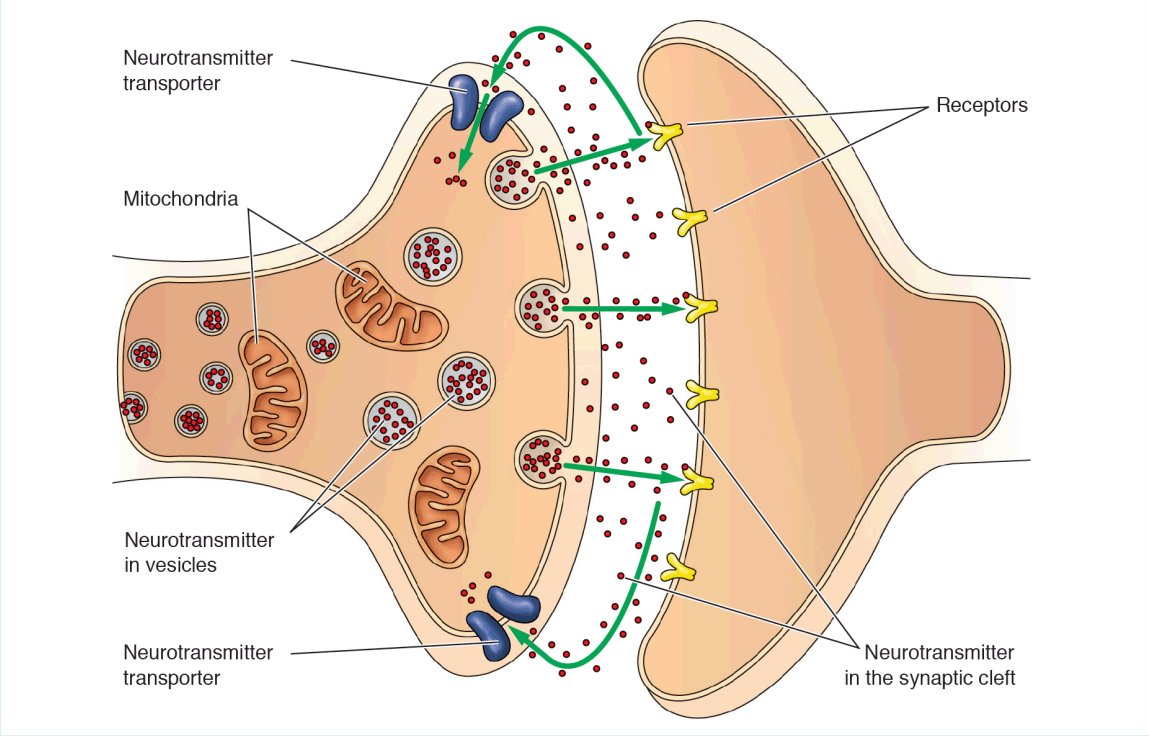


FIGURE 3-8 Area of synaptic transmission that is altered by drugs. The transmission of electrical impulses from the axon terminal of one neuron to the dendrite of another is achieved by the controlled release of neurotransmitters into the synaptic cleft. Neurotransmitters include serotonin, norepinephrine, acetylcholine, dopamine, glutamate, gamma-aminobutyric acid (GABA), and histamine, among others. Before its release, the neurotransmitter is concentrated into specialized synaptic vesicles. Once fired, the neurotransmitter is released into the synaptic cleft where it encounters receptors on the postsynaptic membrane. Each neurotransmitter has receptors specific to it alone. Some neurotransmitters are considered to be *excitatory,* whereas others are *inhibitory,* a feature that determines whether another action potential will occur. In the synaptic cleft, the neurotransmitter rapidly diffuses, is catabolized by enzymatic action, or is taken up by the neurotransmitter transporters and returned to vesicles inside the axon terminal to await another action potential.

Psychotropic medications exert their effects in various ways in this area of synaptic transmission. Reuptake inhibitors block *reuptake* of the neurotransmitters by the transporter proteins, resulting in elevated levels of

extracellular neurotransmitter. Drugs that inhibit catabolic enzymes promote excess buildup of the neurotransmitter at the synaptic site.

Some drugs cause *receptor blockade,* resulting in a reduction in transmission and decreased neurotransmitter activity. These drugs are called *antagonists.* Drugs that increase neurotransmitter activity by *direct stimulation* of the specific receptors are called *agonists.*

To ensure a smooth transition from a strictly psychosocial focus to one of *bio*psychosocial emphasis, nurses must have a clear understanding of the following:

- **Neuroanatomy and neurophysiology:** The structure and functioning of the various parts of the brain and their correlation to human behavior and psychopathology
- **Neuronal processes:** The various functions of the nerve cells, including the role of neurotransmitters, receptors, synaptic activity, and information pathways
- **Neuroendocrinology:** The interaction of the endocrine and nervous systems and the role that the endocrine glands and their respective hormones play in behavioral functioning
- **Circadian rhythms:** The regulation of biochemical functioning over periods of rhythmic cycles and its influence in predicting certain behaviors
- **Genetic influences:** The hereditary factors that predispose individuals to certain psychiatric disorders
- **Psychoneuroimmunology:** The influence of stress on the immune system and its role in the susceptibility to illness
- **Psychopharmacology:** The increasing use of psychotropic drugs in the treatment of mental illness, demanding greater knowledge of psychopharmacological principles and nursing interventions necessary for safe and effective management
- **Diagnostic technology:** The imaging and other technological procedures for identifying alterations in brain structure and function associated with mental illness

Why are these concepts important to the practice of psychiatric-mental health nursing? The interrelationship between psychosocial adaptation and physical functioning has been established. Integrating biological and behavioral concepts into psychiatric nursing practice is essential for nurses to meet the complex needs of patients with mental illness. Psychobiological perspectives must be incorporated into nursing practice, education, and research to attain the evidence-based outcomes necessary for the delivery of competent care.

Summary and Key Points

- It is important for nurses to understand the interaction between biological and behavioral factors in the development and management of mental illness.
- Psychobiology is the study of the biological foundations of cognitive, emotional, and behavioral processes.
- The limbic system has been called the “emotional brain.” It is associated with feelings of fear and anxiety; anger, rage, and aggression; love, joy, and hope; and with sexuality and social behavior.
- The three classes of neurons are afferent (sensory) neurons, efferent (motor) neurons, and interneurons. The junction between two neurons is called a *synapse.*
- Neurotransmitters are chemicals that convey information across synaptic clefts to neighboring target cells. Many neurotransmitters have implications in the etiology of emotional disorders and in the pharmacological treatment of those disorders.
- Major categories of neurotransmitters include cholinergics, monoamines, amino acids, and neuropeptides.
- The endocrine system plays an important role in human behavior through the hypothalamic-pituitary axis.
- Hormones and their circadian rhythms of regulation significantly influence a number of physiological and psychological life cycle phenomena, such as moods, sleep and arousal, stress response, appetite, libido, and fertility.
- Research continues to validate the role of genetics in psychiatric illness.
- Familial, twin, and adoption studies suggest that genetics may be implicated in the etiology of schizophrenia, bipolar disorder, depressive disorder, panic disorder, anorexia nervosa, alcoholism, and obsessive-compulsive disorder. Genetic studies, however, fail to entirely explain the complex factors involved in the development of these illnesses.
- Psychoneuroimmunology examines the relationship between psychological factors, the immune system, and the nervous system.
- Evidence exists to support a link between psychosocial stressors and suppression of the immune response.
- Technologies such as magnetic resonance imaging, computed tomography, positron emission tomography, and electroencephalography are used as diagnostic tools for detecting alterations in psychobiological functioning.
- Psychotropic medications act at the neural synapse to affect neurotransmitter activity and have been associated with improvement in symptoms of many mental disorders.

- Integrating knowledge of the expanding biological focus into psychiatric nursing is essential if nurses are to meet the changing needs of today's psychiatric clients.

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Review Questions

1. Which of the following parts of the brain is associated with multiple feelings and behaviors and is sometimes referred to as the "emotional brain"?
   a. Frontal lobe
   b. Thalamus
   c. Hypothalamus
   d. Limbic system
2. Which of the following parts of the brain is concerned with visual reception and interpretation?
   a. Frontal lobe
   b. Parietal lobe
   c. Temporal lobe
   d. Occipital lobe
3. Which of the following parts of the brain is associated with voluntary body movement, thinking and judgment, and expression of feeling?
   a. Frontal lobe
   b. Parietal lobe
   c. Temporal lobe
   d. Occipital lobe
4. Which of the following parts of the brain integrates all sensory input (except smell) on the way to the cortex?
   a. Temporal lobe
   b. Thalamus
   c. Limbic system
   d. Hypothalamus
5. Which of the following parts of the brain deals with sensory perception and interpretation?
   a. Hypothalamus
   b. Cerebellum
   c. Parietal lobe
   d. Hippocampus

6. Which of the following parts of the brain is concerned with hearing, short-term memory, and sense of smell?
   a. Temporal lobe
   b. Parietal lobe
   c. Cerebellum
   d. Hypothalamus

7. Which of the following parts of the brain has control over the pituitary gland and autonomic nervous system, as well as regulation of appetite and temperature?
   a. Temporal lobe
   b. Parietal lobe
   c. Cerebellum
   d. Hypothalamus

8. At a synapse, the determination of further impulse transmission is accomplished by means of which of the following?
   a. Potassium ions
   b. Interneurons
   c. Neurotransmitters
   d. The myelin sheath

9. A decrease in which of the following neurotransmitters has been implicated in depression?
   a. Gamma-aminobutyric acid, acetylcholine, and aspartate
   b. Norepinephrine, serotonin, and dopamine
   c. Somatostatin, substance P, and glycine
   d. Glutamate, histamine, and opioid peptides

10. Which of the following hormones has been implicated in the etiology of mood disorder with seasonal affective disorder?
   a. Increased levels of melatonin
   b. Decreased levels of oxytocin
   c. Decreased levels of prolactin
   d. Increased levels of thyrotropin

11. Psychotropic medications may act at the neural synapse to accomplish which of the following? (Select all that apply.)
   a. Inhibit the reuptake of certain neurotransmitters, creating more availability
   b. Inhibit catabolic enzymes, promoting more availability of a neurotransmitter
   c. Block receptors, resulting in less neurotransmitter activity
   d. Add synthetic neurotransmitters found in the drug

12. Psychoneuroimmunology is a branch of science that involves which of the following? (Select all that apply.)

a. The impact of psychoactive medications at the neural synapse
b. The relationships between the immune system, the nervous system, and psychological processes including mental illness
c. The correlation between psychosocial stress and the onset of illness
d. The potential role of viruses in the onset of schizophrenia
e. The genetic factors that influence the prevention of mental illness

References

Arreola, R., Becerril-Villanueva, E., Cruz-Fuentes, C., Velasco-Velázquez, M.A., Garcés-Alvarez, M.E., Hurtado-Alvarado, G., … Pavón, L. (2015). Immunomodulatory effects mediated by serotonin. *Journal of Immunology Research.* doi:http://dx.doi.org/10.1155/2015/354957

Cacabelos, R., Torrellas, C., Fernandez-Novoa, L., & Lopez-Munoz, F. (2016). Histamine and immune biomarkers in CNS disorders. *Mediators of Inflammation,* 2016, 1924603. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4846752/

Carmichael, C.Y., & Wainford, R.D. (2015). Hypothalamic signaling mechanisms in hypertension. *Current Hypertension Reports, 17*(5), 39. doi:10.1007/s11906-015-0550-4

Collerton, D. (2013). Psychotherapy and brain plasticity. *Frontiers in Psychology, 4,* 548. doi:10.3389/fpsyg.2013.00548

Coyle, J.T. (2017). Amino acid neurotransmitters. In B.J. Sadock, V.A. Sadock, & P. Ruiz (Eds.), *Comprehensive textbook of psychiatry* (10th ed., pp. 76-84). Philadelphia, PA: Wolters Kluwer.

Cross-Disorder Group of the Psychiatric Genomics Consortium. (2013). Identification of risk loci with shared effects on five major psychiatric disorders: A genome-wide analysis. *Lancet, 381*(9875), 1371-1379. doi:10.1016/S0140-6736(12)62129-1

Del Grande, C., Galli, L., Schiavi, E., Dell'Osso, L., & Bruschi, F. (2017). Is *Toxoplasma gondii* a trigger of bipolar disorder? *Pathogens, 6*(3), 1-20. doi:10.3390/pathogens6010003

Elsworth, J.D., & Roth, R.H. (2017). Biogenic amine transmitters. In B.J. Sadock, V.A. Sadock, & P. Ruiz (Eds.), *Comprehensive textbook of psychiatry* (10th ed., pp. 61-75). Philadelphia, PA: Wolters Kluwer.

Flor, H. (2014). Psychological pain interventions and neurophysiology: Implications for a mechanism-based approach. *American Psychologist, 69*(2), 188-196. doi:http://dx.doi.org/10.1037/a0035254

Garlapow, M. (2016). Timing chemotherapy administration to circadian rhythm improves drug effectiveness. *Oncology Nurse Advisor.* Retrieved from www.oncologynurseadvisor.com/side-effect-management/chemotherapy-more-effective-when-synced-with-circadian-rhythm/article/504455

Gill, M., & McCauley, M. (2015). Psychogenic polydipsia: The result, or cause of, deteriorating psychotic symptoms? A case report of the consequences of water intoxication. *Case Reports in Psychiatry.* doi:10.1155/2015/846459

Harris, D.S., Wolkowitz, M.D., & Reus, V.I. (2017). Psychoneu-roendocrinology. In B.J. Sadock, V.A. Sadock, & P. Ruiz (Eds.), *Comprehensive textbook of psychiatry* (10th ed., pp. 164-178). Philadelphia, PA: Wolters Kluwer.

Lis, C.G., Grutsch, J.F., Wood, P., You, M., Rich, I., & Hrushesky, W.J. (2003). Circadian timing in cancer treatment: The biological foundation for an integrative approach. *Integrative Cancer Therapies, 2*(2), 105-111. doi:10.1177/1534735403253766

Lyall, A.E., Kubicki, M., & Shenton, M.E. (2017). Structural brain imaging in schizophrenia. In B.J. Sadock, V.A. Sadock, & P. Ruiz (Eds.), *Comprehensive textbook of psychiatry* (10th ed., pp. 1463-1475). Philadelphia, PA: Wolters Kluwer.

Mason, L., Peters, E., Williams, S.C., & Kumari, V. (2017). Brain connectivity changes occurring following cognitive behavioural therapy for psychosis predict long-term recovery. *Translational Psychiatry, 7*(1), e1001. doi:10.1038/tp.2016.263

Moore, R.Y. (2019). Clinical update—circadian rhythms, hypothalamus, and regulation of the sleep-wake cycle. Retrieved from https://www.medscape.org/viewarticle/491041

Nasrallah, H.A. (2018). Preventing brain damage in psychosis. *Current Psychiatry, 17*(10), 9-10. Retrieved from https://www.mdedge.com/psychiatry/article/175767/schizophrenia-other-psychotic-disorders/page/0/1

National Institute of Mental Health (NIMH). (No date.) *Brain basics.* Retrieved from https https://www.nimh.nih.gov/brainbasics/index.html

National Institute on Aging. (2015). Alzheimer's disease genetics. The Alzheimer's Disease Education and Referral Center. Retrieved from www.nia.nih.gov/alzheimers/publication/alzheimers-disease-genetics-fact-sheet

National Institutes of Health (NIH). (2018). Is there a link between marijuana use and mental illness? Retrieved from www.drugabuse.gov/publications/research-reports/marijuana/there-link-between-marijuana-use-mental-illness

Ratnayake, U., Quinn, T., Walker, D.W., & Dickinson, H. (2013). Cytokines and the neurodevelopmental basis of mental illness. *Frontiers of Neuroscience, 7.* doi:10.3389/fnins.2013.00180

Sadock, B.J., Sadock, V.A., & Ruiz, P. (2015). *Synopsis of psychiatry: Behavioral sciences/clinical psychiatry* (11th ed.). Philadelphia, PA: Lippincott Williams & Wilkins.

Scanlon, V.C., & Sanders, T. (2018). *Essentials of anatomy and physiology* (8th ed.). Philadelphia: F.A. Davis.

Skudaev, S. (2019). The neurophysiology and neurochemistry of sleep (review). Retrieved from https://www.scribd.com/document/25882706/1022170-Neurophysiology-and-Neurochemistry-of-Sleep

Van Hove, J., Coughlin, C., & Sharer, G. (2013). Glycine encephalopathy. *GeneReviews.* National Library of Medicine. Retrieved from www.ncbi.nlm.nih.gov/books/NBK1357

4 Psychopharmacology

CORE CONCEPTS

Neurotransmitter

Psychotropic medication

Receptor

CHAPTER OUTLINE

Objectives
Homework Assignment
Historical Perspectives
The Role of the Nurse in Psychopharmacology
How Do Psychotropic Medications Work?
Applying the Nursing Process in Psychopharmacological Therapy
Summary and Key Points
Review Questions
Clinical Judgment Questions

KEY TERMS

agranulocytosis
akathisia
akinesia
amenorrhea
dystonia
extrapyramidal symptoms
galactorrhea
gynecomastia
hypertensive crisis
neuroleptic malignant syndrome
oculogyric crisis
priapism
retrograde ejaculation
serotonin syndrome
tardive dyskinesia

OBJECTIVES

After reading this chapter, the student will be able to:

1. Discuss historical perspectives related to psychopharmacology.
2. Describe indications, actions, contraindications, precautions, side effects, and nursing implications for the following classifications of drugs:
   a. Antianxiety agents
   b. Antidepressants
   c. Mood-stabilizing agents
   d. Antipsychotics and agents for the treatment of tardive dyskinesia
   e. Antiparkinsonian agents
   f. Sedative-hypnotics
   g. Agents for attention deficit-hyperactivity disorder
3. Apply the steps of the nursing process to the administration of psychotropic medications.

HOMEWORK ASSIGNMENT

Please read the chapter and answer the following questions:

1. Identify three priority safety concerns for each class of psychotropic medications.
2. Differentiate primary actions and side effects for traditional versus atypical antipsychotics.
3. Differentiate primary actions and side effects for tricyclic versus SSRI antidepressants.

The middle of the 20th century was a pivotal period in the treatment of individuals with mental illness with the introduction of the phenothiazine class of antipsychotics in the United States. They were previously used in France as preoperative medications. As Dr. Henri Laborit (1914–1995) of the Hospital Boucicaut in Paris stated,

> It was our aim to decrease the anxiety of the patients to prepare them in advance for their postoperative recovery. With these new drugs, the phenothiazines, we were seeing a profound psychic and physical relaxation … a real indifference to the environment and to the upcoming operation. It seemed to me these drugs must have an application in psychiatry. (Sage, 1984)

As Laborit foresaw, phenothiazines have had a significant application in psychiatry. Not only have they helped many individuals to function effectively, but they have also provided researchers and clinicians with information to study the origins and etiologies of mental illness. Knowledge gained from learning how these drugs work has promoted advancement in understanding how behavioral disorders develop. Dr. Arnold Scheibel, director of the UCLA Brain Research Institute, stated,

> [When these drugs came out] there was a sense of disbelief that we could actually do something substantive for the patients … see them for the first time as sick individuals and not as something bizarre that we could literally not talk to. (Sage, 1984)

This chapter explores historical perspectives in the use of psychotropic medications in the treatment of mental illness. Seven classifications of medications are discussed, and their implications for psychiatric nursing are presented in the context of the steps of the nursing process.

CORE CONCEPT

Psychotropic Medication
Medication that affects psychic function, behavior, or experience.

Historical Perspectives

Historically, reaction to and treatment of individuals with mental illness have ranged from benign involvement to interventions that some would consider inhumane. Individuals with mental illness were feared because of common beliefs associating them with demons or the supernatural. They were looked upon as loathsome and often were mistreated.

Beginning in the late 18th century, a type of moral reform in the treatment of persons with mental illness began to occur. Community and state hospitals concerned with the needs of persons with mental illness were established. Considered a breakthrough in the humanization of care, these institutions, however well intentioned, fostered the concept of custodial care. Clients were ensured food and shelter but received little or no hope of change for the future. As they became increasingly dependent on the institution to fulfill their needs, the likelihood of their return to the family or community diminished.

The early part of the 20th century saw the advent of somatic therapies in psychiatry. Individuals with mental illness were treated with insulin-shock therapy, wet sheet packs, ice baths, electroconvulsive therapy, and psychosurgery. Before 1950, sedatives and amphetamines were the only significant psychotropic medications available. Even these drugs had limited use because of their toxicity and addictive effects. Since the 1950s, the development

of psychopharmacology has expanded to include widespread use of antipsychotic, antidepressant, antianxiety, and mood-stabilizer medications. Research into how these drugs work has provided an understanding of the biochemical influences in many psychiatric disorders.

Psychotropic medications are not a cure for mental illness. Most mental health practitioners who prescribe these medications for their clients use them as an adjunct to individual or group psychotherapy. Although their contribution to psychiatric care cannot be minimized, it must be emphasized that psychotropic medications relieve some physical and behavioral symptoms. They do not eliminate mental disorders.

The Role of the Nurse in Psychopharmacology

Ethical and Legal Implications

Nurses must understand the ethical and legal implications associated with the administration of psychotropic medications. Laws differ from state to state, but most adhere to the patient's right to refuse treatment. Exceptions exist in emergency situations when it has been determined that patients are likely to harm themselves or others. Many states have adopted laws that allow courts to order outpatient treatment, which may include medication, in circumstances where an individual is not seeking treatment and has a history of violent, aggressive behavior. The original law, called Kendra's law, was enacted after a young woman named Kendra Webdale was pushed in front of a New York City subway train by a man who lived in the community but was not seeking treatment for his mental illness (New York State Office of Mental Health, 2012). This law is perhaps more developed than those in other states but also includes a medication grant clause that provides uninterrupted medication for those transitioning from hospitals or correctional facilities. Some states do not have similar laws, so nurses must be informed about local, state, and federal laws when working in any

health-care setting or correctional facility and providing care to a patient with a psychiatric disorder.

Assessment

A thorough baseline assessment must be conducted before a patient is placed on a regimen of psychopharmacological therapy. A nursing history and assessment (see Chapter 8, “The Nursing Process in Psychiatric-Mental Health Nursing”), an ethnocultural assessment, and a comprehensive medication assessment (see Box 4-1) are all essential components of this database. The ethnocultural assessment is necessary because genetic variations in selected populations and cultural factors, including dietary preferences, may influence response to some medications; CYP450 isoenzyme variations, for example, influence metabolism of some medications and pharmacogenetic testing may be ordered to identify individuals at risk for being poor metabolizers of certain medications (see Table 4–1 for degrees of risk for poor metabolism of selected medications).

Medication Administration and Evaluation

The nurse is the key health-care professional in direct contact with individuals receiving psychotropic medication in inpatient settings, in partial hospitalization programs, day treatment centers, home health care, and other settings. Medication administration is followed by a careful evaluation, which includes continuous monitoring for side effects and adverse reactions. The nurse also evaluates the therapeutic effectiveness of the medication. It is essential for the nurse to have a thorough knowledge of psychotropic medications to be able to anticipate potential problems and outcomes associated with their administration.

BOX 4–1 **Medication Assessment Tool**

Date _____ Patient's Name _____ Age _____
Marital Status _____ Children _____ Occupation _____
Presenting Symptoms (subjective & objective) _____

_____

Diagnosis (DSM-5) _____
Current Vital Signs: Blood Pressure: Sitting _____/_____; Standing _____/_____; Pulse _____ ;
Respirations _____ Height _____ Weight _____

CURRENT/PAST USE OF PRESCRIPTION DRUGS (Indicate with "c" or "p" beside name of drug whether current or past use):

Name	Dosage	How Long Used	Why Prescribed	By Whom	Side Effects/Results

CURRENT/PAST USE OF OVER-THE-COUNTER DRUGS (Indicate with "c" or "p" beside name of drug whether current or past use):

Name	Dosage	How Long Used	Why Prescribed	By Whom	Side Effects/Results

CURRENT/PAST USE OF STREET DRUGS, ALCOHOL, NICOTINE, OR CAFFEINE (Indicate with "c" or "p" beside name of drug):

Name	Amount Used	How Often Used	When Last Used	Effects Produced

Any allergies to food or drugs? _____
Any special diet considerations? _____
Do you have (or have you ever had) any of the following? If yes, provide explanation on the back of this sheet.

	Yes	No		Yes	No		Yes	No
Difficulty swallowing	___	___	Chest pain	___	___	Sexual dysfunction	___	___
Delayed wound healing	___	___	Blood clots/pain in legs	___	___	Lumps in your breasts	___	___
Constipation problems	___	___	Fainting spells	___	___	Blurred or double vision	___	___
Urination problems	___	___	Swollen ankles/legs/hands	___	___	Ringing in the ears	___	___
Recent change in			Asthma	___	___	Insomnia	___	___
elimination patterns	___	___	Varicose veins	___	___	Skin rashes	___	___
Weakness or tremors	___	___	Numbness/tingling			Diabetes	___	___
Seizures	___	___	(location?)	___	___	Hepatitis (or other liver		
Headaches	___	___	Ulcers	___	___	disease)	___	___
Dizziness	___	___	Nausea/vomiting	___	___	Kidney disease	___	___
High blood pressure	___	___	Problems with diarrhea	___	___	Glaucoma	___	___
Palpitations	___	___	Shortness of breath	___	___			

Are you pregnant or breastfeeding? _____ Date of last menses _____ Type of contraception used _____

Describe any restrictions/limitations that might interfere with your use of medication for your current problem. _____

Prescription orders:

Patient teaching related to medications prescribed:

Laboratory work or referrals prescribed:

Nurse's signature _____ **Patient's signature** _____

TABLE 4–1 **Variations in CYP 450 Enzymes and Response to Selected Psychotropic Medications***

CYP 450 ISOENZYME	% RISK FOR BEING POOR METABOLIZERS BY ETHNIC GROUP	SELECTED PSYCHOTROPIC MEDICATIONS AFFECTED	SELECTED POTENTIAL OUTCOMES
2C19	Asian 12%-23% African, African American 18% Caucasian 3%-7%	Diazepam, tricyclics, citalopram	1. Higher blood levels and faster therapeutic response to tricyclic antidepressants. Experience more toxic side effects and more risk for tricyclic antidepressant delirium 2. Increased sensitivity to effects of alcohol
2D6	East Asian 0%–2% African, African American 0%–19% Caucasian 3%–9%	Tricyclics, fluoxetine, paroxetine, venlafaxine, sertraline, chlorpromazine, haloperidol, clozapine, risperidone	1. Higher incidence of extrapyramidal side effects with haloperidol 2. More sensitive to the effects of many psychotropic medications.
3A4	Although results are inconsistent, poor metabolizers are rare (<1%) but drug-drug and drug–food interactions, such as interactions with grapefruit juice, may inhibit metabolism	Mirtazapine, sertraline, haloperidol, clozapine, quetiapine, risperidone, ziprasidone, gabapentin, lamotrigine, clonazepam, diazepam,	1. Higher risk for respiratory depression with alfentanil, fentanyl, ketamine, and oxycodone 2. Higher risk for torsade de pointes with lurasidone,

	zolpidem, buspirone, lurasidone, pimozide, ketamine, fentanyl, oxycodone, alfentanil dextromethorphan triazolam	pimozide, and ziprasidone 3. Risk for hallucinations and somnolence with dextromethorphan 4. Increased sedation with buspirone and triazolam

*CYP 450 enzymes are responsible for metabolizing many medications. Variations can occur due to genetic vulnerability or through drug–drug or drug–food interactions. CYP 450 induction increases the metabolism of selected drugs thereby decreasing their effectiveness. Inhibition of CYP 450 enzymes decreases the metabolism of selected drugs, which can result in severe toxicity and several adverse effects. Sources: Anderson, L. (2018). Drug interactions with grapefruit juice. Retrieved from https://www.drugs.com/article/grapefruit-drug-interactions.html; Horn, J.R., & Hansten, P.D. (2008). Get to know an enzyme: CYP2C19. Retrieved from https://www.pharmacytimes.com/publications/issue/2008/2008-05/2008-05-8538; Jones, D.S. (2006). Racial profiling in psychiatry: does it help patients? *Psychiatric Times, 23*(14); Lynch, T., & Price, A. (2007). The effect of cytochrome P450 metabolism on drug response, interactions, and adverse effects. *American Family Physician, 76*(3), 391-396.

Patient Education

The information associated with psychotropic medications is copious and complex. An important role of the nurse is to translate this complex information into terms that can be easily understood by the patient. Patients must understand why the medication has been prescribed, when it should be taken, and what they may expect in terms of side effects and possible adverse reactions. They must know whom to contact when they have a question and when it is important to report to their physician. Medication education encourages patient cooperation and promotes accurate and effective management of the treatment regimen. For women of childbearing age, pregnancy risk information is an essential aspect of patient education. In 2015, a new U.S. Food and Drug Administration (FDA) rule went into effect that requires drug labeling to include specific narrative information on pregnancy-associated risks, lactation considerations, and reproductive potential. This new system

replaces the lettered risk categories that were criticized for being overly simplistic. Although drugs approved after June 30, 2015 must adopt the new format immediately, for other drugs, the relabeling process is occurring gradually (Drugs.com, 2019). Nurses should use the latest informatics resources to provide current and relevant education on this and other medication-related topics.

CORE CONCEPTS

Neurotransmitter
A chemical that is stored in the axon terminals of the presynaptic neuron. An electrical impulse through the neuron stimulates the release of the neurotransmitter into the synaptic cleft, which in turn determines whether another electrical impulse is generated.

Receptors
Molecules situated on the cell membrane that are binding sites for neurotransmitters.

How Do Psychotropic Medications Work?

Most psychotropic medications affect the neuronal synapse, producing changes in neurotransmitter release and the receptors to which they bind (see Figure 4-1). Researchers hypothesize that most antidepressants work by blocking the reuptake of neurotransmitters, specifically, serotonin and norepinephrine. *Reuptake* is the process of neurotransmitter inactivation by which the neurotransmitter is reabsorbed into the presynaptic neuron from which it was released. Blocking the reuptake process allows more of the neurotransmitter to be available for neuronal transmission. This mechanism of action may also result in undesirable side effects (see Table 4–2). Some antidepressants also block receptor sites that are unrelated to their mechanisms of action. These include α-adrenergic, histaminergic, and muscarinic cholinergic receptors. Blocking these receptors is associated with certain side effects; for example, individuals treated with tricyclic antidepressants are at risk for developing postural hypotension. The specific type of receptor that medications bind to is

also relevant to its level of antianxiety, antidepressant, and sedative properties (see Table 4–2).

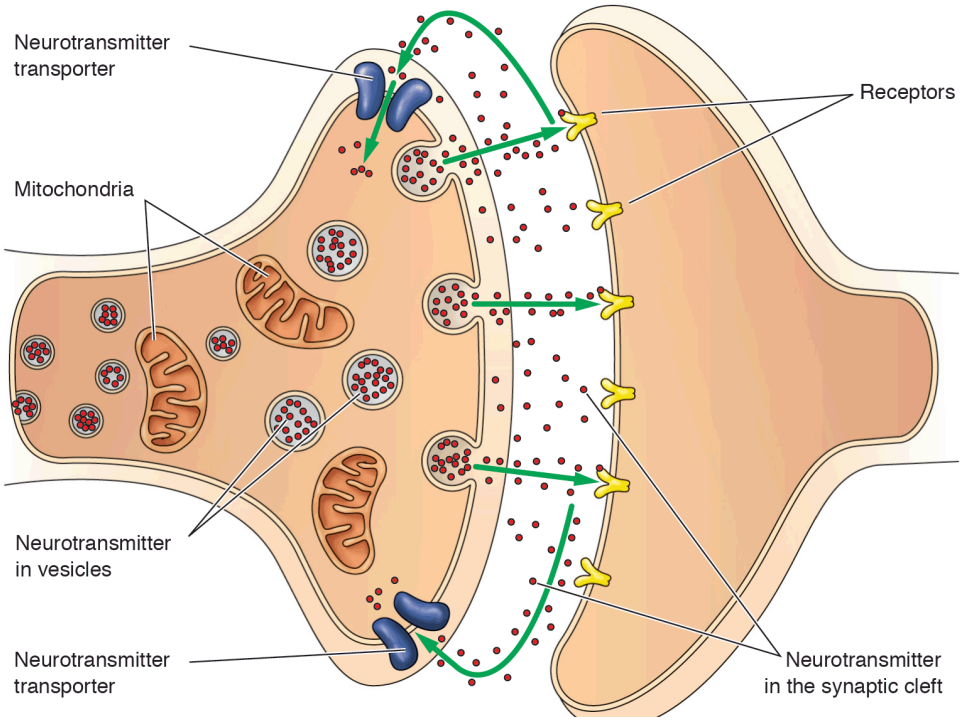

FIGURE 4-1 Area of synaptic transmission that is altered by drugs.

Antipsychotic medications block dopamine receptors, and some affect muscarinic, cholinergic, histaminergic, and α-adrenergic receptors. *Atypical* (or novel) antipsychotics focus primarily on blocking specific serotonin receptors. Benzodiazepines facilitate the transmission of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Psychostimulants work by increasing norepinephrine, serotonin, and dopamine release.

Although each psychotropic medication affects neurotransmission, the specific drugs within each class have varying neuronal effects. Their exact mechanisms of action are unknown. Many neuronal effects occur rapidly; however, therapeutic effects of some medications, such as antidepressants and atypical antipsychotics, may take weeks to manifest full therapeutic benefits. Acute alterations in neuronal function do not fully explain how these medications work. Sadock et al. (2015) note that “if merely raising or lowering levels of neurotransmitter activity is associated with the

clinical effects of a drug, then all drugs that cause these changes should produce equivalent benefits [but] this is not the case" (p. 911).

TABLE 4–2 Effects of Psychotropic Medications on Neurotransmitters

EXAMPLE OF MEDICATION	ACTION ON NEUROTRANSMITTER OR RECEPTOR	DESIRED EFFECTS	SIDE EFFECTS
Selective serotonin reuptake inhibitors (SSRIs)	Inhibit reuptake of serotonin (5-HT)	Reduce depression Control anxiety Control obsessions	Nausea, agitation, headache, sexual dysfunction
Tricyclic antidepressants	Inhibit reuptake of serotonin (5-HT) Inhibit reuptake of NE Block NE (α_1) receptor Block ACh receptor Block histamine (H_1) receptor	Reduce depression Relieve severe pain Prevent panic attacks	Sexual dysfunction (NE and 5-HT) Sedation, weight gain (H_1) Dry mouth, constipation, blurred vision, urinary retention (ACh) Postural hypotension and tachycardia (α_1)
Monoamine oxidase inhibitors (MAOIs)	Increase NE and 5-HT by inhibiting the enzyme that degrades them (MAO-A)	Reduce depression Control anxiety	Sedation, dizziness Sexual dysfunction Hypertensive crisis (interaction with tyramine and foods or beverages with high caffeine content)

Trazodone and nefazodone	5-HT reuptake block 5-HT_2 receptor antagonism Adrenergic receptor blockade	Reduce depression Reduce anxiety	Nausea (5-HT) Sedation (5-HT_2) Orthostasis (α_1) Priapism (α_2)
Selective norephinephrine reuptake inhibitors (SNRIs): venlafaxine, desvenlafaxine, duloxetine, and levomilnacipran	Potent inhibitors of serotonin and norepinephrine reuptake Weak inhibitors of dopamine reuptake	Reduce depression Relieve pain of neuropathy (duloxetine) Relieve anxiety (venlafaxine)	Nausea (5-HT) ↑ Sweating (NE) Insomnia (NE) Tremors (NE) Sexual dysfunction (5-HT)
Bupropion	Inhibits reuptake of NE and D	Reduces depression Aids in smoking cessation Reduces symptoms of ADHD	Insomnia, dry mouth, tremor, seizures
Esketamine (nasal spray)	Nonselective, noncompetitive antagonist of the NMDA receptor (an ionotropic glutamate receptor)	Reduce depression in treatment-resistant depression (in conjunction with an oral antidepressant)	Dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, blood pressure increased, and vomiting
Antipsychotics: phenothiazines and haloperidol	Strong D_2 receptor blockades Weaker blockades of ACh, H_1, α_1-adrenergic, and 5-HT_2 receptors	Relieve psychosis Relieve anxiety (Some) provide relief from nausea and	Blurred vision, dry mouth, ↓ sweating, constipation, urinary retention,

		vomiting and intractable hiccoughs	tachycardia (ACh) EPS (D_2) ↑ Plasma prolactin (D_2) Sedation; weight gain (H,) Ejaculatory difficulty (5-HT_2) Postural hypotension (α; H_1)
Antipsychotics (second generation, atypical): aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone	Receptor antagonism of 5-HT_{1A} and 5-HT_{2A} D_1–D_5 (varies with drug) H_1, α_1-adrenergic muscarinic (ACh)	Relieve psychosis (with minimal or no EPS) Relieve anxiety Relieve acute mania	Potential with some of the drugs for mild EPS (D_2) Sedation, weight gain (H_1) Orthostasis and dizziness (α-adrenergic) Blurred vision, dry mouth, ↓ sweating, constipation, urinary retention, tachycardia (ACh)
Antianxiety: benzodiazepines	Bind to BZ receptor sites on the $GABA_A$ receptor complex; increase receptor affinity for GABA	Relieve anxiety Produce sedation	Dependence (with long-term use) Confusion, memory impairment,

			motor incoordination
Antianxiety: buspirone	5-HT_{1A} agonist D_2 agonist D_2 antagonist	Relieves anxiety	Nausea, headache, dizziness Restlessness

5-HT, 5-hydroxytryptamine (serotonin); ACh, acetylcholine; ADHD, attention deficit-hyperactivity disorder; BZ, benzodiazepine; D, dopamine; EPS, extrapyramidal symptoms; GABA, gamma-aminobutyric acid; H, histamine; MAO, monoamine oxidase; MAO-A, monoamine oxidase A; NE, norepinephrine.

Long-term neuropharmacological reactions to increased norepinephrine and serotonin levels may better explain their mechanisms of action. Recent research suggests that the therapeutic effects are related to the nervous system's adaptation to increased levels of neurotransmitters. These adaptive changes result from a homeostatic mechanism, much like a thermostat, that regulates the cell and maintains equilibrium.

Applying the Nursing Process in Psychopharmacological Therapy

An assessment tool for obtaining a drug history is provided in Box 4-1. This tool may be adapted for use by staff nurses admitting patients to the hospital or by nurse practitioners with prescriptive privileges.

 One of the Quality and Safety Education for Nurses (QSEN) criteria culminating from the Institute of Medicine (IOM) (2003) report on essential competencies for health-care professionals stresses that the patient must be at the center of decisions about treatment (patient-centered care), and this type of assessment tool provides an opportunity to actively engage the patient in describing what medications have been effective or ineffective and identifying side effects that may affect willingness to adhere to a medication regimen.

Antianxiety Agents

Background Assessment Data

Indications

Antianxiety drugs are also called *anxiolytics* and historically were referred to as *minor tranquilizers.* They are used in the treatment of anxiety disorders, anxiety symptoms, acute alcohol withdrawal, skeletal muscle spasms, convulsive disorders, status epilepticus, and preoperative sedation. They are most appropriate for the treatment of acute anxiety states rather than long-term treatment, as their use and efficacy for longer than 4 months have not been evaluated. For long-term management of anxiety disorders, antidepressants (such as selective serotonin reuptake inhibitors [SSRIs] and selective norepinephrine reuptake inhibitors [SNRIs]) are often used as the first line of treatment because they are not addictive. (A table of current FDA-approved antianxiety agents, half-life, and daily dosage ranges can be found online at *DavisPlus* and in Chapter 27, "Anxiety, Obsessive-Compulsive, and Related Disorders.") Other medications that have been used off-label to treat anxiety disorders include anticonvulsants (such as divalproex, gabapentin, and pregabalin), beta blockers (such as atenolol, propranolol, and nadolol), antihistamines (hydroxyzine), and antipsychotic medications (quetiapine is under review by the FDA for approval to treat generalized anxiety disorder).

Action

Antianxiety drugs depress subcortical levels of the central nervous system (CNS), particularly the limbic system and reticular formation. They may potentiate the effects of the powerful inhibitory neurotransmitter GABA in the brain, thereby producing a calming effect. The level of CNS depression can range from mild sedation to hypnosis to coma. The most commonly prescribed antianxiety agents are benzodiazepines, including clonazepam (Klonopin), diazepam (Valium), and alprazolam (Xanax). Benzodiazepines are similar to alcohol in their effects on GABA receptors, which explains

why benzodiazepines may be used for the management of alcohol withdrawal.

The antianxiety agent buspirone (BuSpar) is not a benzodiazepine and does not depress the CNS. Although its action is unknown, the drug is believed to produce its effects through interactions with serotonin, dopamine, and other neurotransmitter receptors. Patients should be instructed that buspirone has a lag period of 7 to 10 days before full therapeutic benefits are achieved. It does not have the addiction potential of the other antianxiety agents and therefore may be a better option for patients with anxiety disorders who also have substance use disorders.

One trend noted by Olfson, King, and Schoenbaum (2015) is the increased use of benzodiazepines in the older adult population despite known safety concerns, including psychomotor impairment, impaired cognitive function, and paradoxical increase in anxiety. The researchers add that 33% of benzodiazepine prescriptions are for long-term use in older adults, a practice that has not been supported by scientific evidence and one that increases risks for side effects and dependence. Nurses are in a position to assess safety risks and, in collaboration with the patient, physician, and other health-care team members, explore other options for treatment of anxiety and insomnia.

Interactions

- Increased effects of antianxiety agents can occur when they are taken concomitantly with alcohol, barbiturates, narcotics, antipsychotics, antidepressants, antihistamines, neuromuscular blocking agents, cimetidine, or disulfiram.
- The FDA (2016a) added a boxed warning (its strongest warning) related to the serious risks and possible death associated with combining benzodiazepines with opioid pain or cough medicines.
- Increased effects can also occur with herbal depressants (e.g., kava, valerian, lemon verbena, L-tryptophan, melatonin, and chamomile).
- Decreased effects can be noted with cigarette smoking and caffeine consumption.

Diagnosis

The following nursing diagnoses may be considered for patients receiving therapy with antianxiety agents:

- Risk for injury related to seizures, panic anxiety, acute agitation from alcohol withdrawal (indications), abrupt withdrawal from the medication after long-term use, or effects of medication intoxication or overdose
- Anxiety (specify) related to threat to physical integrity or self-concept
- Risk for activity intolerance related to side effects of sedation, confusion, and/or lethargy
- Disturbed sleep pattern related to situational crises, physical condition, or severe level of anxiety

Safety Issues in Planning and Implementing Care

 The IOM (2003) identifies *ensuring safety* as a core competency for health professions education. Table 4–3 notes some of the significant safety issues to be considered for clients taking antianxiety agents. Nursing interventions related to each side effect are noted in the right-hand column.

Outcome Criteria and Evaluation

The following criteria may be used for evaluating the effectiveness of therapy with antianxiety agents.

The patient:

- Demonstrates a reduction in anxiety, tension, and restless activity
- Experiences no seizure activity
- Experiences no physical injury
- Is able to tolerate usual activities without excessive sedation
- Exhibits no evidence of confusion
- Tolerates the medication without gastrointestinal distress
- Verbalizes understanding of the need for, side effects of, and regimen for self-administration

- Verbalizes possible consequences of abrupt withdrawal from the medication

TABLE 4–3 Safety Issues and Nursing Interventions for Patients Taking Antianxiety Agents

SAFETY ISSUES	NURSING INTERVENTIONS
Tolerance and physical dependence may develop. **Abrupt withdrawal can be life threatening** (except with buspirone); signs include sweating, agitation, tremors, nausea and vomiting, delirium, seizures.	Instruct patient not to stop taking the drug abruptly. Assess the patient for signs of developing tolerance (requiring higher doses of medication to achieve effects). Educate the patient about symptoms of withdrawal. Contact the doctor immediately if symptoms of withdrawal are assessed.
Drowsiness, confusion, and lethargy are the most common side effects.	Instruct patient not to drive or operate dangerous machinery while taking this medication.
Effects of other CNS depressants are increased.	Instruct the patient not to drink alcohol or take other CNS depressants, antihistamines, cimetidine, antidepressants, neuromuscular blocking agents, or disulfiram while taking these drugs. The FDA (2016a) recently added a boxed warning (its strongest warning) related to the serious risks and possible death associated with combining benzodiazepines with opioid pain or cough medicines.
Antianxiety agents may **aggravate symptoms of depression.**	Assess the patient's mood and assess for suicide risk.
Orthostatic hypotension may occur.	Instruct the patient to rise slowly from a sitting to standing position to minimize risk for falls. Monitor lying and standing blood pressures to assess for orthostatic hypotension.
Paradoxical excitement (opposite from the desired effect) may occur. Especially the elderly may be at higher risk for agitation and increased	Hold the medication and notify the doctor. Assess for other side effects and safety issues, including impaired

anxiety. In general, safety risks associated with benzodiazepines may be greater for the older adult (especially with long-acting benzodiazepines and long-term use), including impaired cognitive function, reduced mobility, risk for falls, and chemical dependence (Olfson, King, & Schoenbaum, 2015).	cognition and impaired mobility. Use a patient-centered, collaborative team approach to explore options in safe management of anxiety and insomnia (lower dose, shorter-acting benzodiazepines; psychological interventions; etc.).
Blood dyscrasias, although rare, can be serious or life threatening.	Assess for sore throat, fever, bruising, or unusual bleeding. Hold medication and report these symptoms immediately to the doctor.
Congenital malformations have been associated with use of these drugs during the first trimester of pregnancy.	Instruct the female patient who is pregnant or anticipating pregnancy while on these drugs to explore alternative treatment options with her physician.

CNS, central nervous system.

Antidepressants

There are several types of antidepressant medications, some of which are also prescribed to treat anxiety disorders. The first “antidepressant” drug was a monoamine oxidase inhibitor (MAOI), isoniazid, which was used to treat tuberculosis. When patients began describing their increased feelings of well-being on these drugs, MAOIs were developed specifically for the treatment of depression. Unfortunately, they were also potentially deadly for anyone who ate foods high in tyramine while taking these drugs, and several serious interactions occurred with other drugs. Because MAOIs increase the availability of norepinephrine, researchers focused on developing drugs that affected norepinephrine without the need for food restrictions, leading to the introduction of *tricyclic antidepressants.*

Tricyclics were the first line of treatment for depression for many years but were effective for only about 70% of those treated. In

addition, because all neurotransmitters bind to various receptor sites, increasing the availability of norepinephrine with tricyclics also causes anticholinergic effects and increases the potential for postural hypotension. These side effects limit their use in the elderly and those with cardiovascular problems.

In the late 1980s and early 1990s, *selective serotonin reuptake inhibitors* (SSRIs) and *serotonin-norepinephrine reuptake inhibitors* (SNRIs) were developed in response to research indicating that serotonin, an antianxiety hormone and neurotransmitter, could promote improvement in depression and anxiety without significant anticholinergic side effects. Common SNRIs, which decrease reuptake of serotonin and norepinephrine, include desvenlafaxine (Pristiq), duloxetine (Cymbalta), levomilnacipran (Fetzima), and venlafaxine (Effexor). With these developments SSRIs and SNRIs became the preferred first line of treatment for depression.

Atypical antidepressants are a group of drugs that work differently and do not fit into the previously mentioned classes. These include the following drugs:

- Bupropion (Wellbutrin)—decreases reuptake of dopamine and, to a lesser extent, serotonin and norepinephrine
- Mirtazapine (Remeron)—potentiates the effects of norepinephrine and serotonin
- Nefazodone—inhibits reuptake of serotonin and norepinephrine by acting as an antagonist at the central 5HT2 receptor
- Vortioxetine (Trintellix)—action not well understood
- Vilazodone (Viibryd)—partial agonist at serotonergic 5HT1A receptors
- Trazodone (Desyrel)—unknown but alters the effect of serotonin

One of the more recent additions to the pharmacological treatments for depression and anxiety are atypical antipsychotics that increase the availability of serotonin and dopamine. These medications are promoted as adjunctive to antidepressant therapy. The most popular example is aripiprazole (Abilify). In a recent large study sponsored by the National Institute of Mental Health, 44% of elderly adults who were not responding to a first-line antidepressant

(venlafaxine) showed improvement in their symptoms when aripiprazole (Abilify) was added to treatment with venlafaxine. This finding has important implications for the treatment of elderly clients with depression because more than one-half of older adults with clinical depression do not respond to antidepressants alone (Lenze et al., 2015).

Despite these developments and client-subjective reports of improvement with antidepressant medications, our understanding of the exact mechanisms of action remains theoretical. Currently, the levels of neurotransmitters in the brain cannot be measured. In the STAR*D study (a large study funded by the National Institute of Mental Health), it was found that two-thirds of patients on antidepressant medication do not experience full recovery (Tartakovsky, 2016).

Research continues with the goal of identifying more broadly effective antidepressant therapies. Several of the newest drugs on the market for treatment of depression are not significantly different from existing products. For example, a “new” antidepressant approved by the FDA in 2016, Oleptro, is a reformulation of trazodone. But new mechanisms are being explored in clinical trials. Glutamate receptors (NMDA) are being studied for potential antidepressant effects; ketamine and midazolam (a benzodiazepine with transient effects similar to those of ketamine) are being explored as potentially faster-acting than traditional antidepressants. Intranasal application of esketamine is demonstrating effectiveness in reducing depressive symptoms within hours, and it is hoped that this treatment may be offered to bridge the gap before which traditional antidepressants begin to demonstrate therapeutic effects (Canuso et al., 2018). In 2019, the FDA approved nasal spray esketamine (Spravato) in conjunction with an oral antidepressant for individuals with treatment-resistant depression. In one of three short-term studies used to evaluate the drug’s efficacy, Spravato demonstrated statistically significant benefit in reducing depressive symptoms, and some effect was seen within 2 days (FDA, 2019). Research into esketamine’s mechanism of action, applications, and risks is ongoing. Because there are risks for serious adverse

outcomes related to sedation, dissociation (difficulty with attention, judgment, and thinking), and the potential for substance abuse and misuse, this drug is classified as a CIII controlled drug and is only available through a restricted distribution system. It must be administered in a certified medical office where the patient is under observation, and it requires a Risk Evaluation and Mitigation Strategy (REMS) (FDA, 2019).

Drugs that act on melatonin receptors are currently in clinical trials for use in depression (one is already approved for use in Europe). One study found a synergistic antidepressant effect when melatonin was combined with fluoxetine (Li et al., 2018), but more research is needed. There is concern that melatonin, although it may improve sleep disturbances in people with depression, may also worsen other symptoms of depression in some individuals (WebMD, 2019). A new group of antidepressants called *triple reuptake inhibitors* that simultaneously block reuptake of serotonin, norepinephrine, and dopamine have been studied but have demonstrated mixed results with regard to any superior benefits over highly selective serotonergic agents alone (Kose & Cetin, 2018).

Current research also continues to explore genetic testing to identify factors that may influence whether an individual is more likely to respond to one type of antidepressant than another. If reliability is established, the research will provide a valuable resource for making decisions about which antidepressant to prescribe first.

Background Assessment Data

Indications

In addition to the indications for antidepressant medications in the treatment of major depressive and dysthymic disorders, some of the newer drugs, such as SSRIs, SNRIs, and atypical antidepressants, have received FDA approval for the treatment of some anxiety disorders, bulimia nervosa and other eating disorders, premenstrual dysphoric disorder, borderline personality disorder, obesity, and

smoking cessation (Sadock et al., 2015). Atypical antidepressants are discussed further later in this chapter.

A hallmark review of the research on antidepressants (Fournier et al., 2010) found that the benefits of antidepressant therapy for patients with mild to moderate symptoms of depression may be minimal or nonexistent but that for clients with severe depression, the benefits, compared with placebo effects, are substantial. Therefore these medications are particularly indicated when an individual is identified as having severe depression. (A table of current FDA-approved antidepressants, half-life, and daily dosage ranges can be found online at Davis*Plus* and in Chapter 25, "Depressive Disorders.")

Action

Antidepressant drugs ultimately work to increase the concentration of norepinephrine, serotonin, or dopamine in the body. This is accomplished in the brain by blocking the reuptake of these neurotransmitters by the neurons (tricyclic antidepressants [TCAs], tetracyclics, SSRIs, and SNRIs). It also occurs when an enzyme, monoamine oxidase (MAO), known to inactivate norepinephrine, serotonin, and dopamine, is *inhibited* at various sites in the nervous system (MAOIs).

CLINICAL PEARL All antidepressants carry an FDA black-box warning for increased risk of suicidality in children, adolescents and young adults up to 25 years of age.

Interactions

It is important to recognize that new information about drug interactions is discovered and published frequently. To fully understand safety issues related to medication administration, nurses need to access the most current, evidence-based informatics on drug interaction information. Tables 4–4, 4–5, 4–6, and 4–7 identify some of the significant, dangerous interactions between antidepressants and other drugs or foods.

Drug interactions vary widely within these groups; the following are several examples:

- Concomitant use with MAOIs results in serious, sometimes fatal, effects resembling **neuroleptic malignant syndrome.** Coadministration is contraindicated.
- **Serotonin syndrome** may occur when any of the following are used together: St. John's wort, sumatriptan, sibutramine, trazodone, nefazodone, venlafaxine, duloxetine, levomilnacipran, SSRIs, 5-HT-receptor agonists (triptans).
- Increased effects of haloperidol, clozapine, and desipramine may occur with concomitant use of venlafaxine.
- Increased effects of levomilnacipran may occur with concomitant use of CYP3A4 inhibitors.
- Increased effects of venlafaxine may occur with concomitant use of cimetidine.
- Increased effects of duloxetine may occur with concomitant use of CYP1A2 inhibitors (e.g., fluvoxamine, quinolone antibiotics) or CYP2D6 inhibitors (e.g., fluoxetine, quinidine, paroxetine).

TABLE 4–4 Drug Interactions With Selective Serotonin Reuptake Inhibitors (SSRIs)

INTERACTING DRUGS	ADVERSE EFFECTS
Buspirone (BuSpar), tricyclic antidepressants (especially clomipramine), selegiline (Eldepryl), St. John's wort	Serotonin syndrome*
Monoamine oxidase inhibitors	Hypertensive crisis
Warfarin, NSAIDs	Increased risk of bleeding
Alcohol, benzodiazepines	Increased sedation
Antiepileptics	Lowered seizure threshold

*Serotonin syndrome is a potentially fatal syndrome of serotonin overstimulation with rapid onset that progresses from diarrhea, restlessness, agitation, hyperreflexia, fluctuations in vital signs to later symptoms of myoclonus, seizures, hyperthermia, uncontrolled shivering, muscle rigidity, and ultimately can lead to delirium, coma, status epilepticus, cardiovascular collapse, and death. Immediate cessation of offending drugs and comprehensive supportive intervention are essential (Sadock et al., 2015).

TABLE 4–5 Drug Interactions With Tricyclic Antidepressants (TCAs)	
INTERACTING DRUGS	ADVERSE EFFECTS
Monoamine oxidase inhibitors	High fever, convulsions, death
St. John's wort, tramadol (Ultram)	Seizures, serotonin syndrome
Clonidine (Catapres), epinephrine	Severe hypertension
Acetylcholine blockers	Paralytic ileus
Alcohol and carbamazepine (Tegretol)	Blocks antidepressant action, increases sedation
Cimetidine (Tagamet), bupropion (Wellbutrin)	Increased TCA blood levels and increased side effects

TABLE 4–6 Drug Interactions With Monoamine Oxidase Inhibitors (MAOIs)	
INTERACTING DRUGS	ADVERSE EFFECTS
Selective serotonin reuptake inhibitor, tricyclic antidepressants, atomoxetine (Strattera), duloxetine (Cymbalta), dextromethorphan (an ingredient in many cough syrups), venlafaxine (Effexor), St. John's wort, ginkgo biloba	Serotonin syndrome
Morphine and other narcotic pain relievers, antihypertensives	Hypotension
All other antidepressants, pseudoephedrine, amphetamines, cocaine cyclobenzaprine (Flexeril), dopamine, methyldopa, levodopa, epinephrine, buspirone (BuSpar)	Hypertensive crisis (these side effects can occur even if taken within 2 weeks of stopping MAOIs)
Buspirone	Psychosis, agitation, seizures
Antidiabetics	Hypoglycemia
Tegretol	Fever, hypertension, seizures

- Risk of liver injury is increased with concomitant use of alcohol and duloxetine.
- Risk of toxicity or adverse effects from drugs extensively metabolized by CYP2D6 (e.g., flecainide, phenothiazines, propafenone, tricyclic antidepressants, thioridazine) is increased when these drugs are used concomitantly with duloxetine or bupropion.
- Decreased effects of bupropion and trazodone may occur with concomitant use of carbamazepine.
- The anticoagulant effect of warfarin may be altered with concomitant use of bupropion, venlafaxine, desvenlafaxine, duloxetine, levomilnacipran, or trazodone.
- Risk of seizures is increased when bupropion is coadministered with drugs that lower the seizure threshold (e.g., antidepressants, antipsychotics, systemic steroids, theophylline, tramadol).
- Effects of midazolam are decreased with concomitant use of desvenlafaxine.
- Effects of desvenlafaxine and levomilnacipran are increased with concomitant use of potent CYP3A4 inhibitors (e.g., ketoconazole).

Diagnosis

The following nursing diagnoses may be considered for patients receiving therapy with antidepressant medications:

- Risk for suicide related to depressed mood
- Risk for injury related to side effects of sedation, lowered seizure threshold, orthostatic hypotension, **priapism,** photosensitivity, arrhythmias, **hypertensive crisis,** or serotonin syndrome
- Social isolation related to depressed mood
- Risk for constipation related to side effects of the medication
- Insomnia related to depressed mood and elevated level of anxiety

Safety Issues in Planning and Implementing Care

Some of the common but manageable side effects of antidepressant medications include dry mouth, sedation, and nausea. General nursing interventions such as offering hard candies, ice, and frequent sips of water are helpful in alleviating dry mouth. Clients

may find that sedation is less bothersome if they take the daily dose of antidepressant at bedtime; they should be encouraged to discuss the time of day that their medication should be taken with the prescribing physician or nurse practitioner. Taking antidepressant medication with food may help minimize nausea.

Some patients taking SSRIs or SNRIs complain of sexual dysfunction. Men may report abnormal ejaculation or impotence, and women may report loss of orgasm. Because of these side effects, clients sometimes stop the medication abruptly, which may put them at risk for discontinuation syndrome and worsen symptoms of depression. Nurses must develop an open attitude regarding discussion and assessment of patient sexual concerns, and patients who are particularly troubled by this side effect can be encouraged to discuss their concerns with the prescribing physician or nurse practitioner to explore an alternative medication.

TABLE 4–7 **Diet Restrictions for Clients on Monoamine Oxidase Inhibitor (MAOI) Therapy**

FOODS CONTAINING TYRAMINE		
HIGH TYRAMINE CONTENT (AVOID WHILE ON MAOI THERAPY)	**MODERATE TYRAMINE CONTENT (MAY EAT OCCASIONALLY WHILE ON MAOI THERAPY)**	**LOW TYRAMINE CONTENT (LIMITED QUANTITIES PERMISSIBLE WHILE ON MAOI THERAPY)**
Aged cheeses (cheddar, Swiss, Camembert, blue cheese, parmesan, provolone, Romano, brie)	Gouda cheese, processed American cheese, mozzarella	Pasteurized cheeses (cream cheese, cottage cheese, ricotta)
Raisins, fava beans, flat Italian beans, Chinese pea pods	Yogurt, sour cream	Figs
Red wines (chianti, burgundy, cabernet sauvignon)	Avocados, bananas	Distilled spirits (in moderation)
Liqueurs	Beer, white wine	
Smoked and processed meats (salami, bologna, pepperoni, summer sausage)	Coffee, colas, tea, hot chocolate (caffeinated beverages)	
Caviar, pickled herring, corned beef, chicken or beef liver	Meat extracts, such as bouillon	
Soy sauce, brewer's yeast, meat tenderizer (MSG)	Chocolate	
Sauerkraut		

Source: Sadock, B.J., Sadock, V.A., & Ruiz, P. (2015). *Synopsis of psychiatry: Behavioral sciences/clinical psychiatry* (11th ed.). Philadelphia: Lippincott Williams & Wilkins; Vallerand, A.H., & Sanoski, C.A. (2019). *Davis's drug guide for nurses* (16th ed.). Philadelphia: F.A. Davis.

Other side effects or adverse reactions may be dangerous or even fatal. Many of these are related to drug–drug or drug–food interactions, as discussed previously.

Because there is so much information and new drug development is ongoing, practicing nurses should ensure that they are accessing evidence-based informatics to keep up to date on side effects as well. Many health-care organizations provide online medication resources to employees, and mobile device applications provide a readily available resource for updated drug information. Some important safety issues and nursing interventions are listed in Table 4–8.

CLINICAL PEARL As antidepressant drugs take effect and mood begins to lift, the individual may have increased energy with which to implement a suicide plan. Suicide potential may increase as the level of depression decreases. The nurse should be particularly alert to sudden lifts in mood.

Outcome Criteria and Evaluation

The following criteria may be used for evaluating the effectiveness of therapy with antidepressant medications.

The patient:

- Has not harmed self
- Has not experienced injury caused by side effects
- Exhibits vital signs within normal limits
- Manifests symptoms of improvement in mood (presents brighter affect, interacts with others, demonstrates improved hygiene, expresses clear thought, conveys hopefulness, shows improved ability to make decisions)
- Willingly participates in activities and interacts appropriately with others

Mood-Stabilizing Agents

Background Assessment Data

For many years, the drug of choice for treatment and management of bipolar mania was lithium carbonate. In recent years, several

other medications have demonstrated effectiveness either alone or in combination with lithium. Most notable are many drugs in the class of anticonvulsant medications, which are now FDA approved for mood stabilization. Some second generation atypical antipsychotics have also demonstrated benefits for management of this disorder.

Bipolar disorder is characterized by cycles of depression and manic episodes, which may manifest as grandiose thinking and behavior, rapid thoughts, hyperactivity, or impulsive agitation. The effective medication treatment for this disorder is one that reduces the rollercoaster of “ups and downs” often described by clients; thus the name “mood stabilizer” is an apt description of their purpose. Lithium was first identified as an antimanic but was later recognized as useful for stabilizing the mood swings of bipolar disorder as well.

TABLE 4–8 **Safety Issues and Nursing Interventions for Patients Taking Antidepressants**

SAFETY ISSUES	NURSING INTERVENTIONS
Drug interactions (multiple, as discussed in the text)	Instruct patients to inform their physician or nurse practitioner of *all* medications they are taking, including herbal preparations, over-the-counter drugs, and any medications they have stopped taking within the previous 2 weeks. Notify the physician immediately when any symptoms of serotonin syndrome are assessed. Do not administer the offending agent. ■ Monitor vital signs. ■ Protect from injury secondary to muscle rigidity or change in mental status. ■ Provide cooling blankets for temperature regulation. ■ Monitor intake and output. The condition usually resolves when the offending agent is promptly discontinued but can be fatal without intervention (Cooper & Sejnowski, 2013).
Increased risk for suicide	Assess frequently for presence or worsening of suicide ideation. Initiate suicide precautions as needed. Monitor patients' use of medication as prescribed, because these medications can be lethal in overdose.
Sedation	Instruct patients not to drive or operate dangerous machinery when experiencing sedation.
Discontinuation syndrome: SSRIs—dizziness, lethargy, headache, nausea TCAs—hypomania, akathisia, cardiac arrhythmias, gastrointestinal upset, panic attacks MAOIs—flu-like symptoms, confusion, hypomania	Instruct patients that all antidepressants have some potential for discontinuation syndrome and should not be stopped abruptly but rather tapered off. Paroxetine is associated with the highest risk for discontinuation syndrome (Janicak & Hussain, 2017).

Photosensitivity	Instruct patients of their vulnerability to severe sunburn and recommend sunscreen.
Orthostatic hypotension (TCAs)	Instruct patients to rise slowly from sitting to standing. Monitor blood pressure to assess for symptoms.
Tachycardia, arrhythmias (TCAs)	Monitor vital signs, especially in elderly with preexisting cardiovascular disorders.
Hyponatremia (SSRIs), especially among the elderly	Instruct patients to report any symptoms of nausea, malaise, lethargy, muscle cramps. Assess for disorientation or restlessness. Monitor sodium levels: ■ <120 mEq/L risk for seizure, coma, respiratory arrest ■ Withhold medication, contact physician, restrict water intake ■ Take a detailed history of antidepressant therapy, particularly the duration of new antidepressant use (Lien, 2018)
Blurred vision (TCAs and atypicals)	Instruct patients to avoid driving, and reassure them that this side effect usually resolves within 3 weeks. Monitor blood pressure to rule out symptoms of hypertension.
Constipation	Recommend a high-fiber diet and regular exercise, and instruct patients to report any symptoms of ongoing difficulty with bowel movements.

MAOIs, monoamine oxidase inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

Lithium is a salt present in mineral springs and added to spa baths. Although it was also used for other medicinal purposes, in 1949 Australian physician John Cade reported using lithium to treat manic excitement. It was so effective that some of his patients became symptom free and were able to be discharged after years of institutionalization (Shorter, 2009). It remains true that people who respond to lithium and remain on the medication may show no

evidence of bipolar mood swings. Although it is not a cure, it is often described as “like insulin to a diabetic” in that proper use and response can reduce or eliminate symptoms. Unfortunately, not everyone responds with the same degree of success, and too much lithium can be fatal. Today, however, we are able to measure the blood levels of lithium and be confident of its safety when maintained within the specified therapeutic range (0.6–1.2 mEq/L). The exact mechanism of action remains unknown, but it is believed to have an impact on the same neurotransmitters (serotonin, norepinephrine, glutamate, GABA, and dopamine) as previously discussed.

In 1995 the FDA approved valproate (Depakote) as a mood stabilizer; since then, a significant shift toward this group of anticonvulsant mood stabilizers (including carbamazepine, clonazepam, topiramate, and lamotrigine) and away from lithium has occurred (Shorter, 2009). As with lithium, the mechanism of action for these drugs is unclear. Impact on cellular sodium transport, GABA modulation, and raising the seizure threshold have all been advanced as possible explanations for their effectiveness. Both first and second generation antipsychotics have been used alone or as adjuncts to other medication treatment for bipolar mania. Since lithium has a lag period of 7 to 10 days, first generation antipsychotics, such as haloperidol, may be helpful in initial treatment because of their immediate sedative effects. They also increase the effects of lithium, so monitoring blood serum levels is especially important in the initial phase of treatment when these two drugs are used in combination. (A table of current FDA-approved mood-stabilizer medications, half-life, and daily dosage ranges can be found online at Davis*Plus* and in Chapter 26, “Bipolar and Related Disorders.”)

Interactions

One of the interesting things about drug interactions with mood stabilizers is that many drugs either increase or decrease their effectiveness, as shown in Table 4–9. Understanding that lithium is a salt is relevant in explaining some of these interactions. Because lithium is an imperfect substitute for sodium, anything that depletes

sodium will make more receptor sites available to lithium and increase the risk for lithium toxicity. This effect is why individuals taking lithium must maintain regular dietary sodium and fluid intake to avoid major fluctuations in their lithium levels and the resulting effects. For example, significant increases in dietary sodium intake may reduce the effectiveness of lithium because sodium will bind at more receptor sites and decrease the amount of lithium that can bind to these receptors. Other drugs that increase or decrease serum sodium levels also have an impact on lithium levels.

Diagnosis

The following nursing diagnoses may be considered for patients receiving therapy with mood-stabilizing agents:

- Risk for injury related to manic hyperactivity
- Risk for self-directed or other-directed violence related to unresolved anger turned inward on the self or outward on the environment
- Risk for injury related to lithium toxicity
- Risk for injury related to adverse effects of mood-stabilizing drugs
- Risk for activity intolerance related to side effects of drowsiness and dizziness

Planning and Implementing Care

One of the primary safety issues with lithium is its narrow therapeutic range. A description of lithium toxicity, other safety concerns with mood-stabilizing agents, and relevant nursing interventions are discussed in Table 4–10.

Lithium Maintenance

Patients who respond to lithium typically remain on the medication indefinitely. To ensure safe maintenance and prevent lithium toxicity, patient education and regular monitoring are essential. An important component of monitoring is evaluation of serum lithium levels to ensure that they remain within the therapeutic range. The usual ranges of therapeutic serum concentrations differ for initiation of

treatment in an acute manic state and maintenance (Vallerand & Sanoski, 2019):

- For acute mania: 1.0 to 1.5 mEq/L
- For maintenance: 0.6 to 1.2 mEq/L

Serum lithium levels should be monitored once or twice a week after initial treatment until dosage and serum levels are stable and then monthly during maintenance therapy. Blood samples should be drawn 12 hours after the last dose is taken.

Some clients complain that they miss the “high” feeling of being in a manic or hypomanic state once they begin mood-stabilizer medications. They may be at risk for self-adjusting medication or discontinuing it altogether.

TABLE 4–9 **Drug Interactions With Mood-Stabilizing Agents**

THE EFFECTS OF:	ARE INCREASED BY:	ARE DECREASED BY:	CONCURRENT USE MAY RESULT IN:
ANTIMANIC AGENTS			
Lithium	Carbamazepine, fluoxetine, haloperidol, loop diuretics, methyldopa, NSAIDs, and thiazide diuretics	Acetazolamide, osmotic diuretics, theophylline, and urinary alkalinizers	Increased effects of neuromuscular blocking agents and tricyclic antidepressants; decreased pressor sensitivity of sympathomimetics; neurotoxicity may occur with phenothiazines or calcium channel blockers
ANTICONVULSANTS			
Clonazepam	CNS depressants, cimetidine, hormonal contraceptives, disulfiram, fluoxetine, isoniazid, ketoconazole, metoprolol, propranolol, valproic acid, probenecid	Rifampin, theophylline (↓ sedative effects), phenytoin	Increased phenytoin levels; decreased efficacy of levodopa
Carbamazepine	Verapamil, diltiazem, propoxyphene, erythromycin, clarithromycin, SSRIs, tricyclic antidepressants, cimetidine, isoniazid, danazol,	Cisplatin, doxorubicin, felbamate, rifampin, barbiturates, hydantoins, primidone, theophylline	Decreased levels of corticosteroids, doxycycline, quinidine, warfarin, estrogen-containing contraceptives, cyclosporine, benzodiazepines, theophylline,

	lamotrigine, niacin, acetazolamide, dalfopristin, valproate, nefazodone		lamotrigine, valproic acid, bupropion, haloperidol, olanzapine, tiagabine, topiramate, voriconazole, ziprasidone, felbamate, levothyroxine, or antidepressants; increased levels of lithium; life-threatening hypertensive reaction with MAOIs
Valproic acid	Chlorpromazine, cimetidine, erythromycin, felbamate, salicylates	Rifampin, carbamazepine, cholestyramine, lamotrigine, phenobarbital, ethosuximide, hydantoins	Increased effects of tricyclic antidepressants, carbamazepine, CNS depressants, ethosuximide, lamotrigine, phenobarbital, warfarin, zidovudine, hydantoins
Lamotrigine	Valproic acid	Primidone, phenobarbital, phenytoin, rifamycin, succinimides, oral contraceptives, oxcarbazepine, carbamazepine, acetaminophen	Decreased levels of valproic acid; increased levels of carbamazepine and topiramate
Topiramate	Metformin, hydrochlorothiazide	Phenytoin, carbamazepine, valproic acid, lamotrigine	Increased risk of CNS depression with alcohol or other CNS depressants; increased risk of

			kidney stones with carbonic anhydrase inhibitors; increased effects of phenytoin, metformin, amitriptyline; decreased effects of oral contraceptives, digoxin, lithium, risperidone, and valproic acid
Oxcarbazepine		Carbamazepine, phenobarbital, phenytoin, valproic acid, verapamil	Increased concentrations of phenobarbital and phenytoin; decreased effects of oral contraceptives, felodipine, and lamotrigine
CALCIUM CHANNEL BLOCKER			
Verapamil	Amiodarone, beta blockers, cimetidine, ranitidine, and grapefruit juice	Barbiturates, calcium salts, hydantoins, rifampin, and antineoplastics	Increased effects of beta blockers, disopyramide, flecainide, doxorubicin, benzodiazepines, buspirone, carbamazepine, digoxin, dofetilide, ethanol, imipramine, nondepolarizing muscle relaxants, prazosin, quinidine, sirolimus, tacrolimus, and theophylline; altered serum lithium levels
ANTIPSYCHOTIC AGENTS			
Olanzapine	Fluvoxamine and	Carbamazepine	Decreased effects of

	other CYP1A2 inhibitors, fluoxetine	and other CYP1A2 inducers, omeprazole, rifampin	levodopa and dopamine agonists; increased hypotension with antihypertensives; increased CNS depression with alcohol or other CNS depressants
Aripiprazole	Ketoconazole and other CYP3A4 inhibitors; quinidine, fluoxetine, paroxetine, or other potential CYP2D6 inhibitors	Carbamazepine, famotidine, valproate	Increased CNS depression with alcohol or other CNS depressants; increased hypotension with antihypertensives
Chlorpromazine	Beta blockers, paroxetine	Centrally acting anticholinergics	Increased effects of beta blockers; excessive sedation and hypotension with meperidine; decreased hypotensive effect of guanethidine; decreased effect of oral anticoagulants; decreased or increased phenytoin levels; increased orthostatic hypotension with thiazide diuretics; increased CNS depression with alcohol or other CNS depressants; increased hypotension with antihypertensives;

			increased anticholinergic effects with anticholinergic agents
Quetiapine	Cimetidine; ketoconazole, itraconazole, fluconazole, erythromycin, or other CYP3A4 inhibitors	Phenytoin, thioridazine	Decreased effects of levodopa and dopamine agonists; increased CNS depression with alcohol or other CNS depressants; increased hypotension with antihypertensives
Risperidone	Clozapine, fluoxetine, paroxetine, or ritonavir	Carbamazepine	Decreased effects of levodopa and dopamine agonists; increased effects of clozapine and valproate; increased CNS depression with alcohol or other CNS depressants; increased hypotension with antihypertensives
Ziprasidone	Ketoconazole and other CYP3A4 inhibitors	Carbamazepine	Life-threatening prolongation of QT interval with quinidine, dofetilide, other class Ia and III antiarrhythmics, pimozide, sotalol, thioridazine, chlorpromazine, pentamidine, arsenic trioxide, mefloquine, dolasetron, tacrolimus, droperidol, gatifloxacin, or

			moxifloxacin; decreased effects of levodopa and dopamine agonists; increased CNS depression with alcohol or other CNS depressants; increased hypotension with antihypertensives
Asenapine	Fluvoxamine, imipramine, valproate	Carbamazepine, cimetidine, paroxetine	Increased effects of paroxetine and dextromethorphan; increased CNS depression with alcohol or other CNS depressants; increased hypotension with antihypertensives; additive effects of QT interval prolongation with quinidine, dofetilide, other class Ia and III antiarrhythmics, pimozide, sotalol, thioridazine, chlorpromazine, pentamidine, arsenic trioxide, mefloquine, dolasetron, tacrolimus, droperidol, gatifloxacin, or moxifloxacin

TABLE 4–10 **Safety Issues and Nursing Interventions for Patients Taking Mood Stabilizers**

SAFETY ISSUES	NURSING INTERVENTIONS
Lithium toxicity (blood levels >1.2 mEq/L) or <1.2 in elderly or debilitated but most common at 1.5 mEq/L ■ Early signs: vomiting, diarrhea ■ Over 2 mEq/L: tremors, sedation, confusion ■ Levels over 3.5 mEq/L: delirium, seizures, coma, cardiovascular collapse, death Chlorpromazine (Thorazine) may mask early signs of lithium toxicity (Vallerand & Sanoski, 2019)	Instruct patients to report all medications, herbals, and caffeine use to physician or nurse practitioner to evaluate for drug interactions. Encourage patients to maintain fluid intake at 2,000–3,000 mL/day and avoid activities in which excessive sweating and fluid loss are a risk because inadequate fluid intake can affect lithium levels. Instruct patients about the importance of regular monitoring of serum lithium levels. Blood levels should be drawn 12 hours after the last dose.
Increased risk of suicide for all antiepileptics (FDA, 2008)	Assess for suicide risk regularly and inform patients of risks associated with anticonvulsants.
Hyponatremia (lithium, carbamazepine)	Instruct patients to maintain usual dietary intake of sodium. Assess for and educate patients to report any episodes of nausea, vomiting, headache, muscle weakness, confusion, seizures, because these may be signs of hyponatremia.
Stevens-Johnson syndrome (especially with lamotrigine and carbamazepine) This toxic skin necrolysis can be life threatening	Assess for and educate patients to report any signs of rash or unusual skin breakdown.
Hypotension, arrhythmias (lithium)	Monitor vital signs and instruct patients to report any symptoms of dizziness or palpitations.
Blood dyscrasias (valproic acid, carbamazepine)	Educate patients to report infections or other illness while on these medications.

	Ensure that platelet counts and bleeding time are determined before initiation of therapy. Monitor for spontaneous bleeding or bruising.
Increased risk of birth defects (anticonvulsant mood stabilizers)	Inform female patients of the risks of birth defects and provide education about contraception as desired.
Drowsiness (lithium and all anticonvulsants)	Instruct patients to avoid driving or operating dangerous machinery when experiencing this side effect. Assess patients' mental status for level of alertness.

 Open discussion and exploring the benefits versus disadvantages of medication treatment promotes patient-centered care and enables the nurse to troubleshoot with the client ways to minimize risks.

Another generally undesirable side effect of lithium is weight gain. Patients should be educated about this potential, and weight should be monitored at regular intervals. It may be helpful to discuss low-calorie diets while stressing the importance of not making significant changes in sodium intake because of its impact on serum blood levels of lithium.

CLINICAL PEARL The FDA requires that all antiepileptic (anticonvulsant) drugs carry a warning label indicating that use of the drugs increases risk for suicidal thoughts and behaviors. Patients treated with these medications should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior.

Outcome Criteria and Evaluation

The following criteria may be used for evaluating the effectiveness of therapy with mood-stabilizing agents.

The patient:

- Is maintaining stability of mood
- Has not harmed self or others
- Has experienced no injury from hyperactivity
- Is able to participate in activities without excessive sedation or dizziness
- Is maintaining appropriate weight
- Exhibits no signs of lithium toxicity
- Verbalizes importance of taking medication regularly and reporting for regular laboratory blood tests

Antipsychotic Agents

Background Assessment Data

Antipsychotic medications are also called *neuroleptics.* Historically, they have been referred to as major tranquilizers and have clear sedative effects. The term *antipsychotic* is most descriptive because the primary benefit over time is the alleviation of psychotic symptoms, such as hallucinations and delusions. Antipsychotic agents were introduced in the United States in the 1950s with the phenothiazines. Other drugs in this classification soon followed. Unfortunately, this group of medications has the potential for extrapyramidal side effects, also called **extrapyramidal symptoms** (EPS), that interfere with normal movements, including acute **dystonias** (muscle spasms) that can be life threatening, Parkinson-like symptoms, and **tardive dyskinesia** (later-onset involuntary movement disorders primarily in the tongue, lips, and jaw that may also involve other movement disturbances). Some of these side effects can be permanent, continuing even after the drug is discontinued.

Second generation antipsychotic medications have since been developed with less potential for EPS. These drugs have become the first line of treatment for clients with psychotic disorders, such as schizophrenia. This group of drugs may also be effective for treating negative symptoms of schizophrenia and alleviating positive symptoms such as hallucinations, delusions, and agitation. More

recently, aripiprazole (Abilify), an atypical antipsychotic, has been introduced as a third generation antipsychotic. It has a unique functional profile with dopamine receptors and minimal risk for EPS (Brust et al., 2015). In 2017 the FDA approved a novel (and controversial) formulation of Abilify (called Abilify MyCite) that includes a sensor device embedded in the pill that enables the patient (and others) to track whether they are taking the medication. In 2020 the FDA approved a novel antipsychotic medication, lumateperone (Caplyta), expected to be available in late 2020, which, although the action is unknown, reportedly demonstrates benefit in treating both positive and negative symptoms of schizophrenia.

Typical antipsychotics include the phenothiazines, haloperidol, loxapine, pimozide, and thiothixene. The atypical antipsychotics include aripiprazole, asenapine, clozapine, olanzapine, quetiapine, risperidone, paliperidone, iloperidone, lurasidone, and ziprasidone; the newest are brexpiprazole (Rexulti), cariprazine (Vraylar), and pimavanserin (Nuplazid). Pimavanserin is indicated for hallucinations and delusions associated with Parkinson's disease psychosis.

Indications

Antipsychotics are used in the treatment of schizophrenia and other psychotic disorders. Selected agents are used in the treatment of bipolar mania (see previous section, "Mood-Stabilizing Agents"). Others are used as antiemetics (chlorpromazine, perphenazine, prochlorperazine), in the treatment of intractable hiccoughs (chlorpromazine), and for the control of tics and vocal utterances in Tourette's disorder (haloperidol, pimozide). Selected atypical antipsychotics, including aripiprazole (Abilify), are also being identified as adjuncts to the treatment of major depressive disorder. (A table of current FDA-approved antipsychotics, half-life, and daily dosage ranges, as well as antiparkinsonian agents used to treat EPS caused by antipsychotic medication, can be found online at DavisPlus and in Chapter 24, "Schizophrenia Spectrum and Other Psychotic Disorders.")

Action

Typical antipsychotics work by blocking postsynaptic dopamine receptors in the basal ganglia, hypothalamus, limbic system, brainstem, and medulla. They also demonstrate varying affinity for cholinergic, alpha$_1$-adrenergic, and histaminic receptors. Antipsychotic effects may be related to inhibition of dopamine-mediated transmission of neural impulses at the synapses.

Atypical antipsychotics are weaker dopamine receptor antagonists than conventional antipsychotics but are more potent antagonists of the serotonin type 2A ($5HT_{2A}$) receptors. They also exhibit antagonism for cholinergic, histaminic, and adrenergic receptors. As mentioned previously, aripiprazole (Abilify) is a dopamine receptor antagonist that seems to have a unique way of accomplishing its action and thus has a minimal risk of EPS.

Contraindications and Precautions

Certain individuals may be at greater risk for experiencing side effects associated with antipsychotic agents. The elderly have been identified as an at-risk population because of reports of stroke and sudden death while taking antipsychotic medication. Studies have indicated that elderly patients with psychosis related to neurocognitive disorder (NCD) who are treated with antipsychotic drugs are at increased risk of death compared with those taking a placebo (Steinberg & Lyketsos, 2012). Causes of death are most commonly related to infections or cardiovascular problems. All antipsychotic drugs now carry black-box warnings about these risks. They are not approved for treatment of elderly patients with NCD-related psychosis.

Typical antipsychotics are contraindicated in clients with known hypersensitivity (cross-sensitivity may exist among phenothiazines). They should not be used in patients who are comatose or when CNS depression is evident; when blood dyscrasias exist; in clients with Parkinson's disease or narrow-angle glaucoma; for those with liver, renal, or cardiac insufficiency; in individuals with poorly controlled

seizure disorders; or in elderly clients with dementia-related psychosis.

Caution is indicated when administering typical antipsychotic medications to clients who are elderly, severely ill, or debilitated and to clients with diabetes or with respiratory insufficiency, prostatic hypertrophy, or intestinal obstruction. The risk for metabolic disturbances such as weight gain can have particularly dangerous consequences in the elderly adult.

Atypical antipsychotics are contraindicated in hypersensitive, comatose, or severely depressed patients; in elderly patients with dementia-related psychosis; and in women who are breastfeeding. Ziprasidone, risperidone, paliperidone, asenapine, and iloperidone are contraindicated in patients with a history of QT prolongation or cardiac arrhythmias, recent myocardial infarction (MI), uncompensated heart failure, and concurrent use with other drugs that prolong the QT interval. Clozapine is contraindicated in patients with myeloproliferative disorders, a history of clozapine induced **agranulocytosis** or severe granulocytopenia, or uncontrolled epilepsy. Lurasidone is contraindicated in individuals also using strong inhibitors of cytochrome P450 isozyme 3A4 (CYP3A4) (e.g., ketoconazole, an antifungal) and strong CYP3A4 inducers (e.g., rifampin, an antitubercular).

Caution is indicated when administering atypical antipsychotic medications to elderly or debilitated patients; patients with cardiac, hepatic, or renal insufficiency; those with a history of seizures; patients with diabetes or risk factors for diabetes; clients exposed to temperature extremes; pregnant women and children (safety not established); and under conditions that cause hypotension (dehydration, hypovolemia, treatment with antihypertensive medication). As with typical antipsychotics medications, the risk for metabolic disturbances such as weight gain can have particularly dangerous consequences in the elderly.

Interactions

Table 4–11 highlights some drug interactions that warrant monitoring and assessment by nurses.

TABLE 4–11 **Drug Interactions With Antipsychotic Medications**	
DRUG INTERACTION	ADVERSE EFFECT
Antihypertensives, central nervous system depressants Epinephrine or dopamine in combination with haloperidol or phenothiazines	Additive and potentially severe hypotension
Oral anticoagulants with phenothiazines	Less effective anticoagulant effects
Drugs that prolong QT intervals	Additive effects
Drugs that trigger orthostatic hypotension	Additive hypotension
Drugs with anticholinergic effects, including prescription and over-the-counter drugs	Additive anticholinergic effects, including anticholinergic toxicity, signs of which are ■ Flushing ■ Dry mouth ■ Mydriasis ■ Altered mental status ■ Tachycardia ■ Urinary retention ■ Tremulousness ■ Hypertension (Ramnarine & Ahmed, 2015)

Diagnosis

The following nursing diagnoses may be considered for patients receiving antipsychotic therapy:

- Risk for other-directed violence related to panic anxiety and mistrust of others
- Risk for injury related to medication side effects of sedation, photosensitivity, reduction of seizure threshold, agranulocytosis, extrapyramidal symptoms, tardive dyskinesia, neuroleptic malignant syndrome, or QT prolongation
- Risk for activity intolerance related to medication side effects of sedation, blurred vision, and weakness

- Nonadherence with medication regimen related to suspiciousness and mistrust of others

Safety Issues in Planning and Implementing Care

Table 4–12 discusses some significant safety issues to consider and relevant nursing interventions for patients taking antipsychotic medication.

TABLE 4–12 Safety Issues and Nursing Interventions for Patients Taking Antipsychotic Medication

SAFETY ISSUES	NURSING INTERVENTIONS
Extrapyramidal side effects[a]	Instruct patient to report any signs of muscle stiffness or spasms. Hold the medication if this occurs. Administer antiparkinsonian agents as ordered and immediately when signs of acute dystonia are present. Assess the patient for abnormal involuntary movements (see Box 4-2). (See "Additional Issues for Patient Education" for further discussion.)
Hyperglycemia, weight gain, and diabetes (more common with atypical antipsychotic agents)	Assess for a history of diabetes. Evaluate blood sugars. Instruct the patient in these risks and the importance of diet and exercise. Assess for signs of hyperglycemia including polydipsia, polyphagia, polyuria, and weakness.
Hypotension	Educate the patient about the risk for hypotension. Monitor blood pressure.
Orthostatic hypotension	Instruct patient to rise slowly from sitting to standing. Monitor blood pressure lying and then standing to assess for postural changes.
Lower seizure threshold (especially with clozapine)	Assess patient for history of seizure disorder. Monitor the patient for evidence of seizure activity and report to prescribing physician or nurse practitioner.
Prolonged QT interval,[b] especially ziprasidone, thioridazine, pimozide, haloperidol, paliperidone, iloperidone, asenapine, and clozapine.	Assess for history of arrhythmias, recent myocardial infarction, heart failure, and report to prescribing physician or nurse practitioner because these events are contraindications. Assess for other medications the patient is taking that prolong QT interval (there are many; online resources such as www.crediblemeds.org provide a composite list for comparison), but note that erythromycin and clarithromycin are two that are commonly prescribed. Instruct patient to report any rapid heartbeat, dizziness, or fainting. Check baseline ECG before beginning treatment.
Anticholinergic effects	Instruct patient about additive effects of other anticholinergic drugs in combination with

	antipsychotics, and to report any other medications taken including over-the-counter and herbal remedies. For minor symptoms such as dry mouth, recommend hard candies and sips of water. Instruct patient about the importance of good oral hygiene. Instruct patient to report and assess for any evidence of urinary retention, tachycardia, tremulousness, or hypertension, which may be signs of anticholinergic toxicity.
Sedation	Educate patient about this side effect and instruct patient not to drive or operate dangerous machinery if experiencing sedation.
Photosensitivity	Instruct patient to use sunblock and sunglasses and to wear protective clothing when in the sun because of the increased risk for severe sunburn while on these medications.
Agranulocytosis (more common with typical antipsychotics but especially with the atypical antipsychotic agent clozapine)	Instruct the patient receiving clozapine that regular monitoring of white blood cell and absolute neutrophil counts is essential. Instruct the patient to report any signs of sore throat, fever, or malaise. (See additional guidelines in the section “Issues in Antipsychotic Maintenance Therapy.”)
Neuroleptic malignant syndrome (NMS)[c]	Instruct patient to report immediately any fever, muscle rigidity, diaphoresis, tachycardia. Assess vital signs regularly, including temperature. Assess for deteriorating mental status or any other sign of NMS. Presence of any of these signs requires holding the medication and contacting the prescribing physician or nurse practitioner immediately, as well as monitoring vital signs and intake and output.
Drug reaction with eosinophilia and systemic symptoms (DRESS)	Assess for symptoms of DRESS including fever, rash, swollen lymph glands, swelling in the face. Hold medication and contact physician immediately. Assess for newly developing impulse control problems for patients taking aripiprazole.

(olanzapine)[d] (FDA, 2016b) New impulse control problems such as compulsive or uncontrollable urges to gamble, binge eat, shop, and have sex (aripiprazole) (FDA, 2016c)	Closely monitor patients who may be at increased risk for impulse control problems such as those with personal or family history of obsessive-compulsive disorder, bipolar disorder, impulsive personality, alcohol, drug, or other addictive behaviors.

[a]Acute dystonias can be life threatening (more common with typical antipsychotic agents).

[b]Potentially life threatening.

[c]Rare but potentially life-threatening side effect characterized by muscle rigidity, severe hyperthermia, and cardiac effects that can progress rapidly over 24–72 hours.

[d]Rare but serious; can lead to organ injury and even death.

Additional Issues for Patient Education

A comparison of side effects associated with antipsychotic agents is presented in Table 4–13. Patients should be apprised of health risks, including the following:

- Smoking increases the metabolism of antipsychotics, requiring an adjustment in dosage to achieve a therapeutic effect. Encourage patients to discuss this issue with the prescribing physician or nurse practitioner.
- Body temperature is harder to maintain with this medication, so patients should be encouraged to dress warmly in cold weather and avoid extended exposure to very high or low temperatures.
- Antipsychotic medications increase photosensitivity to sunlight. Advise patients to wear sunscreen and protective clothing when exposed to the sun.
- Alcohol and antipsychotic drugs potentiate each other's effects, so patients should be advised to avoid drinking alcohol while on antipsychotic therapy.

- Many medications contain substances that interact with antipsychotics in a way that may be harmful. Patients should avoid taking other medications, including over-the-counter products, without the physician's approval.
- A significant number of patients on clozapine report excessive salivation. Sugar-free gum and medications (anticholinergic or alpha$_2$-adrenoceptor agonists) may alleviate symptoms.

  Encourage patients to discuss these options with the prescribing physician or nurse practitioner.
- Safe use of antipsychotics during pregnancy has not been established. Antipsychotics are thought to readily cross the placental barrier; if so, a fetus could experience adverse effects of the drug. Patients should be aware of the possible risks and should inform the physician immediately if pregnancy occurs, is suspected, or is planned.

TABLE 4–13 **Sedative-Hypnotic Agents**

CHEMICAL CLASS	GENERIC (TRADE) NAME	CONTROLLED CATEGORIES	DAILY DOSAGE RANGE
Barbiturates	Amobarbital	CII	60–200 mg
	Butabarbital (Butisol)	CIII	45–120 mg
	Pentobarbital (Nembutal)	CII	150–200 mg
	Phenobarbital (Luminal; Solfoton)	CIV	30–200 mg
	Secobarbital (Seconal)	CII	100 mg (hypnotic); 200–300 mg (preoperative sedation)
Benzodiazepines	Estazolam	CIV	0.5–2 mg
	Flurazepam	CIV	15–30 mg
	Temazepam (Restoril)	CIV	7.5–30 mg
	Triazolam (Halcion)	CIV	0.125–0.5 mg
Miscellaneous			
	Eszopiclone (Lunesta)	CIV	1–3 mg
	Ramelteon (Rozerem)	N/A	8 mg
	Zaleplon (Sonata)	CIV	5–20 mg
	Zolpidem (Ambien)	CIV	5–10 mg (immediate release) 6.25–12.5 mg (extended release
	Lemborexant (Dayvigo)	(pending)	5–10 mg

Issues in Antipsychotic Maintenance Therapy

The nurse must understand the management of side effects associated with antipsychotic medication to conduct a thorough assessment and minimize risks. In addition, some of these side

effects can be difficult for patients to manage or understand, particularly when they are struggling with impaired mental status including psychosis and cognitive deficits. Three of these are discussed here.

Clozaril and the Risk for Agranulocytosis The FDA requires close monitoring of patients on medications that increase the risk for life-threatening side effects. Clozaril is one such drug. Due to the risk of agranulocytosis, the FDA requires that clozapine be part of a Risk Evaluation and Mitigation Strategy (REMS) program to ensure that risk for agranulocytosis is monitored, managed, and reported. Agranulocytosis is a potentially fatal blood disorder in which the patient's absolute neutrophil count (ANC) drops to extremely low levels (less than or equal to 500 μL). This condition is called neutropenia. An ANC must be assessed before initiation of treatment with clozapine and weekly for the first 6 months of treatment. Initially, only a 1-week supply of medication is dispensed at a time. If the ANC remains within acceptable levels (i.e., ANC at least 1,500 μL) during the first 6 months, blood counts may be monitored biweekly for another 6 months and monthly thereafter. Some darker-skinned ethnic groups, particularly those of African and Middle Eastern descent, have normally lower ANC (benign ethnic neutropenia) than other ethnic groups; in such cases the parameters for identifying clinically significant neutropenia are altered (Clozapine REMS, 2015).

Although the benefits of clozapine can be profound, this medication is typically used when patients fail to respond to other antipsychotics because of the strict protocols for adherence. If the patient agrees to this option, the nurse can be a vital resource in ensuring that support services, both professional and personal (such as family members or peers), are engaged to assist the patient with follow-through as needed.

Extrapyramidal Side Effects (See Table 4–13 for differences between typical and atypical antipsychotics.) To conduct a thorough assessment, the nurse must be familiar with several distinct types of extrapyramidal side effects:

- **Pseudoparkinsonism:** Symptoms of pseudoparkinsonism—tremor, shuffling gait, drooling, rigidity—may appear 1 to 5 days following initiation of antipsychotic medication. This side effect occurs most often in women, the elderly, and dehydrated clients.
- **Akinesia:** Absence or impairment in voluntary movement.
- **Akathisia:** Continuous restlessness and fidgeting, or **akathisia,** occurs most often in women and may manifest 50 to 60 days after therapy begins. Combining atypical antipsychotics has demonstrated a three-fold risk for developing akathisia compared with monotherapy with a single second generation antipsychotic (Berna et al., 2015).
- **Dystonia:** This side effect—involuntary muscle spasms in the face, arms, legs, and neck—occurs most often in men and those younger than age 25. **Dystonia** should be treated as an emergency because laryngospasm follows these symptoms and can be fatal. The physician should be contacted, and intravenous or intramuscular benztropine mesylate (Cogentin) is commonly administered (see Chapter 24, “Schizophrenia Spectrum and Other Psychotic Disorders,” for a list of antiparkinsonian agents used to treat EPS). Nurses should stay with the patient and offer reassurance.
- **Oculogyric crisis:** Uncontrolled rolling back of the eyes, or **oculogyric crisis,** is a symptom of acute dystonia and can be mistaken for seizure activity. As with other symptoms of acute dystonia, this side effect should be treated as a medical emergency.
- **Tardive dyskinesia:** This extrapyramidal side effect involves bizarre face and tongue movements, stiff neck, and difficulty swallowing. It may occur with all classifications but most commonly takes place with typical antipsychotics. All clients receiving antipsychotic therapy for months or years are at risk. Symptoms are potentially irreversible. Nurses should immediately report early signs of **tardive dyskinesia** (usually vermiform movements of the tongue) to the prescribing physician or nurse practitioner. Often, the drug is discontinued, changed to a different antipsychotic, or the dosage is altered. In 2017 the FDA approved

the first drug for treating tardive dyskinesia, valbenazine (Ingrezza). It is hoped that this novel drug will effectively reduce this troubling condition and its sometimes stigmatizing effects (FDA, 2017). The involuntary movements associated with tardive dyskinesia can be measured by the Abnormal Involuntary Movement Scale (AIMS), developed in the 1970s by the National Institute of Mental Health. AIMS aids in early detection of movement disorders and provides means for ongoing surveillance. AIMS is featured in Box 4-2.

BOX 4–2 **Abnormal Involuntary Movement Scale (AIMS)**

NAME _____ **RATER NAME** _____ **DATE** _____

Instructions: Complete the examination procedure before making ratings. For movement ratings, circle the highest severity observed. Rate movements that occur upon activation one less than those observed spontaneously. Circle movement as well as code number that applies.

Code: 0 = None
1 = Minimal, may be normal
2 = Mild
3 = Moderate
4 = Severe

Facial and Oral Movements	1. **Muscles of Facial Expression** (e.g., movements of forehead, eyebrows, periorbital area, cheeks, including frowning, blinking, smiling, grimacing)	0 1 2 3 4
	2. **Lips and Perioral Area** (e.g., puckering, pouting, smacking)	0 1 2 3 4
	3. **Jaw** (e.g., biting, clenching, chewing, mouth opening, lateral movement)	0 1 2 3 4
	4. **Tongue** (Rate only increases in movement both in and out of mouth. NOT inability to sustain movement. Darting in and out of mouth.)	0 1 2 3 4
Extremity Movements	5. **Upper (arms, wrists, hands, fingers)** Include choreic movements (i.e., rapid, objectively purposeless, irregular, spontaneous) and athetoid movements (i.e., slow, irregular, complex serpentine). *Do not include tremor* (i.e., repetitive, regular, rhythmic)	0 1 2 3 4
	6. **Lower (legs, knees, ankles, toes)** (e.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot)	0 1 2 3 4
Trunk Movements	7. **Neck, shoulders, hips** (e.g., rocking, twisting, squirming, pelvic gyrations)	0 1 2 3 4
Global Judgments	8. **Severity of abnormal movements overall**	0 1 2 3 4
	9. **Incapacitation due to abnormal movements**	0 1 2 3 4
	10. **Patient's awareness of abnormal movements** (Rate only the patient's report) No awareness Aware, no distress Aware, mild distress Aware, moderate distress Aware, severe distress	0 1 2 3 4

Dental Status	11. Current problems with teeth and/or dentures?	No	Yes
	12. Are dentures usually worn?	No	Yes
	13. Edentia?	No	Yes
	14. Do movements disappear in sleep?	No	Yes

AIMS EXAMINATION PROCEDURE

Either before or after completing the Examination Procedure, observe the patient unobtrusively, at rest (e.g., in waiting room). The chair to be used in this examination should be a hard, firm one without arms.

1. Ask patient to remove shoes and socks.
2. Ask patient whether there is anything in his/her mouth (i.e., gum, candy, etc.), and if there is, to remove it.
3. Ask patient about the current condition of his/her teeth. Ask client if he/she wears dentures. Do teeth or dentures bother patient now?
4. Ask patient whether he/she notices any movements in mouth, face, hands, or feet. If yes, ask to describe and to what extent they currently bother client or interfere with his/her activities.
5. Have patient sit in chair with both hands on knees, legs slightly apart, and feet flat on floor. (Look at entire body for movements while in this position.)
6. Ask patient to sit with hands hanging unsupported. If male, between legs, if female and wearing a dress, hanging over knees. (Observe hands and other body areas.)
7. Ask patient to open mouth. (Observe tongue at rest within mouth.) Do this twice.
8. Ask patient to protrude tongue. (Observe abnormalities of tongue movement.) Do this twice.
9. Ask patient to tap thumb with each finger as rapidly as possible for 10 to 15 seconds; separately with right hand, then with left hand. (Observe facial and leg movements.)
10. Flex and extend patient's left and right arms (one at a time). (Note any rigidity.)
11. Ask patient to stand up. (Observe in profile. Observe all body areas again, hips included.)
12. Ask patient to extend both arms outstretched in front with palms down. (Observe trunk, legs, and mouth.)
13. Have patient walk a few paces, turn, and walk back to chair. (Observe hands and gait.) Do this twice.

INTERPRETATION OF AIMS SCORE

Add patient scores and note areas of difficulty.
Score of:

- 0 to 1 = Low risk
- 2 in only ONE of the areas assessed = borderline/observe closely
- 2 in TWO or more of the areas assessed **or** 3 to 4 in ONLY ONE area = indicative of TD

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Some EPS can be life threatening, and those that are not can sometimes be permanent. The abnormal movements in the tongue and lips are sometimes very visible and severe enough to interfere with a person's ability to speak or swallow.

The nurse's empathic approach in listening to the patient's wishes with regard to medication and advocating for exploring other options for management of symptoms is one way to promote patient-centered care, an essential nursing competency (IOM, 2003), and to promote a recovery model that empowers the patient to make decisions about management of the illness. There is evidence (Haddad, Brain, & Scott, 2014) that remaining on antipsychotic medication can reduce the frequency of hospitalizations, and early treatment at the first psychotic episode may reduce some long-term consequences of illness. Educating patients about these risks and benefits is important in assisting them to make informed decisions about medication treatment.

Hormonal Side Effects The following are sexual side effects that may accompany these medications:

- Decreased libido, **retrograde ejaculation** (the discharge of seminal fluid into the bladder rather than through the urethra); **gynecomastia** (men)
- Amenorrhea (women); galactorrhea

These side effects can be troubling for anyone, but for a patient struggling with thought disturbances, they can become the foundation for delusions. A male patient with gynecomastia, for example, might begin to believe that external forces are taking over his body and turning him into a woman. An amenorrheic woman may begin to believe that she has been divinely impregnated. It is important for the nurse to clarify that these are side effects of the medication and offer reassurance that they are reversible. Women with amenorrhea should be instructed that this side effect does not indicate cessation of ovulation, so contraception use should continue as usual. Patients should be encouraged to explore alternative treatment if these side effects are deemed intolerable.

Current Developments in Psychopharmacological Treatment of Schizophrenia

One of the identified limitations of medication treatments available for schizophrenia is the cognitive deficits that are core symptoms of this illness, including deficits in working memory and long-term memory, reduced processing speed, limited verbal fluency, and impaired executive functions. Some atypical antipsychotics have demonstrated efficacy in lessening cognitive deficits but do not eliminate residual effects.

Cariprazine (Vraylor) has demonstrated efficacy in treating the negative symptoms of schizophrenia, including flat affect, social withdrawal, and apathy (Harrison, 2015). Although cariprazine is similar to other atypical antipsychotics, its particular affinity for certain dopamine receptors (D3) is believed to be associated with its superior impact on negative symptoms, particularly improving social behavior and self-care. In addition, cariprazine has demonstrated effectiveness in reducing substance use, a common comorbidity in patients with schizophrenia, and its long half-life enables maintenance of therapeutic levels even when a few doses are missed (Scarff, 2017). Negative symptoms can complicate the prognosis in treatment of schizophrenia and as Scarff (2017) points out, the evidence supports "cautious optimism" that cariprazine may become the first-line treatment for patients with "disabling negative symptoms or impairment in self-care and interpersonal relationships" (p. 237).

Outcome Criteria and Evaluation

The following criteria may be used for evaluating the effectiveness of therapy with antipsychotic medications.

The patient:

- Has not harmed self or others
- Has not experienced injury secondary to lowered seizure threshold or photosensitivity
- Maintains an ANC within normal limits
- Exhibits no symptoms of EPS, tardive dyskinesia, neuroleptic malignant syndrome, or hyperglycemia
- Maintains weight within normal limits

- Tolerates activity unaltered by the effects of sedation or weakness
- Takes medication willingly
- Verbalizes understanding of medication regimen and the importance of regular administration
- Demonstrates improvement in self-care and prosocial behavior

Sedative-Hypnotics

Background Assessment Data

Indications

Sedative-hypnotics are used in the short-term management of various anxiety states and to treat insomnia. Selected agents are used as anticonvulsants (pentobarbital, phenobarbital) and preoperative sedatives (pentobarbital, secobarbital) and to reduce anxiety associated with alcohol withdrawal (chloral hydrate). (A table of current FDA-approved sedative-hypnotics, half-lives, and daily dosage ranges can be found online at Davis*Plus.*) Examples of commonly used sedative-hypnotics are presented in Table 4–13.

Action

Sedative-hypnotics cause generalized CNS depression. They may produce tolerance with chronic use and have the potential for psychological or physical dependence.

> **EXCEPTION:** Ramelteon (Rozerem) is not a controlled substance. It does not produce tolerance or physical dependence. Sleep-promoting properties are the result of ramelteon's agonist activity on selective melatonin receptors.

Contraindications and Precautions

Sedative-hypnotics are contraindicated in individuals with hypersensitivity to the drug or to any drug within the chemical class; in pregnancy (exceptions may be made in certain cases based on benefit-to-risk ratio); during lactation; in severe hepatic, cardiac, respiratory, or renal disease; and in children younger than age 15 years for flurazepam and those younger than age 18 years for

estazolam, quazepam, temazepam, and triazolam. Triazolam is contraindicated with concurrent use of medications that impair the metabolism of triazolam by cytochrome P4503A (CYP3A), such as, ketoconazole, itraconazole, and nefazodone. Ramelteon is contraindicated with concurrent use of fluvoxamine. Zolpidem, zaleplon, eszopiclone, and ramelteon are contraindicated in children. Chloral hydrate is contraindicated in persons with esophagitis, gastritis, or peptic ulcer disease and those with hepatic, renal, or cardiac impairment.

Caution should be used in administering these drugs to patients with cardiac, hepatic, renal, or respiratory insufficiency. They should be used with caution in patients who may be suicidal or who previously may have been addicted to drugs. Hypnotic use should be short term. Elderly patients may be more sensitive to CNS depressant effects, and dosage reduction may be required. Chloral hydrate should be used with caution in patients susceptible to acute intermittent porphyria.

Interactions

Barbiturates The effects of barbiturates are increased with concomitant use of alcohol, other CNS depressants, MAOIs, or valproic acid. The effects of barbiturates may be decreased with rifampin. Possible decreased effects of the following drugs may occur when used concomitantly with barbiturates: anticoagulants, beta blockers, carbamazepine, clonazepam, oral contraceptives, corticosteroids, digitoxin, doxorubicin, doxycycline, felodipine, fenoprofen, griseofulvin, metronidazole, phenylbutazone, quinidine, theophylline, or verapamil. Concomitant use with methoxyflurane may enhance renal toxicity.

Benzodiazepines The effects of the benzodiazepine hypnotics are increased with concomitant use of alcohol or other CNS depressants, cimetidine, oral contraceptives, disulfiram, isoniazid, or probenecid. The effects of the benzodiazepine hypnotics are decreased with concomitant use of rifampin, theophylline, carbamazepine, or St. John’s wort and with cigarette smoking. The

effects of digoxin or phenytoin are increased when used concomitantly with benzodiazepines. Bioavailability of triazolam is increased with concurrent use of macrolides.

Eszopiclone (Lunesta) Additive effects of eszopiclone occur with alcohol or other CNS depressants. Decreased effects of eszopiclone occur with CYP3A4 inducers (e.g., rifampin, phenytoin, carbamazepine, phenobarbital), with lorazepam, or following a high-fat or heavy meal. Increased effects of eszopiclone occur with CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, nefazodone, ritonavir, and nelfinavir).

Zaleplon (Sonata) Additive effects of zaleplon occur with alcohol or other CNS depressants. Decreased effects of zaleplon occur with CYP3A4 inducers (e.g., rifampin, phenytoin, carbamazepine, phenobarbital) or following a high-fat or heavy meal. There are increased effects of zaleplon with cimetidine.

Zolpidem (Ambien, Ambien CR, Edluar, Intermezzo, Zolpimist) Increased effects of zolpidem occur with alcohol or other CNS depressants, azole antifungals, ritonavir, or SSRIs. Decreased effects of zolpidem occur with flumazenil, rifampin, and with food. There is a risk of life-threatening cardiac arrhythmias with concomitant use of amiodarone.

Ramelteon (Rozerem) Increased effects of ramelteon occur with alcohol, ketoconazole (and other CYP3A4 inhibitors), and fluvoxamine (and other CYP1A2 inhibitors). Decreased effects of ramelteon occur with rifampin (and other CYP3A4 inducers) and following a heavy or high-fat meal.

Diagnosis

The following nursing diagnoses may be considered for patients receiving therapy with sedative-hypnotics:

- Risk for injury related to abrupt withdrawal from long-term use or decreased mental alertness caused by residual sedation
- Disturbed sleep pattern or insomnia related to situational crises, physical condition, or severe level of anxiety

- Risk for activity intolerance related to side effects of lethargy, drowsiness, and dizziness
- Risk for acute confusion related to action of the medication on the CNS

Safety Issues in Planning and Implementing Care

Refer to the earlier discussion of safety issues in the section "Antianxiety Agents." In addition to the side effects listed in that section, abnormal thinking and behavioral changes, including aggressiveness, hallucinations, and suicidal ideation, have also been noted in some individuals taking sedative-hypnotics. Certain complex behaviors, such as sleep-driving, preparing and eating food, and making phone calls, with amnesia for the behavior, have occurred. Although a direct correlation between these behaviors and the use of sedative-hypnotics cannot be made, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

Outcome Criteria and Evaluation

The following criteria may be used for evaluating the effectiveness of therapy with sedative-hypnotic medications.

The patient:

- Demonstrates reduced anxiety, tension, and restless activity
- Falls asleep within 30 minutes of taking the medication and remains asleep for 6 to 8 hours without interruption
- Is able to participate in usual activities without residual sedation
- Experiences no physical injury
- Exhibits no evidence of confusion
- Verbalizes understanding of taking the medication on a short-term basis
- Verbalizes understanding of potential for development of tolerance and dependence with long-term use

Agents for Attention Deficit-Hyperactivity Disorder (ADHD)

Background Assessment Data

Indications

The medications in this section are used to treat ADHD in children and adults. Amphetamines are also used in the treatment of narcolepsy and exogenous obesity. Bupropion is used in the treatment of major depression and for smoking cessation (Zyban only). Clonidine and guanfacine are used to treat hypertension. (A table of current FDA-approved agents for ADHD, half-life, and daily dosage ranges can be found online at Davis*Plus* and in Chapter 32, "Children and Adolescents.")

Action

CNS stimulants increase levels of neurotransmitters (probably norepinephrine, dopamine, and serotonin) in the CNS. They produce CNS and respiratory stimulation, vasoconstriction, dilated pupils, increased motor activity, mental alertness, decreased fatigue, and improved attention span in ADHD. The CNS stimulants discussed in this section include dextroamphetamine sulfate, methamphetamine, lisdexamfetamine, amphetamine mixtures, methylphenidate, and dexmethylphenidate. Their mechanism of action in the treatment of ADHD is unclear. However, recent research indicates that their effectiveness in the treatment of hyperactivity disorders is based on the activation of dopamine D_4 receptors in the basal ganglia and thalamus, which depress rather than enhance motor activity (Erlij et al., 2012).

Atomoxetine inhibits the reuptake of norepinephrine, and bupropion blocks the neuronal uptake of serotonin, norepinephrine, and dopamine. Clonidine and guanfacine stimulate central alpha-adrenergic receptors in the brain, resulting in reduced sympathetic outflow from the CNS. The exact mechanism by which these nonstimulant drugs produce the therapeutic effect in ADHD is unclear.

Contraindications and Precautions

CNS stimulants are contraindicated in individuals with hypersensitivity to sympathomimetic amines. They should not be used in patients with advanced arteriosclerosis, cardiovascular disease, hypertension, hyperthyroidism, glaucoma, or agitated or hyperexcitability states; in clients with a history of drug abuse; during or within 14 days of receiving therapy with MAOIs; in children younger than age 3; or during pregnancy and lactation. Atomoxetine and bupropion are contraindicated in clients with hypersensitivity to the drugs or their components, in lactation, and in concomitant use with or within 2 weeks of using MAOIs. Atomoxetine is contraindicated in clients with narrow-angle glaucoma. Bupropion is contraindicated in individuals with known or suspected seizure disorder, in the acute phase of MI, and in clients with bulimia or anorexia nervosa. Alpha-agonists are contraindicated in clients with known hypersensitivity to the drugs.

Caution is advised in using CNS stimulants in children with psychosis; in Tourette's disorder; in clients with anorexia or insomnia; in elderly, debilitated, or asthenic clients; and in clients with a history of suicidal or homicidal tendencies. Prolonged use may result in tolerance and physical or psychological dependence. Atomoxetine and bupropion should be used with caution in clients with urinary retention, hypertension, or hepatic, renal, or cardiovascular disease; in suicidal clients; during pregnancy; and in elderly and debilitated clients. Alpha-agonists should be used with caution in clients with coronary insufficiency, recent MI, or cerebrovascular disease; in chronic renal or hepatic failure; in the elderly; and in pregnancy and lactation.

Interactions

CNS Stimulants (Amphetamines) Effects of amphetamines are increased with furazolidone or urinary alkalinizers. Hypertensive crisis may occur with concomitant use of (and up to several weeks after discontinuing) MAOIs. Increased risk of serotonin syndrome occurs with coadministration of SSRIs. Decreased effects of amphetamines occur with urinary acidifiers, and decreased hypotensive effects of guanethidine occur with amphetamines.

Dexmethylphenidate and Methylphenidate Effects of antihypertensive agents and pressor agents (e.g., dopamine, epinephrine, phenylephrine) are decreased with concomitant use of methylphenidates. Effects of coumarin anticoagulants, anticonvulsants (e.g., phenobarbital, phenytoin, primidone), tricyclic antidepressants, and SSRIs are increased with the methylphenidates. Hypertensive crisis may occur with coadministration of MAOIs.

Atomoxetine Effects of atomoxetine are increased with concomitant use of CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, quinidine). Potentially fatal reactions may occur with concurrent use of (or within 2 weeks of discontinuation of) MAOIs. Risk of cardiovascular effects is increased with concomitant use of albuterol or vasopressors.

Bupropion Effects of bupropion are increased with amantadine, levodopa, or ritonavir. Effects of bupropion are decreased with carbamazepine. There is an increased risk of acute toxicity with MAOIs. Increased risk of hypertension may occur with nicotine replacement agents, and adverse neuropsychiatric events may occur with alcohol. Increased anticoagulant effects of warfarin and increased effects of drugs metabolized by CYP2D6 (e.g., nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, sertraline, haloperidol, risperidone, thioridazine, metoprolol, propafenone, and flecainide) occur with concomitant use.

Alpha Agonists Synergistic pharmacological and toxic effects, possibly causing atrioventricular block, bradycardia, and severe hypotension, may occur with concomitant use of calcium channel blockers or beta blockers. Additive sedation occurs with CNS depressants, including alcohol, antihistamines, opioid analgesics, and sedative-hypnotics. Effects of clonidine may be decreased with concomitant use of tricyclic antidepressants and prazosin. Decreased effects of levodopa may occur with clonidine, and effects of guanfacine are decreased with barbiturates or phenytoin.

Diagnosis

The following nursing diagnoses may be considered for patients receiving therapy with agents for ADHD:

- Risk for injury related to overstimulation and hyperactivity (CNS stimulants) or seizures (possible side effect of bupropion)
- Risk for suicide secondary to major depression related to abrupt withdrawal after extended use (CNS stimulants)
- Risk for suicide (children and adolescents) as a side effect of atomoxetine and bupropion (black-box warning)
- Imbalanced nutrition, less than body requirements, related to side effects of anorexia and weight loss (CNS stimulants)
- Insomnia related to side effects of overstimulation
- Nausea related to side effects of atomoxetine or bupropion
- Pain related to side effect of abdominal pain (atomoxetine, bupropion) or headache (all agents)
- Risk for activity intolerance related to side effects of sedation and dizziness with atomoxetine or bupropion

Planning and Implementation

The plan of care should include monitoring for the following side effects from agents for ADHD. Nursing implications related to each side effect are designated by an asterisk (*).

- Overstimulation, restlessness, insomnia (CNS stimulants)
  *Assess mental status for changes in mood, level of activity, degree of stimulation, and aggressiveness.
  *Ensure that the patient is protected from injury.
  *Keep stimuli low and environment as quiet as possible to discourage overstimulation.
  *To prevent insomnia, administer the last dose at least 6 hours before bedtime. Administer sustained-release forms in the morning.
- Palpitations, tachycardia (CNS stimulants, atomoxetine, bupropion, clonidine), or bradycardia (clonidine, guanfacine)
  *Monitor and record vital signs at regular intervals (two or three times a day) throughout therapy. Report significant changes to the physician immediately.

NOTE: The FDA has issued warnings for CNS stimulants and atomoxetine about the risk for sudden death in patients who have cardiovascular disease. A careful personal and family history of heart disease, heart defects, or hypertension should be obtained before these medications are prescribed. Careful monitoring of cardiovascular function during administration must be ongoing.

- Anorexia, weight loss (CNS stimulants, atomoxetine, bupropion)
  *To reduce anorexia, the medication may be administered immediately after meals.
  *The patient should be weighed regularly (at least weekly) when receiving therapy with CNS stimulants, atomoxetine, or bupropion because of the potential for anorexia and weight loss and temporary interruption of growth and development.
- Tolerance, physical and psychological dependence (CNS stimulants)
  *In children with ADHD, a drug “holiday” should be attempted periodically under the direction of the physician to determine the effectiveness of the medication and the need for continuation.
  *The drug should not be withdrawn abruptly. To do so could initiate a syndrome of symptoms with nausea, vomiting, abdominal cramping, headache, fatigue, weakness, mental depression, suicidal ideation, increased dreaming, and psychotic behavior.
- Nausea and vomiting (atomoxetine and bupropion) *Recommend taking medication with food to minimize gastrointestinal upset.
- Constipation (atomoxetine, bupropion, clonidine, guanfacine)
  *Recommend increasing fiber and fluid in diet if not contraindicated.
- Dry mouth (clonidine and guanfacine)
  *Offer the patient sugarless candy, ice, and frequent sips of water.
  *Strict oral hygiene is very important.
- Sedation (clonidine and guanfacine)
  *Warn the patient that this effect is increased by concomitant use of alcohol and other CNS drugs.

*Warn the patient to refrain from driving or performing hazardous tasks until response has been established.

- Potential for seizures (bupropion)
  *Protect the patient from injury if seizure should occur.
  *Instruct family and significant others of patients on bupropion therapy how to protect the patient during a seizure if one should occur.
  *Ensure that doses of the immediate-release medication are administered at least 4 to 6 hours apart and doses of the sustained-release medication at least 8 hours apart.
- Severe liver damage (with atomoxetine)
  *Monitor for the following side effects and report to the physician immediately: itching, dark urine, right upper quadrant pain, yellow skin or eyes, sore throat, fever, malaise.
- New or worsened psychiatric symptoms (with CNS stimulants and atomoxetine)
  *Monitor for psychotic symptoms (e.g., hearing voices, paranoid behaviors, delusions).
  *Monitor for manic symptoms, including aggressive and hostile behaviors.
- Rebound syndrome (with clonidine and guanfacine)
  *The patient should be instructed not to discontinue therapy abruptly. To do so may result in symptoms of nervousness, agitation, headache, tremor, and a rapid rise in blood pressure. In addition, sudden withdrawal from stimulants may increase the risk of depression and suicide.
  *Dosage should be tapered gradually under the supervision of the physician.

Patient and Family Education

Instruct the patient and family that the patient should:

- Use caution when driving or operating dangerous machinery. Drowsiness, dizziness, and blurred vision can occur.
- Not stop taking CNS stimulants abruptly. To do so could produce serious withdrawal symptoms.

- Avoid taking CNS stimulants late in the day to prevent insomnia. Take medication no later than 6 hours before bedtime.
- Not take other medications (including over-the-counter drugs) without the physician's approval. Many medications contain substances that, in combination with agents for ADHD, can be harmful.
- Monitor blood sugar two or three times a day or as instructed by the physician if the patient is diabetic. Be aware of the need for possible alteration in insulin requirements because of changes in food intake, weight, and activity.
- Avoid consumption of large amounts of caffeinated products (coffee, tea, colas, chocolate), as they may enhance the CNS stimulant effect.
- Notify physician if restlessness, insomnia, anorexia, or dry mouth becomes severe or if rapid, pounding heartbeat becomes evident.
- Report any of the following side effects to the physician immediately: shortness of breath, chest pain, jaw/left arm pain, fainting, seizures, sudden vision changes, weakness on one side of the body, slurred speech, confusion, itching, dark urine, right upper quadrant pain, yellow skin or eyes, sore throat, fever, malaise, increased hyperactivity, believing things that are not true, or hearing voices.
- Be aware of possible risks of taking agents for ADHD during pregnancy. Safe use during pregnancy and lactation has not been established. Inform the physician immediately if pregnancy is suspected or planned.
- Be aware of potential side effects of agents for ADHD. Refer to written materials furnished by health-care providers for safe self-administration.
- Carry a card or other identification at all times describing current medications.

Outcome Criteria and Evaluation

The following criteria may be used for evaluating the effectiveness of therapy with agents for ADHD.

The patient:

- Does not exhibit excessive hyperactivity
- Has not experienced injury
- Is maintaining expected parameters of growth and development
- Verbalizes understanding of safe self-administration and the importance of not withdrawing medication abruptly

Summary and Key Points

- Psychotropic medications are intended to be used as adjunctive therapy to individual or group psychotherapy.
- *Antianxiety agents* are used in the treatment of anxiety disorders and to alleviate acute anxiety symptoms. Benzodiazepines are the most commonly used group. They are CNS depressants and have the potential for physical and psychological dependence. They should not be discontinued abruptly following long-term use because they can produce a life-threatening withdrawal syndrome. The most common side effects are drowsiness, confusion, and lethargy.
- *Antidepressants* elevate mood and alleviate other symptoms associated with moderate-to-severe depression. These drugs work by increasing the concentration of norepinephrine, serotonin, or dopamine in the body.
- The tricyclics and related drugs accomplish their effects by blocking the reuptake of norepinephrine at the neuron.
- Another group of antidepressants inhibits MAO, an enzyme that is known to inactivate norepinephrine and serotonin. They are called MAOIs.
- A third category of drugs blocks neuronal reuptake of serotonin and has minimal or no effect on reuptake of norepinephrine or dopamine (SSRIs).
- SNRIs are antidepressant medications that block reuptake of serotonin and norepinephrine.
- Atypical antidepressants are a group of medications that act differently than other classes of antidepressants to decrease

reuptake of serotonin, norepinephrine, and/or dopamine.

- Esketamine nasal spray is a novel treatment for treatment-resistant depression that acts as an NMDA receptor antagonist. How it exerts antidepressant effects is unknown.
- Antidepressant medications may take up to 2 weeks before desired effects are noticed and may take up to 4 weeks to produce full therapeutic benefits. The most common side effects are anticholinergic effects, sedation, and orthostatic hypotension. They can also reduce the seizure threshold. MAOIs can cause a hypertensive crisis if food or other products containing tyramine are consumed while taking these medications.
- Lithium carbonate is widely used as a *mood-stabilizing agent.* Its mechanism of action is not fully understood, but it is thought to enhance the reuptake of norepinephrine and serotonin in the brain, thereby lowering the levels in the body, resulting in decreased hyperactivity. The most common side effects are dry mouth, gastrointestinal upset, polyuria, and weight gain.
- There is a narrow margin between the therapeutic and toxic levels of lithium. Serum levels must be drawn regularly to monitor for toxicity. Symptoms of lithium toxicity begin to appear at serum levels of approximately 1.5 mEq/L. If left untreated, lithium toxicity can be life threatening.
- Several other medications are used as mood-stabilizing agents. Two groups, anticonvulsants (carbamazepine, clonazepam, valproic acid, lamotrigine, oxcarbazepine, and topiramate) and the calcium channel blocker verapamil, have been used with some effectiveness. Their action in the treatment of bipolar mania is not well understood.
- More recently, several atypical antipsychotic medications have been used with success in the treatment of bipolar mania. These include olanzapine, aripiprazole, quetiapine, risperidone, asenapine, and ziprasidone. The phenothiazine chlorpromazine has also been used effectively. The action of antipsychotics in the treatment of bipolar mania is not understood.
- *Antipsychotic drugs* are used in the treatment of acute and chronic psychoses. The action of typical antipsychotics is a result of

blocking postsynaptic dopamine receptors in the basal ganglia. Their most common side effects include anticholinergic effects, sedation, weight gain, reduction in seizure threshold, photosensitivity, and extrapyramidal symptoms.

- The newer generation of antipsychotic medications (atypical or second generation), which includes clozapine, risperidone, paliperidone, olanzapine, quetiapine, aripiprazole, asenapine, iloperidone, lurasidone, and ziprasidone, may have an effect on dopamine, serotonin, and other neurotransmitters. They show promise of greater efficacy with fewer side effects but have been associated with increased risk for metabolic disturbances and weight gain.
- *Antiparkinsonian agents* are used to counteract the extrapyramidal symptoms associated with antipsychotic medications. Antiparkinsonian drugs restore the natural balance of acetylcholine and dopamine in the brain. The most common side effects of these drugs are anticholinergic effects. They may also cause sedation and orthostatic hypotension.
- Agents for the treatment of tardive dyskinesia are used to reduce movement disturbances associated with antipsychotic medications. Their action is unknown but believed to be associated with inhibition of monoamine transport. Valbenazine (Ingrezza) and deutetrabenazine (Austeda) were both approved by the FDA for this indication in 2017.
- *Sedative-hypnotics* are used in the management of anxiety states and to treat insomnia. These CNS depressants (with the exception of ramelteon) have the potential for physical and psychological dependence. They are indicated for short-term use only. Side effects and nursing implications are similar to those described for antianxiety medications.
- Several medications are used to treat ADHD. These include CNS stimulants, which have the potential for physical and psychological dependence. Tolerance develops quickly with CNS stimulants, and they should not be withdrawn abruptly because they can produce serious withdrawal symptoms. The most common side effects are restlessness, anorexia, and insomnia. Other

medications that have shown to be effective in treating ADHD include atomoxetine, bupropion, and the alpha-adrenergic agonists clonidine and guanfacine. Their mechanism of action in the treatment of ADHD is not clear.

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Review Questions

1. How do antianxiety medications, such as benzodiazepines, produce a calming effect?
   a. Depressing the CNS
   b. Decreasing levels of norepinephrine and serotonin in the brain
   c. Decreasing levels of dopamine in the brain
   d. Inhibiting production of the enzyme MAO
2. There is a narrow margin between the therapeutic and toxic levels of lithium carbonate. Symptoms of toxicity are most likely to appear when the serum levels exceed:
   a. 0.15 mEq/L
   b. 1.5 mEq/L
   c. 15.0 mEq/L
   d. 150 mEq/L
3. Initial symptoms of lithium toxicity include:
   a. Constipation, dry mouth
   b. Dizziness, thirst
   c. Vomiting, diarrhea
   d. Anuria, arrhythmias
4. Antipsychotic medications are thought to decrease psychotic symptoms by:
   a. Blocking reuptake of norepinephrine and serotonin
   b. Blocking the action of dopamine in the brain
   c. Inhibiting production of the enzyme MAO
   d. Depressing the CNS

5. Part of the nurse's ongoing assessment of the client taking antipsychotic medications is to observe for extrapyramidal symptoms. Which of the following are examples of extrapyramidal symptoms?
   a. Muscular weakness, rigidity, tremors, facial spasms
   b. Dry mouth, blurred vision, urinary retention, orthostatic hypotension
   c. Amenorrhea, gynecomastia, retrograde ejaculation
   d. Elevated blood pressure, severe occipital headache, stiff neck

Clinical Judgment Questions

6. A client who is prescribed haloperidol is observed to be staring at the ceiling and says he cannot move his eyes. The nurse notices that he also appears to have muscle spasms in his legs and hands. What is the most appropriate action for the nurse to take at this point?
   a. Conduct an AIMS test.
   b. Administer prn benztropine (Cogentin).
   c. Withhold the next dose of antipsychotic medication.
   d. Contact the physician.

7. A client reports to the nurse that she has been on her antidepressant medication (fluoxetine) for almost 2 weeks and does not feel much better. Which of these actions by the nurse demonstrates the best clinical judgment?
   a. Educate the client that this medication may not be fully effective for up to 4 weeks.
   b. Hold the next dose and contact the physician to recommend an alternative antidepressant.
   c. Check the client's vital signs and check labs for therapeutic blood levels.
   d. Assess whether the client is aware of mood swings or history of bipolar disorder in her family.

8. A client who was recently prescribed an MAOI tells the nurse that he drinks 3 to 4 cups of coffee with each meal. Which of these

actions by the nurse demonstrates the best clinical judgment?

a. Instruct the client that he only needs to avoid foods high in tyramine; coffee consumption is not an issue with this medication.
b. Inform the client that foods or beverages with high caffeine content increase the risk for serious hypertension and arrhythmias.
c. Inform the client that caffeine interferes with the effectiveness of this medication.
d. Instruct the client that red wines are a better beverage choice because they do not contain tyramine.

9. A young adult client has been prescribed an SSRI antidepressant, which she has been taking for 1 week. She reports that she feels like she is getting worse and feels like nothing is going to help. Which of these actions by the nurse is a priority?

a. Educate the client that SSRIs have a lag period before full therapeutic effectiveness is apparent.
b. Ask the client to describe why she thinks she is depressed.
c. Contact the physician to recommend a different medication.
d. Conduct a suicide risk assessment.

10. A licensed practical nurse who is administering medications reports to the RN in charge that he forgot to give the last scheduled dose of bupropion to a client. He asks the RN if he should give the client two doses at the next scheduled time. Which of these responses by the nurse demonstrates the best clinical judgment?

a. “Yes, that would be fine. Just make sure the client stays in bed since this is a sedating medication.”
b. “No. Doses of this medication should not be doubled since that poses an increased risk for seizures.”
c. “Yes, as long as the client has not changed his sodium intake recently.”
d. “No, doses should not be doubled because there is an increased risk of tolerance and addiction.”

References

Anderson, L. (2018). Drug interactions with grapefruit juice. Retrieved from https://www.drugs.com/article/grapefruit-drug-interactions.html

Berna, F., Misdrahi, D., Boyer, L., Aouizerate, B., Brunel, L., Capdevielle, D., & Liorca, P.M. (2015). Prevalence and risk factors in a community dwelling sample of patients with schizophrenia. Results from the FACE-SZ dataset. *Schizophrenia Research, 169*(1-3), 255-261.

Brust, T.F., Hayes, M.P., Roman, D.L., & Watts, V.J. (2015). New functional activity of aripiprazole revealed: Robust antagonism of D2 dopamine receptor-stimulated Gβγ signaling. *Biochemical Pharmacology, 93*(1), 85-91. doi:10.1016/j.bcp.2014.10.014

Canuso, C.M., Singh, J.B., Fedgchin, M., Alphs, L., Lane, R., Lim, P., … Drevets, W.C. (2018, April). Efficacy and safety of intranasal esketamine for the rapid reduction of symptoms of depression and suicidality in patients at imminent risk for suicide: Results of a double-blind, randomized, placebo-controlled study. *American Journal of Psychiatry.* Retrieved from https://doi.org/10.1176/appi.ajp.2018.17060720

Clozapine REMS. (2015). Clozapine and the risk of neutropenia: A guide for healthcare providers. Retrieved from https://www.clozapinerems.com/CpmgClozapineUI/rems/pdf/resources/Clozapine_REMS_HCP_Guide.pdf

Cooper, B.E., & Sejnowski, C.A. (2013). Serotonin syndrome: Recognition and treatment. *AACN Advanced Critical Care, 24*(1), 15-20. doi:10.1097/NCI.0b013e31827eecc6

Drugs.com. (2019). FDA pregnancy categories: FDA pregnancy risk information: An update. Retrieved from https://www.drugs.com/pregnancy-categories.html

Erlij, D., Acosta-Garcia, J., Rojas-Marquez, M., Gonzalez-Hernandez, B., Escartin-Perez, E., Aceves, J., & Floran, B. (2012). Dopamine D4 receptor stimulation in GABAergic projections of the globus pallidus to the reticular thalamic nucleus and the substantia nigra reticulata of the rat decreases locomotor activity. *Neuropharmacology, 62*(2), 1111-1118. doi:10.1016/j.neuropharm.2011.11.001

Food and Drug Administration (FDA). (2008). FDA requires warnings about risk of suicidal thoughts and behavior for antiepileptic medications. Retrieved from https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformation-forPatientsandProviders/ucm100197.htm

Food and Drug Administration (FDA). (2016a). FDA Drug Safety Communication: FDA warns about serious risks and death when combining

opioid pain or cough medicines with benzodiazepines; requires its strongest warning. Retrieved from http://www.fda.gov/Drugs/DrugSafety/ucm518473.htm

Food and Drug Administration (FDA). (2016b). FDA Drug Safety Communication: FDA warns about rare but serious skin reactions with mental health drug olanzapine (Zyprexa, Zyprexa Zydis, Zyprexa Relprevv, and Symbyax). Retrieved from https://www.fda.gov/Drugs/DrugSafety/ucm499441.htm

Food and Drug Administration (FDA). (2016c). FDA Drug Safety Communication: FDA warns about new impulse-control problems associated with mental health drug aripiprazole (Abilify, Abilify Maintena, Aristada). Retrieved from https://www.fda.gov/Drugs/DrugSafety/ucm498662.htm

Food and Drug Administration (FDA). (2017). FDA approves first drug to treat tardive dyskinesia. Retrieved from https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm552418.htm

Food and Drug Administration (FDA). (2019). FDA approves new nasal spray medication for treatment-resistant depression; available only at a certified doctor's office or clinic [Press Release]. Retrieved from https://www.fda.gov/news-events/press-announcements/fda-approves-new-nasal-spray-medication-treatment-resistant-depression-available-only-certified

Fournier, J.C., DeRubeis, R.J., Hollon, S.D., Dimidjian, S., Amsterdam, J.D., Shelton, R.C., & Fawcett, J. (2010). Antidepressant drug effects and depression severity: A patient-level meta-analysis. *Journal of the American Medical Association, 303*(1), 47-53. doi:10.1001/jama.2009.1943

Haddad, P. M., Brain, C., & Scott, J. (2014). Nonadherence with antipsychotic medication in schizophrenia: Challenges and management strategies. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4085309/

Harrison, P. (2015). Novel drug first to treat negative symptoms in schizophrenia. Retrieved from www.medscape.com/viewarticle/850701

Institute of Medicine. (2003). *Health professions education: A bridge to quality.* Washington, DC: Author.

Janicak, P.G., & Hussain, K. (2017). Medication induced movement disorders. In B.J. Sadock, V.A. Sadock, & P. Ruiz (Eds.), *Comprehensive textbook of psychiatry* (10th ed., pp. 2936-2944). Philadelphia, PA: Wolters Kluwer.

Jones, D.S. (2006). Racial profiling in psychiatry: Does it help patients? *Psychiatric Times, 23*(14).

Kose, S., & Cetin, M. (2018). Triple reuptake inhibitors (TRIs): Do they promise us a rose garden? *Psychiatry and Clinical Pharmacology, 28*(2), 119-122. doi.org/10.1080/24750573.2018.1443386

Lenze, E.J., Mulsant, B.H., Blumberger, D.M., Karp, J.F., Newcomer, J.W., Anderson, S.J., … Reynolds, C.F. (2015). Efficacy, safety, and tolerability of augmentation pharmacotherapy with aripiprazole for treatment resistant depression in late life: A randomized placebo-controlled study. *Lancet, 386*(10011), 2404-2412. doi:http://dx.doi.org/10.1016/So140-6736(15)00308-6

Li, K., Shen, S., Ji, Y.T., Li, X.Y., Zhang, L., &Wang, X.D. (2018). Melatonin BDNF-TrkB signaling. *Neuroscience Bulletin, 34*(2), 303-311. doi:10.1007/s12264-017-019-z

Lien, Y.H.H. (2018). Antidepressants and hyponatremia. *American Journal of Medicine, 131*(1), 7-8. doi.org/10.1016/j.amjmed.2017.09.002

Lynch, T., & Price, A. (2007). The effect of cytochrome P450 metabolism on drug response, interactions, and adverse effects. *American Family Physician, 76*(3), 391-396.

New York State Office of Mental Health. (2012). An explanation of Kendra's law. Retrieved from https://www.omh.ny.gov/omhweb/kendra_web/ksummary.htm

Olfson, M., King, M., & Schoenbaum, M. (2015). Benzodiazepine use in the United States. *JAMA Psychiatry, 72*(2), 136-142. doi:10.1001/jamapsychiatry. 2014.1763

Ramnarine, M., & Ahmed, D. (2015). Anticholinergic toxicity. Retrieved from http://emedicine.medscape.com/article/812644-overview

Sadock, B.J., Sadock, V.A., & Ruiz, P. (2015). *Synopsis of psychiatry: Behavioral sciences/clinical psychiatry* (11th ed.). Philadelphia: Lippincott Williams & Wilkins.

Sage, D.L. (Producer). (1984). *The brain: Madness* [television broadcast]. Washington, DC: Public Broadcasting Company.

Scarff, J.R. (2017). The prospects of cariprazine in the treatment of schizophrenia. *Therapeutic Advances in Psychopharmacology, 7*(11), 237-239. doi:10.1177/2045125317727260

Shorter, E. (2009). The history of lithium therapy. *Bipolar Disorders, 11*(Suppl. 2), 4-9. doi:10.1111/j.1399-5618.2009.00706.x

Steinberg, M., & Lyketsos, C.G. (2012). Atypical antipsychotic use in patients with dementia: Managing safety concerns. *American Journal of Psychiatry, 169*(9), 900-906. doi:10.1176/appi.aip.2012.12030342

Tartakovsky, M. (2016). *Depression: New medications on the horizon.* Retrieved from https://psychcentral.com/lib/depression-new-medications-on-the-horizon/

WebMD. (2019). Melatonin. Retrieved from https://www.webmd.com/vitamins/ai/ingredientmono-940/melatonin

Vallerand, A.H., & Sanoski, C.A. (2019). *Davis's drug guide for nurses* (16th ed.). Philadelphia: F.A. Davis.