Lippincott's Illustrated Reviews:

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Editors: **Finkel, Richard; Clark, Michelle A.; Cubeddu, Luigi X.**
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Chapter 11

Anesthetics

I. Overview

General anesthesia is essential to surgical practice, because it renders patients analgesic, amnesic, and unconscious, and provides muscle relaxation and suppression of undesirable reflexes. No single drug is capable of achieving these effects both rapidly and safely. Rather, several different categories of drugs are utilized to produce optimal anesthesia (Figure 11.1). Preanesthetic medication serves to calm the patient, relieve pain, and protect against undesirable effects of the subsequently administered anesthetic or the surgical procedure. Skeletal muscle relaxants facilitate intubation and suppress muscle tone to the degree required for surgery. Potent general anesthetics are delivered via inhalation or intravenous injection. With the exception of *nitrous oxide*, modern inhaled anesthetics are all volatile, halogenated hydrocarbons that derive from early research and clinical experience with *diethyl ether* and *chloroform*. On the other hand, intravenous general anesthetics consist of a number of chemically unrelated drug types that are commonly used for the rapid induction of anesthesia.

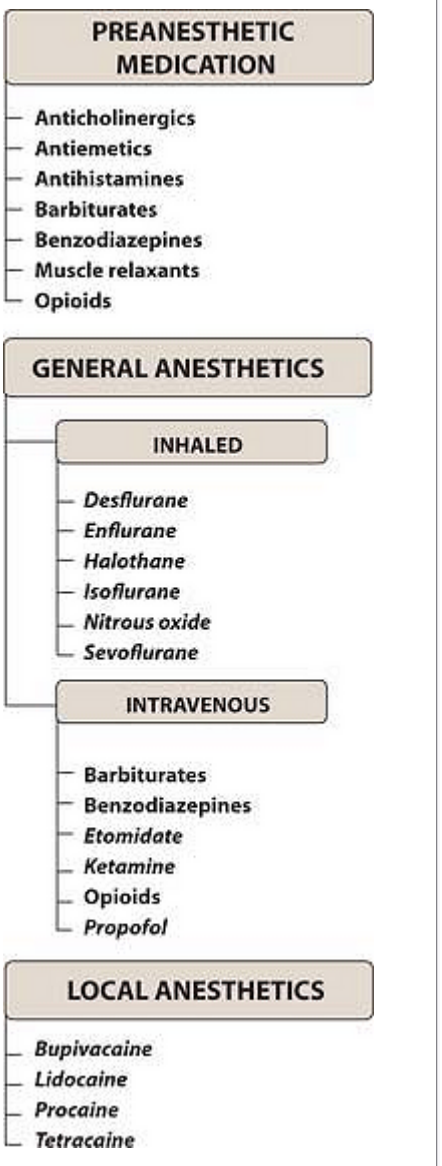

Figure 11.1 Summary of anesthetics.

II. Patient Factors in Selection of Anesthesia

During the preoperative phase, the anesthesiologist selects drugs that provide a safe and efficient anesthetic regimen based on the nature of the surgical or diagnostic procedure as well as on the patient's physiologic, pathologic, and pharmacologic state.

A. Status of organ systems

1. **Liver and kidney:** Because the liver and kidney not only influence the long-term distribution and clearance of anesthetic agents but can also be the target organs for toxic effects, the physiologic status of these organs must be considered. Of particular concern is that the release of fluoride, bromide, and other metabolic products of the halogenated hydrocarbons can affect these organs, especially if the metabolites accumulate with repeated anesthetic administration over a short period of time.

2. **Respiratory system:** The condition of the respiratory system must be considered if inhalation anesthetics are indicated. For example, asthma and ventilation or perfusion abnormalities complicate control of an inhalation anesthetic. All inhaled anesthetics depress the respiratory system. Additionally, they also are bronchodilators.

3. **Cardiovascular system:** Whereas the hypotensive effect of most anesthetics is sometimes desirable, ischemic injury of tissues could follow reduced perfusion pressure. If a hypotensive episode during a surgical procedure necessitates treatment, a vasoactive substance is administered. This is done after consideration of the possibility that some anesthetics, such as *halothane*, may sensitize the heart to the arrhythmogenic effects of sympathomimetic agents.

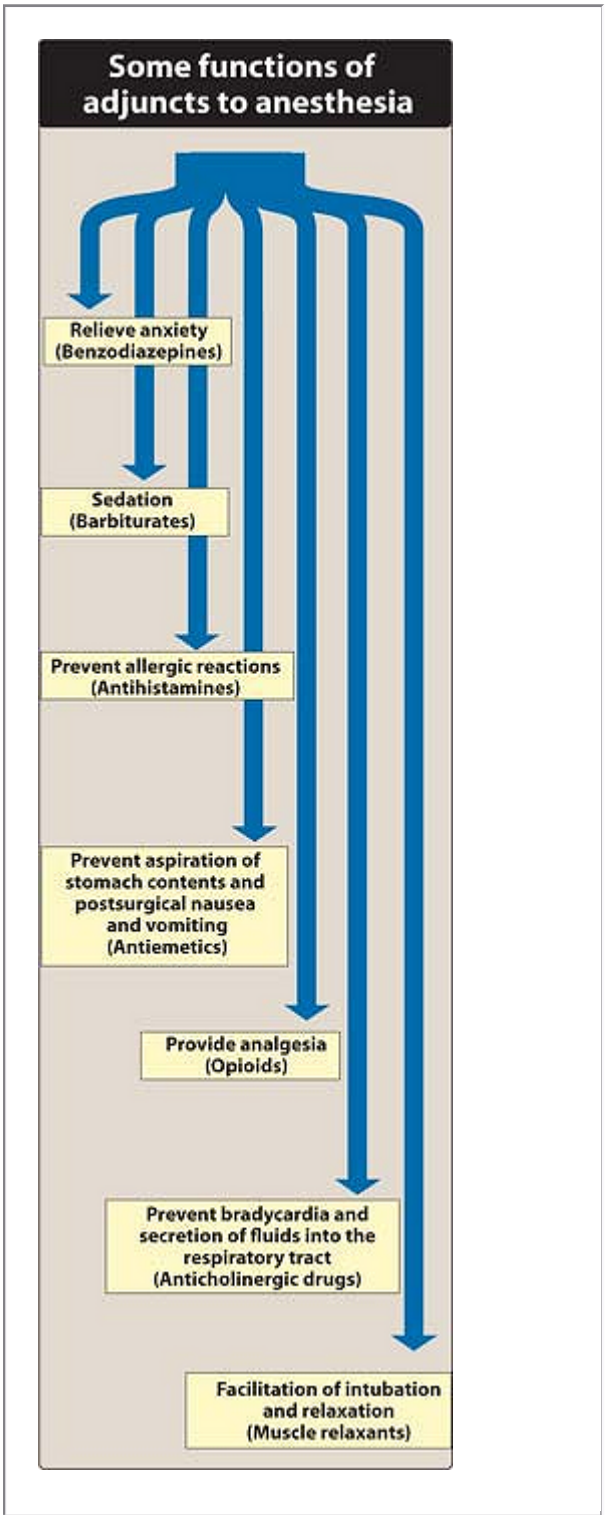

Figure 11.2 Components of balanced anesthesia.

4. **Nervous system:** The existence of neurologic disorders (for example, epilepsy or myasthenia gravis) influences the selection of an anesthetic. So, too, would a patient history suggestive of a genetically determined sensitivity to halogenated hydrocarbonâ€“induced malignant hyperthermia.

5. **Pregnancy:** Some precautions should be kept in mind when anesthetics and adjunct drugs are administered to a pregnant woman. There has been at least one report that transient use of *nitrous oxide* can cause aplastic anemia in the unborn child. Oral clefts have occurred in the fetuses of women who have received benzodiazepines. *Diazepam* should not be used routinely during labor, because it results in temporary hypotonia and altered thermoregulation in the newborn.

B. Concomitant use of drugs

1. **Multiple adjunct agents:** Commonly, surgical patients receive one or more of the following preanesthetic medications: benzodiazepines, such as *midazolam* or *diazepam*, to allay anxiety and facilitate amnesia; barbiturates, such as *pentobarbital*, for sedation; antihistamines, such as *diphenhydramine*, for prevention of allergic reactions, or *ranitidine*, to reduce gastric acidity; antiemetics, such as *ondansetron*, to prevent the possible aspiration of stomach contents; opioids, such as *fentanyl*, for analgesia; and/or anticholinergics, such as *scopolamine*, for their amnesic effect and to prevent bradycardia and secretion of fluids into the respiratory tract (Figure 11.2). These agents facilitate smooth induction of anesthesia, and when administered continuously, they also lower the dose of anesthetic required to maintain the desired level of surgical (Stage III) anesthesia. However, such coadministration can also enhance undesirable anesthetic effects (for example, hypoventilation), and it may produce negative effects that are not observed when each drug is given individually.

2. **Concomitant use of additional nonanesthetic drugs:** Surgical patients may be chronically exposed to agents for the treatment of the underlying disease as well as to drugs of abuse that alter the response to anesthetics. For example, alcoholics have elevated levels of hepatic microsomal enzymes involved in the metabolism of barbiturates, and drug abusers may be overly tolerant of opioids.

III. Induction, Maintenance, and Recovery from Anesthesia

Anesthesia can be divided into three stages: induction, maintenance, and recovery. Induction is defined as the period of time from the onset of administration of the anesthetic to the development of effective surgical anesthesia in the patient. Maintenance provides a sustained surgical anesthesia.

Recovery is the time from discontinuation of administration of the anesthesia until consciousness and protective physiologic reflexes are regained. Induction of anesthesia depends on how fast effective concentrations of the anesthetic drug reach the brain; recovery is the reverse of induction and depends on how fast the anesthetic drug diffuses from the brain.

A. Induction

During induction, it is essential to avoid the dangerous excitatory phase (Stage II delirium) that was observed with the slow onset of action of some earlier anesthetics (see below). Thus, general anesthesia is normally induced with an intravenous anesthetic like *thiopental*, which produces unconsciousness within 25 seconds after injection. At that time, additional inhalation or intravenous drugs comprising the selected anesthetic combination may be given to produce the desired depth of surgical (Stage III) anesthesia. [Note: This often includes coadministration of an intravenous skeletal muscle relaxant to facilitate intubation and relaxation. Currently used muscle relaxants include *pancuronium, doxacurium, rocuronium, vecuronium, cisatricurium, atracurium, mevacurium* and

succinylcholine.] For children, without intravenous access, nonpungent agents, such as *halothane* or *sevoflurane*, are used to induce general anesthesia. This is termed inhalation induction.

B. Maintenance of anesthesia

Maintenance is the period during which the patient is surgically anesthetized. After administering the selected anesthetic mixture, the anesthesiologist monitors the patient's vital signs and response to various stimuli throughout the surgical procedure to carefully balance the amount of drug inhaled and/or infused with the depth of anesthesia. Anesthesia is usually maintained by the administration of volatile anesthetics, because these agents offer good minute-to-minute control over the depth of anesthesia. Opioids, such as *fentanyl*, are often used for pain along with inhalation agents, because the latter are not good analgesics.

C. Recovery

Postoperatively, the anesthesiologist withdraws the anesthetic mixture and monitors the return of the patient to consciousness. For most anesthetic agents, recovery is the reverse of induction; that is, redistribution from the site of action (rather than metabolism of the anesthetic) underlies recovery. The anesthesiologist continues to monitor the patient to be sure that he or she is fully recovered with normal physiologic functions (for example, is able to breathe on his/her own). Patients are observed for delayed toxic reactions, such as hepatotoxicity caused by halogenated hydrocarbons.

D. Depth of anesthesia

The depth of anesthesia has been divided into four sequential stages. Each stage is characterized by increased central nervous system (CNS) depression, which is caused by accumulation of the anesthetic drug in the brain (Figure 11.3). These stages were discerned and defined with *ether*, which produces a slow onset of anesthesia. However, with *halothane* and other commonly used anesthetics, the stages are difficult to characterize clearly because of the rapid onset of anesthesia.

1. **Stage Iâ€”Analgesia:** Loss of pain sensation results from interference with sensory transmission in the spinothalamic tract. The patient is

conscious and conversational. Amnesia and a reduced awareness of pain occur as Stage II is approached.

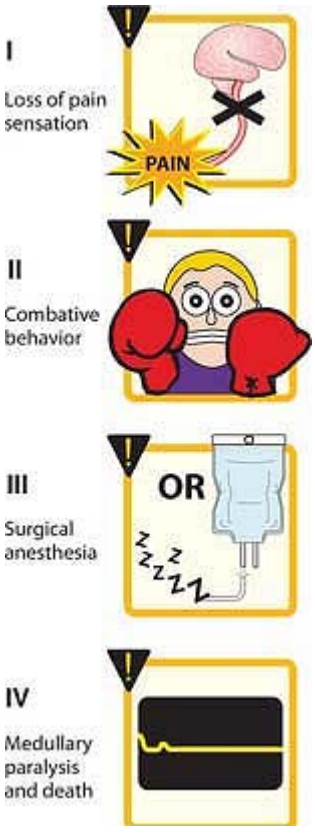

Figure 11.3 Stages of anesthesia. OR = operating

2. **Stage IIâ€"Excitement:** The patient experiences delirium and possibly violent, combative behavior. There is a rise and irregularity in blood pressure. The respiratory rate may increase. To avoid this stage of anesthesia, a short-acting barbiturate, such as *thiopental*, is given intravenously before inhalation anesthesia is administered.
3. **Stage IIIâ€"Surgical anesthesia:** Regular respiration and relaxation of the skeletal muscles occur in this stage. Eye reflexes decrease progressively, until the eye movements cease and the pupil is fixed. Surgery may proceed during this stage.
4. **Stage IVâ€"Medullary paralysis:** Severe depression of the respiratory and vasomotor centers occur during this stage. Death can rapidly ensue unless measures are taken to maintain circulation and respiration.

IV. Inhalation Anesthetics

Inhaled gases are the mainstay of anesthesia and are used primarily for the maintenance of anesthesia after administration of an intravenous agent. No one anesthetic is superior to another under all circumstances. Inhalation anesthetics have a benefit that is not available with intravenous agents, because the depth of anesthesia can be rapidly altered by changing the concentration of the drug. Inhalation anesthetics are also reversible, because most are rapidly eliminated from the body by exhalation.

A. Common features of inhalation anesthetics

Modern inhalation anesthetics are nonflammable, nonexplosive agents that include the gas *nitrous oxide* as well as a number of volatile, halogenated hydrocarbons. As a group, these agents decrease cerebrovascular resistance, resulting in increased perfusion of the brain. They also cause bronchodilation and decrease both minute ventilation

(volume of air per unit time moved into or out of the lungs) and hypoxic pulmonary vasoconstriction (increased pulmonary vascular resistance in poorly aerated regions of the lungs, which allows redirection of pulmonary blood flow to regions that are richer in oxygen content). The movement of these agents from the lungs to the different body compartments depends upon their solubility in blood and tissues as well as on blood flow. These factors play a role not only in induction but also in recovery.

B. Potency

The potency of inhaled anesthetics is defined quantitatively as the median alveolar concentration (MAC). This is the end-tidal concentration of anesthetic gas needed to eliminate movement among 50 percent of patients challenged by a standardized skin incision. [Note: MAC is the median effective dose (ED_{50}) of the anesthetic.] MAC is usually expressed as the percentage of gas in a mixture required to achieve the effect. Numerically, MAC is small for potent anesthetics, such as *halothane*, and large for less potent agents, such as *nitrous oxide*. Therefore, the inverse of MAC is an index of the potency of the anesthetic. MAC values are useful in comparing pharmacologic effects of different anesthetics (Figure 11.4). The more lipid soluble an anesthetic, the lower the concentration of anesthetic needed to produce anesthesia and, thus, the higher the potency of the anesthetic.

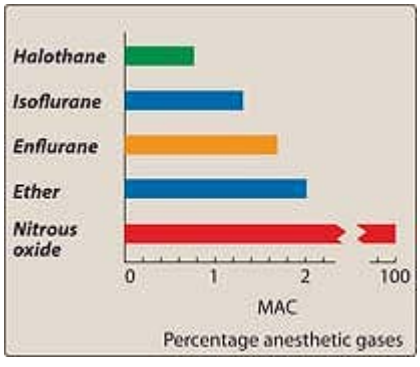

Figure 11.4 Minimal alveolar concentrations (MAC) for anesthetic gases.

C. Uptake and distribution of inhalation anesthetics

The partial pressure of an anesthetic gas at the origin of the respiratory pathway is the driving force that moves the anesthetic into the alveolar space and, thence, into the blood, which delivers the drug to the brain and various other body compartments. Because gases move from one compartment to another within the body according to partial pressure gradients, a steady state is achieved when the partial pressure in each of these compartments is equivalent to that in the inspired mixture. The time course for attaining this steady state is determined by the following factors:

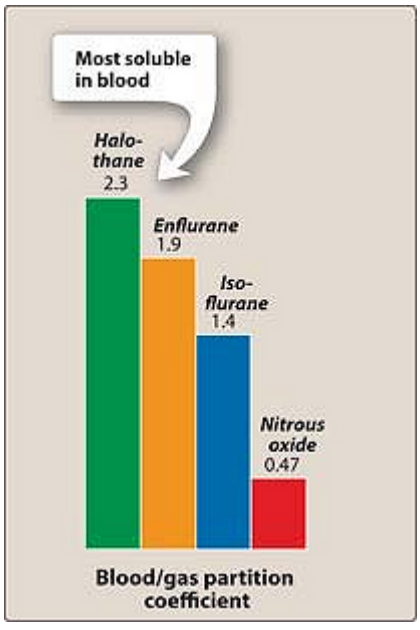

Figure 11.5 Blood/gas partition coefficients for some inhalation anesthetics.

1. **Alveolar wash-in:** This term refers to the replacement of the normal lung gases with the inspired anesthetic mixture. The time required for this process is directly proportional to the functional residual capacity of the lung and inversely proportional to the ventilatory rate; it is independent of the physical properties of the gas. As the partial pressure builds within the lung, anesthetic transfer from the lung begins.
2. **Anesthetic uptake:** Anesthetic uptake is the product of gas solubility in the blood, cardiac output, and the anesthetic gradient between alveolar and venous partial pressure gradients.
    a. **Solubility in the blood:** This is determined by a physical property of the anesthetic molecule called the blood/gas partition coefficient, which is the ratio of the total amount of gas in the blood relative to the gas equilibrium phase (Figure 11.5). Drugs with low versus high solubility in blood differ in their speed of induction of anesthesia. For example, when an anesthetic gas with low blood solubility, such as *nitrous oxide*, diffuses from the alveoli into the circulation, little of the anesthetic dissolves in the blood. Therefore, the equilibrium between the inhaled anesthetic and arterial blood occurs rapidly, and relatively few additional molecules of anesthetic are required to raise arterial anesthetic partial pressureâ€"that is, steady state is rapidly achieved. In contrast, an anesthetic gas with high blood solubility, such as *halothane*, dissolves more completely in the blood, and greater amounts of the anesthetic and longer periods of time are required to raise arterial partial pressure. This results in increased times of induction as well as recovery and slower changes in the depth of anesthesia in response to alterations in the concentration of the inhaled drug. Figure 11.6 illustrates the uptake curves for some inhalation anesthetics. The solubility in blood is ranked in the following order: *halothane* > *enflurane* > *isoflurane* > *sevoflurane* > *desflurane* > *nitrous oxide*.
    b. **Cardiac output:** It is obvious that cardiac output affects the delivery of anesthetic to tissues. Low cardiac output will result in slow delivery of the anesthetic.
    c. **Alveolar to venous partial pressure gradient of the anesthetic:** This is the driving force of anesthetic delivery. For all practical purposes, the pulmonary end-capillary anesthetic partial pressure may be considered as the anesthetic alveolar partial pressure if the patient does not have severe lung diffusion

disease. The arterial circulation distributes the anesthetic to various tissues, and the pressure gradient drives free anesthetic

gas into tissues. As the venous circulation returns blood depleted of anesthetic to the lung, more gas moves into the blood from the lung according to the partial pressure difference. Over time, the partial pressure in the venous blood closely approximates the partial pressure in the inspired mixture; that is, no further net anesthetic uptake from the lung occurs.

3. **Effect of different tissue types on anesthetic uptake:** The time required for a particular tissue to achieve a steady state with the partial pressure of an anesthetic gas in the inspired mixture is inversely proportional to the blood flow to that tissue; that is, faster flow results in a more rapidly achieved steady state. It is also directly proportional to the capacity of that tissue to store anesthetic; that is, a larger capacity results in a longer time required to achieve steady state. Capacity, in turn, is directly proportional to the tissue's volume and the tissue/blood solubility coefficient of the anesthetic molecules. Four major tissue compartments determine the time course of anesthetic uptake.

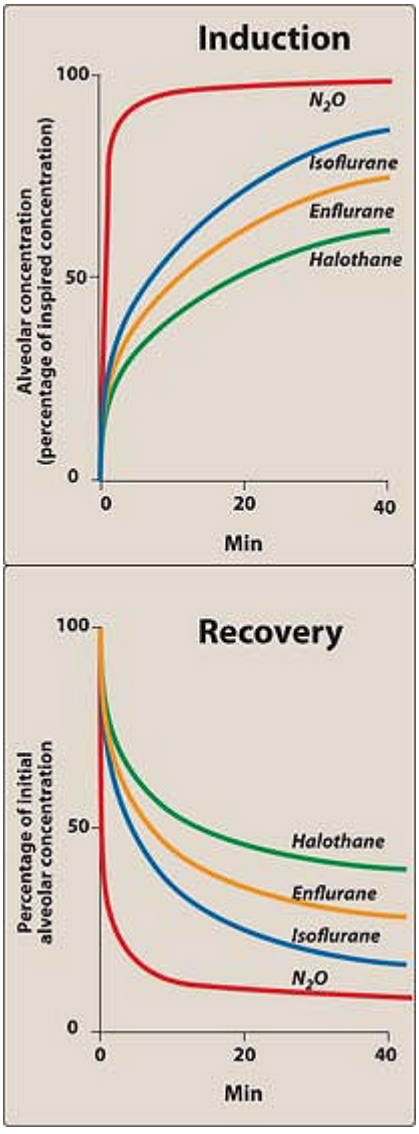

Figure 11.6 Changes in the alveolar blood concentrations of some inhalation anesthetics over time. N_20 =

nitrous oxide.

a. **Brain, heart, liver, kidney, and endocrine glands:** These highly perfused tissues rapidly attain a steady state with the partial pressure of anesthetic in the blood.

b. **Skeletal muscles:** These are poorly perfused during anesthesia. This, and the fact that they have a large volume, prolong the time required to achieve steady state.

c. **Fat:** This tissue is also poorly perfused. However, potent general anesthetics are very lipid soluble. Therefore, fat has a large capacity to store anesthetic. This combination of slow delivery to a high-capacity compartment prolongs the time required to achieve steady state.

d. **Bone, ligaments, and cartilage:** These are poorly perfused and have a relatively low capacity to store anesthetic. Therefore, these tissues have only a slight impact on the time course of anesthetic distribution in the body.

4. **Washout:** When the administration of an inhalation anesthetic is discontinued, the body becomes the â€œsourceâ€ that drives the anesthetic into the alveolar space. The same factors that influence attainment of steady state with an inspired anesthetic determine the time course of clearance of the drug from the body. Thus, *nitrous oxide* exits the body faster than *halothane* (see Figure 11.6).

D. Mechanism of action

No specific receptor has been identified as the locus of general anesthetic action. Indeed, the fact that chemically unrelated compounds produce the anesthetic state argues against the existence of such a receptor. The focus is now on interactions of the inhaled anesthetics with proteins comprising ion channels. For example, the general anesthetics increase the sensitivity of the Î³-aminobutyric acid ($GABA_A$) receptors to the neurotransmitter, GABA, at clinically effective concentrations of the drug. This causes a prolongation of the inhibitory chloride ion current after a pulse of GABA release. Postsynaptic neuronal excitability is thus diminished (Figure 11.7). Other receptors are also affected

by volatile anesthetics; for example, the activity of the inhibitory glycine receptors in the spinal motor neurons is increased. In addition, the inhalation anesthetics block the excitatory postsynaptic current of the nicotinic receptors. The mechanism by which the anesthetics perform these modulatory roles is not understood.

E. Halothane

This agent is the prototype to which newer inhalation anesthetics have been compared. When *halothane* (HAL-oh-thane) was introduced, its ability to induce the anesthetic state rapidly and to allow quick recoveryâ€”and the fact that it was nonexplosiveâ€”made it an anesthetic of choice. However, with the recognition of the adverse effects discussed below and the availability of other anesthetics that cause fewer complications, *halothane* is largely being replaced in the United States.

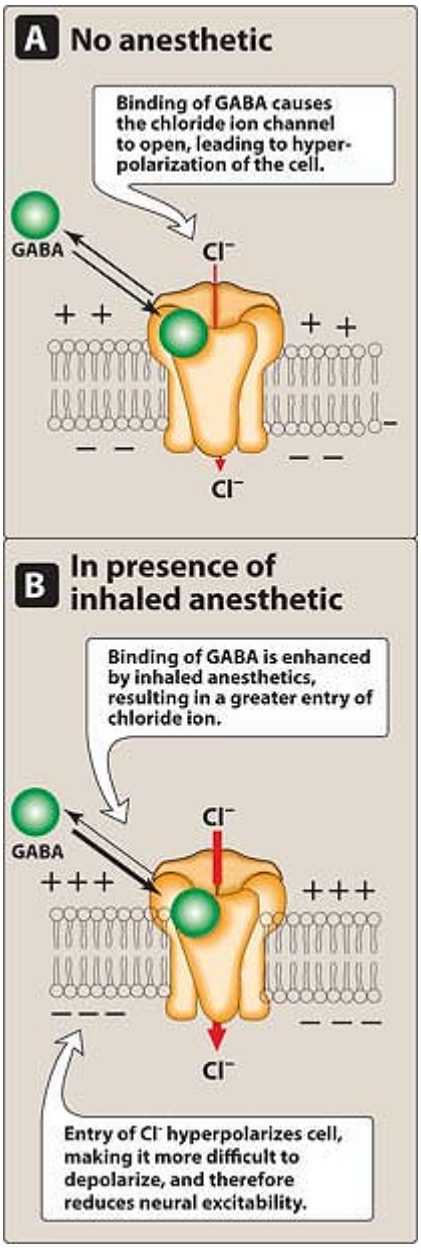

Figure 11.7 An example of modulation of a ligand-gated membrane channel modulated by inhaled anthestics. GABA = Î»-aminobutyric acid.

1. **Therapeutic uses:** Whereas *halothane* is a potent anesthetic, it is a relatively weak analgesic. Thus, *halothane* is usually coadministered with *nitrous oxide*, opioids, or local anesthetics. *Halothane* relaxes both skeletal and uterine muscle, and it can be used in obstetrics when uterine relaxation is indicated. *Halothane* is not hepatotoxic in pediatric patients (unlike its potential effect on adults, see below), and combined with its pleasant odor, this makes it suitable in children for inhalation induction.

2. **Pharmacokinetics:** *Halothane* is oxidatively metabolized in the body to tissue-toxic hydrocarbons (for example, trifluoroethanol) and bromide ion. These substances may be responsible for the toxic reaction that some patients (especially females) develop after *halothane* anesthesia. This reaction begins as a fever, followed by anorexia, nausea, and vomiting, and patients may exhibit signs of hepatitis. [Note: Although the incidence of

this reaction is lowâ€”approximately 1 in 10,000 individualsâ€”50 percent of affected patients will die of hepatic necrosis. To avoid this condition, *halothane* anesthesia is not repeated at intervals of less than 2 to 3 weeks.]

3. **Adverse effects:**

   a. **Cardiac effects:** Like other halogenated hydrocarbons, *halothane* is vagomimetic and causes *atropine*-sensitive bradycardia. In addition, *halothane* has the undesirable property of causing cardiac arrhythmias. [Note: These are especially serious if hypercapnia (increased arterial carbon dioxide partial pressure) develops due to reduced alveolar ventilation or an increase in the plasma concentration of catecholamines.] *Halothane*, like the other halogenated anesthetics, produces concentration-dependent hypotension. Should it become necessary to counter excessive hypotension during *halothane* anesthesia, it is recommended that a direct-acting vasoconstrictor, such as *phenylephrine*, be given.

   b. **Malignant hyperthermia:** In a very small percentage of patients, all of the halogenated hydrocarbon anestheticsâ€”as well as the muscle relaxant *succinylcholine*â€”have the potential to induce malignant hyperthermia. Whereas the etiology of this condition is poorly understood, recent investigations have identified a dramatic increase in the myoplasmic calcium ion concentration. Strong evidence indicates that malignant hyperthermia is due

   to an excitationâ€“contraction coupling defect. Burn victims and individuals with Duchenne dystrophy, myotonia, osteogenesis imperfecta, and central-core disease are susceptible to malignant hyperthermia. Should a patient exhibit the characteristic symptoms of malignant hyperthermia, *dantrolene* is given as the anesthetic mixture is withdrawn. Therefore, *dantrolene* should be available for emergency use when needed. The patient must be carefully monitored and supported for respiratory, circulatory, and renal problems.

F. Enflurane

This gas is less potent than *halothane*, but it produces rapid induction and recovery. About 2 percent of the anesthetic is metabolized to fluoride ion, which is excreted by the kidney. Therefore, *enflurane* [EN-floo-rane] is contraindicated in patients with kidney failure. *Enflurane* anesthesia exhibits the following differences from *halothane* anesthesia: fewer arrhythmias, less sensitization of the heart to catecholamines, and greater potentiation of muscle relaxants due to a more potent â€œ*curare*-likeâ€ effect. A disadvantage of *enflurane* is that it causes CNS excitation at twice the MAC and also at lower doses if hyperventilation reduces the partial pressure of carbon dioxide. For this reason, it is not used in patients with seizure disorders.

G. Isoflurane

This halogenated anesthetic is widely used in the United States. It is a very stable molecule that undergoes little metabolism; as a result, little fluoride is produced. *Isoflurane* [eye-soe-FLURE-ane] is not tissue toxic. Unlike the other halogenated anesthetic gases, *isoflurane* does not induce cardiac arrhythmias and does not sensitize the heart to the action of catecholamines. However, it produces concentration-dependent hypotension due to peripheral vasodilation. It also dilates the coronary vasculature, increasing coronary blood flow and oxygen consumption by the myocardium. This property may make it beneficial in patients with ischemic heart disease. [Note: All halogenated inhalation anesthetics have been reported to cause hepatitis, but at a much lower incidence than with *halothane*. For example, *isoflurane* does so in 1 in 500,000 individuals.]

H. Desflurane

The rapidity with which *desflurane* causes anesthesia and emergence has made it a popular anesthetic for outpatient surgery. However, *desflurane* [DES-flure-ane] has a low volatility and, thus, must be delivered using a special vaporizer. Like *isoflurane*, it decreases vascular resistance and perfuses all major tissues very well. Because it is irritating to the airway and can cause laryngospasm, coughing, and excessive secretions, *desflurane* is not used to induce extended anesthesia. Its degradation is minimal; thus, tissue toxicity is rare.

I. Sevoflurane

Sevoflurane [see-voe-FLOO-rane] has low pungency, allowing rapid uptake without irritating the airway during induction, thus making it suitable for induction in children. It is replacing *halothane* for this purpose. The drug has low solubility in blood and is rapidly taken up and excreted. Recovery is faster than with other anesthetics. It is metabolized by the liver, releasing fluoride ions; thus, like *enflurane*, it may prove to be nephrotoxic.

J. Nitrous oxide

Nitrous oxide [NYE-truss-OX-ide] (â€œlaughing gasâ€) is a potent analgesic but a weak general anesthetic. For example, *nitrous oxide* is frequently employed at concentrations of 30 percent in combination with oxygen for analgesia, particularly in dental surgery. However, *nitrous oxide* at 80 percent (without adjunct agents) cannot produce surgical anesthesia. It is therefore frequently combined with other, more potent agents to attain pain-free anesthesia. *Nitrous oxide* is poorly soluble in blood and other tissues, allowing it to move very rapidly in and out of the body. [Note: *Nitrous oxide* can concentrate the halogenated anesthetics in the alveoli when they are concomitantly administered because of its fast uptake from the alveolar gas. This phenomenon is known as the â€œsecond gas effect.â€] Within closed body compartments, *nitrous oxide* can increase the volume (for example, causing a pneumothorax) or increase the pressure (for example, in the sinuses), because it replaces nitrogen in the various air spaces faster than the nitrogen leaves. Furthermore, its speed of movement allows *nitrous oxide* to retard oxygen uptake during recovery, thus causing diffusion hypoxia. This anesthetic does not depress respiration, nor does it produce muscle relaxation. Under the usual circumstances of coadministration with other anesthetics, it also has moderate to no effect on the cardiovascular system or on increasing cerebral blood flow, and it is the least hepatotoxic of the inhalation anesthetics. It is therefore probably the safest of these anesthetics, provided that at least 20 percent oxygen is always administered simultaneously.

Some characteristics of the inhalation anesthetics are summarized in Figure 11.8

V. Intravenous Anesthetics

Intravenous anesthetics are often used for the rapid induction of anesthesia, which is then maintained with an appropriate inhalation agent. They rapidly induce anesthesia and must therefore be injected slowly. Recovery from intravenous anesthetics is due to redistribution from sites in the CNS.

A. Barbiturates

Thiopental is a potent anesthetic but a weak analgesic. It is an ultrashort-acting barbiturate and has a high lipid solubility. When agents such as *thiopental* and *methohexital* [meth-oh-HEX-i-tal] are administered intravenously, they quickly enter the CNS and depress function, often in less than 1 minute. However, diffusion out of the brain can occur very rapidly as well because of redistribution of the drug to other body tissues, including skeletal muscle and, ultimately, adipose tissue (Figure 11.9). [Note: This latter site serves as a reservoir of drugs from which the agent slowly leaks out and is metabolized and excreted.] The short duration of anesthetic action is due to the decrease of its concentration in the brain to a level below that necessary to produce anesthesia. These drugs may remain in the body for relatively long periods of time after their administration, because only about 15 percent of the dose of barbiturates entering the circulation is metabolized by the liver per hour. Thus, metabolism of *thiopental* is much slower than its tissue redistribution. The barbiturates are not significantly analgesic and, therefore, require some type of supplementary analgesic administration during anesthesia to avoid objectionable changes in blood pressure and autonomic function. *Thiopental* has minor effects on the cardiovascular system, but

it may contribute to severe hypotension in patients with hypovolemia or shock. All barbiturates can cause apnea, coughing, chest wall spasm, laryngospasm, and bronchospasm. [Note: The latter is of particular concern for asthmatic patients.] Barbiturates are contraindicated in patients with acute intermittent or variegate porphyria.

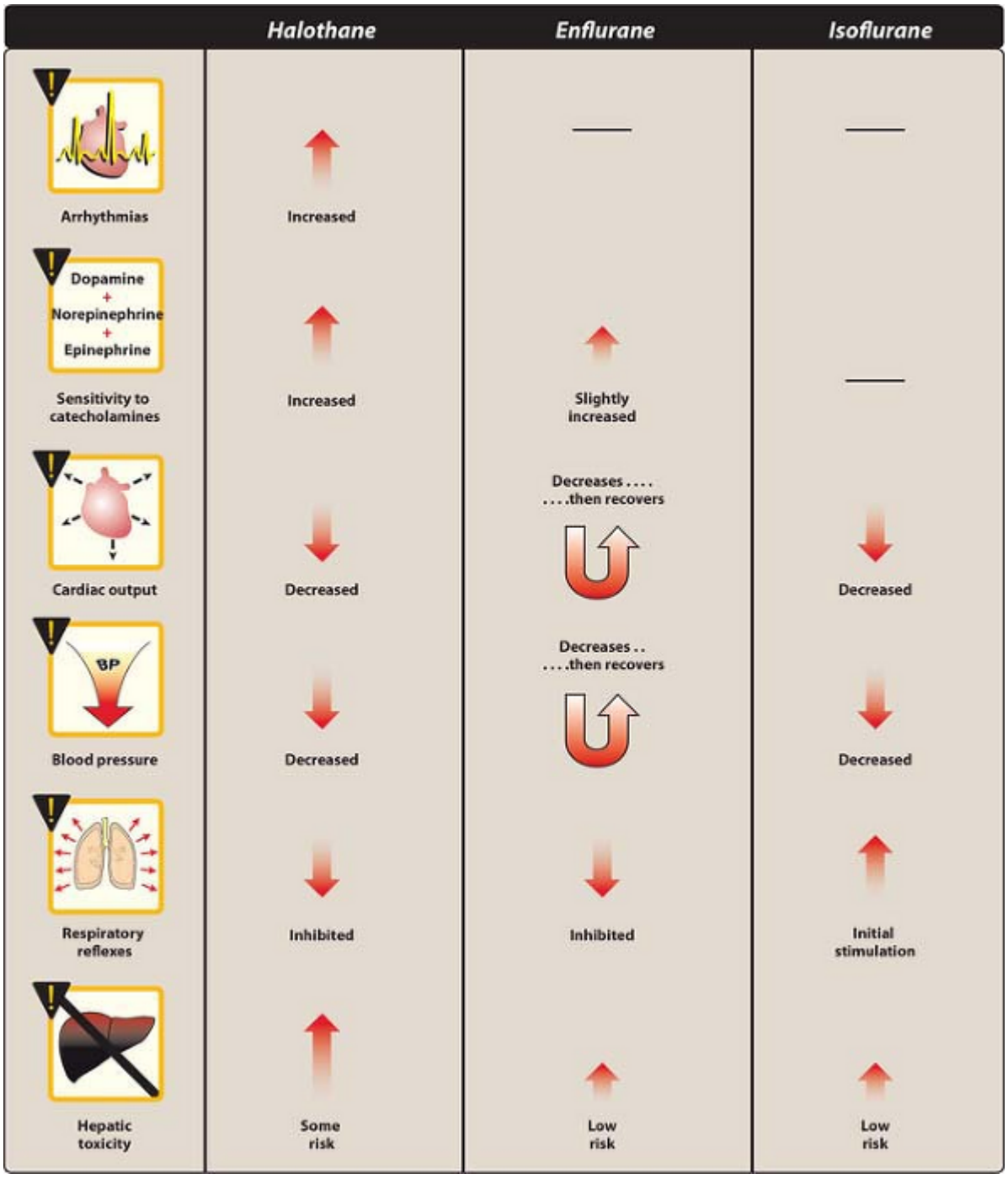

Figure 11.8 Characteristics of some inhalation anesthetics.

B. Benzodiazepines

The benzodiazepines are used in conjunction with anesthetics to sedate the patient. The most commonly employed is *midazolam*, which is available in many formulations, including oral. *Diazepam* and *lorazepam* are alternatives. All three facilitate amnesia while causing sedation.

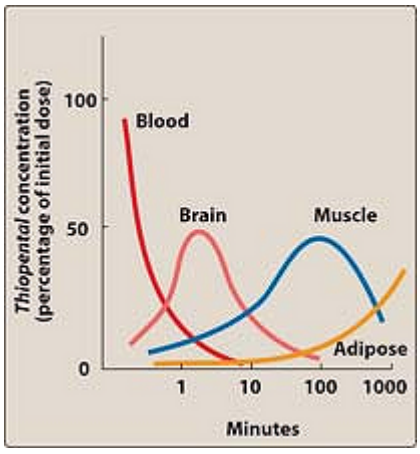

Figure 11.9 Redistribution of *thiopental* from brain to muscle and adipose tissue.

C. Opioids

Because of their analgesic property, opioids are frequently used together with anesthetics; for example, the combination of *morphine* and *nitrous oxide* provides good anesthesia for cardiac surgery. The choice of opioid used perioperatively is based primarily on the duration of action needed. The most frequently employed opioids are *fentanyl* and its congeners, *sufentanil* or *remifentanil*, because they induce analgesia more rapidly than *morphine* does. They are administered either intravenously, epidurally, or intrathecally. Opioids are not good amnesics, and they can all cause hypotension, respiratory depression, and muscle rigidity as well as postanesthetic nausea and vomiting. Opioid effects can be antagonized by *naloxone* (see p. 168).

D. Etomidate

Etomidate (eh-TOE-mid-ate) is used to induce anesthesia. It is a hypnotic agent but lacks analgesic activity. Its water solubility is poor, so *etomidate* is formulated in a propylene glycol solution. Induction is rapid, and the drug is short-acting. It is only used for patients with coronary artery disease or cardiovascular dysfunction, such as shock. *Etomidate* is hydrolyzed in the liver. Among its benefits are little to no effect on the heart and circulation. Its adverse effects include a decrease in plasma cortisol and aldosterone levels, which can persist for up to 8 hours. This is apparently due to inhibition of 11-Î²-hydroxylase.[1] [Note: *Etomidate* should not be infused for an extended time, because prolonged suppression of these hormones can be hazardous.] Venous pain can occur, and skeletal muscle movements are not uncommon. The latter are managed by administration of benzodiazepines and opioids.

E. Ketamine

Ketamine [KET-a-meen], a short-acting, nonbarbiturate anesthetic, induces a dissociated state in which the patient is unconscious but appears to be awake and does not feel pain. This dissociative anesthesia provides sedation, amnesia, and immobility. *Ketamine* interacts with the N-methyl-D-aspartate receptor. It also stimulates the central sympathetic outflow, which, in turn, causes stimulation of the heart and increased blood pressure and cardiac output. This property is especially beneficial in patients with either hypovolemic or cardiogenic shock as well as in patients with asthma. *Ketamine* is therefore used when circulatory depression is undesirable. On the other hand, these effects mitigate

against the use of *ketamine* in hypertensive or stroke patients. The drug is lipophilic and enters the brain circulation very quickly, but like the barbiturates, it redistributes to other organs and tissues. It is metabolized in

the liver, but small amounts can be excreted unchanged. *Ketamine* is employed mainly in children and young adults for short procedures. However, it is not widely used, because it increases cerebral blood flow and induces postoperative hallucinations (â€œnightmaresâ€), particularly in adults.

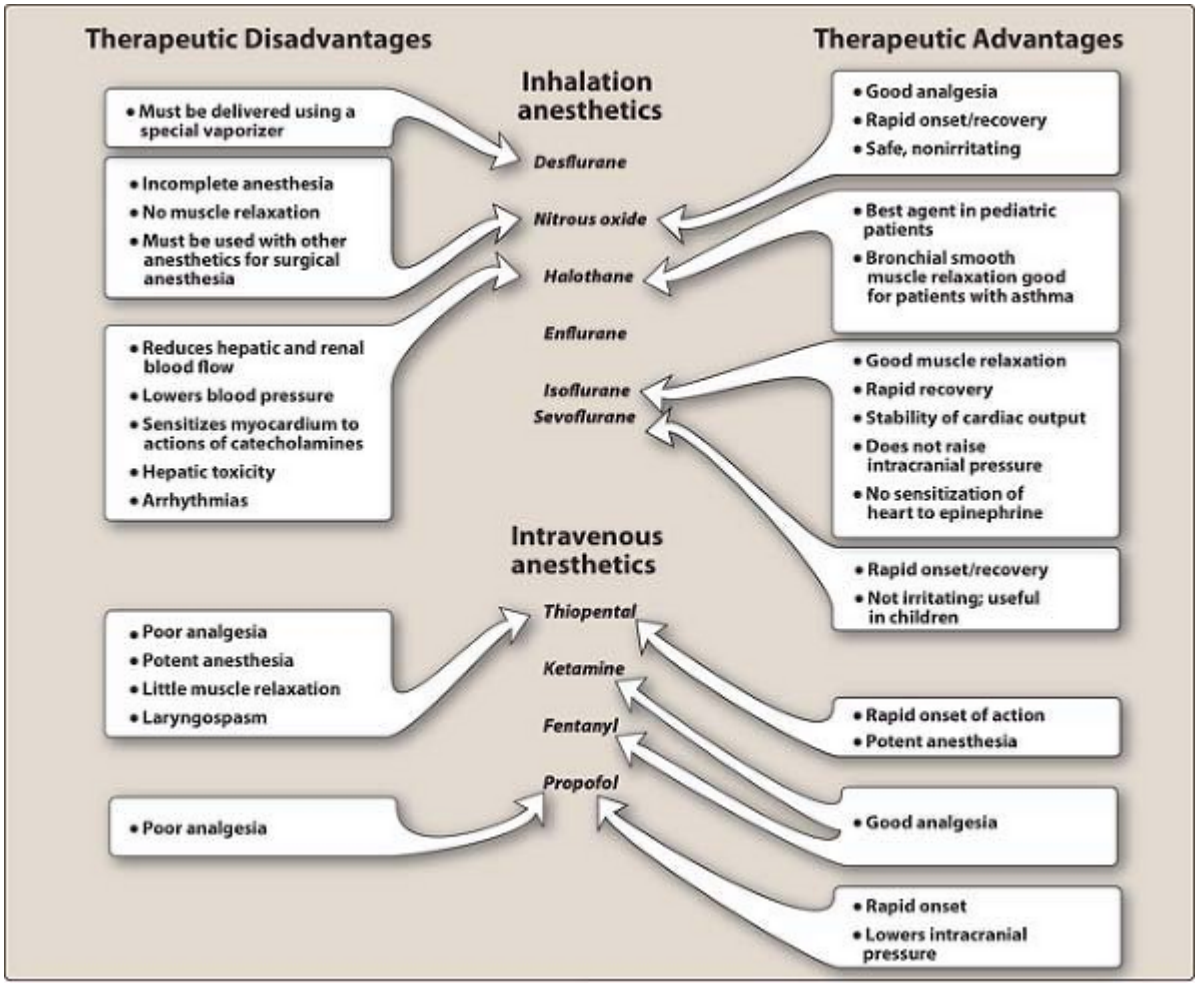

Figure 11.10 *Therapeutic disadvantages and advantages of some anesthetic agents*.

F. Propofol

Propofol [pro-POF-ol] is an intravenous sedative/hypnotic used in the induction or maintenance of anesthesia. Onset is smooth and occurs within about 40 seconds of administration. Supplementation with narcotics for analgesia is required. Whereas *propofol* facilitates depression in the CNS, it is occasionally accompanied by excitatory phenomena, such as muscle twitching, spontaneous movement, or hiccups. *Propofol*

decreases blood pressure without depressing the myocardium. It also reduces intracranial pressure. *Propofol* is widely used and has replaced *thiopental* as the first choice for anesthesia induction and sedation, because it produces a euphoric feeling in the patient and does not cause postanesthetic nausea and vomiting. It has much less of a depressant effect than the volatile anesthetics on CNS-evoked potentials, such as somatosensory evoked potentials. This makes *propofol* very useful for such surgeries as resection of spinal tumors, in which somatosensory evoked potentials are monitored to assess spinal cord functions.

Some therapeutic advantages and disadvantages of the anesthetic agents are summarized in Figure 11.10.

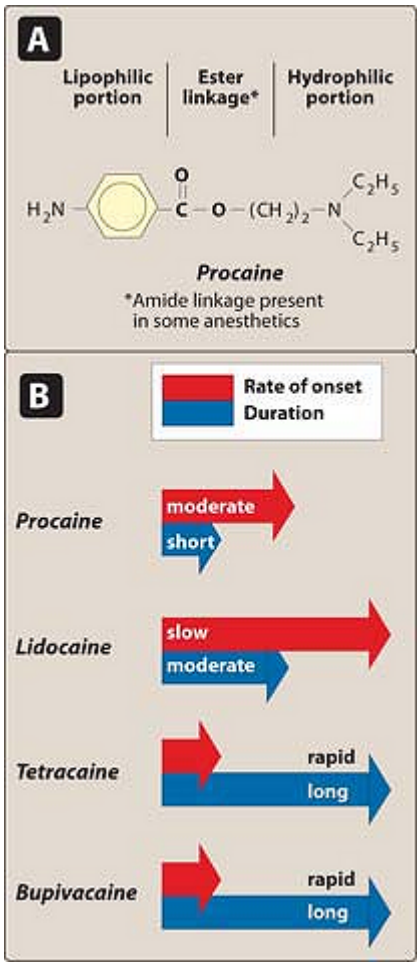

Figure 11.11 A. Structural formula of *procaine*. B. Pharmacokinetic properties of local anesthetics.

VI. Local Anesthetics

Local anesthetics are generally applied locally and block nerve conduction of sensory impulses from the periphery to the CNS. [Note: Some of these agents do have additional usesâ€"for example, the antiarrhythmic effect of *lidocaine*â€"and they are then administered by other routes.] Local anesthetics abolish sensation (and, in higher concentrations, motor activity) in a limited area of the body without producing unconsciousness (for example, during spinal anesthesia). The small, unmyelinated nerve fibers that conduct impulses for pain, temperature, and autonomic activity are most sensitive to actions of local anesthetics. The most widely used of these compounds are *bupivacaine* [byoo-PIV-ah-kane], *lidocaine* [LYE-doe-kane], *mepivacaine* [me-PIV-a-kane], *procaine* [PRO-kane], *ropivacaine* [roe-PIV-a-kane], and *tetracaine* [TET-ra-kane]. Of these, *lidocaine* is the most frequently employed. At physiologic pH, these compounds are charged; it is this ionized form that interacts with the protein receptor of the Na^+ channel to inhibit its function and, thereby, achieve local anesthesia. [Note: The natural product, *cocaine*, was recognized years ago as a local anesthetic. However, its toxicity and abuse have limited its use to topical application in anesthesia of the upper respiratory tract.] The local anesthetics differ pharmacokinetically as to onset and duration of action (Figure 11.11). By adding the vasoconstrictor *epinephrine* to the local anesthetic, the rate of anesthetic absorption is decreased. This both minimizes systemic toxicity and increases the duration of action. Adverse effects result from systemic absorption of toxic amounts of the locally applied anesthetic. Seizures and cardiovascular collapse are the most significant of these systemic effects. *Bupivacaine* is noted for its

cardiotoxicity. *Mepivacaine* should not be used in obstetric anesthesia due to its increased toxicity to the neonate. Allergic reactions may be encountered with *procaine*, which is metabolized to *p*-aminobenzoic acid.

Study Questions

Choose the ONE best answer.

11.1 Halogenated anesthetics may produce malignant hyperthermia in:

A. Patients with poor renal function.

B. Patients allergic to the anesthetic.

C. Pregnant women.

D. Alcoholics.

E. Patients with a genetic defect in muscle calcium regulation.

View Answer

11.2 Children with asthma undergoing a surgical procedure are frequently anesthetized with sevoflurane, because it:

A. Is rapidly taken up.

B. Does not irritate the airway.

C. Has a low nephrotoxic potential.

D. Does not undergo metabolism.

View Answer

11.3 Which one of the following is most likely to require administration of a muscle relaxant?

A. Ethyl ether.

B. Halothane.

C. Methoxyflurane.

D. Benzodiazepines.

E. Nitrous oxide.

View Answer

11.4 Which one of the following is a potent intravenous anesthetic but a weak analgesic?

A. Thiopental.

B. Benzodiazepines.

C. Ketamine.

D Etomidate.

E. Isoflurane.

View Answer

11.5 Which one of the following is a potent analgesic but a weak anesthetic?

A. Methoxyflurane.

B. Succinylcholine.

C. Diazepam.

D. Halothane.

E. Nitrous oxide.

View Answer

Editors: **Finkel, Richard; Clark, Michelle A.; Cubeddu, Luigi X.**
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Chapter 12

Antidepressants

I. Overview

Depression is a serious disorder that afflicts approximately 14 million adults in the United States each year. The lifetime prevalence rate of depression in the United States has been estimated to include 16 percent of adults (21 percent of women, 13 percent of men), or more than 32 million people. The symptoms of depression are intense feelings of sadness, hopelessness, and despair, as well as the inability to experience pleasure in usual activities, changes in sleep patterns and appetite, loss of energy, and suicidal thoughts. Mania is characterized by the opposite behaviorâ€”that is, enthusiasm, rapid thought and speech patterns, extreme self-confidence, and impaired judgment. [Note: Depression and mania are different from schizophrenia (see p. 151), which produces disturbances in thought.]

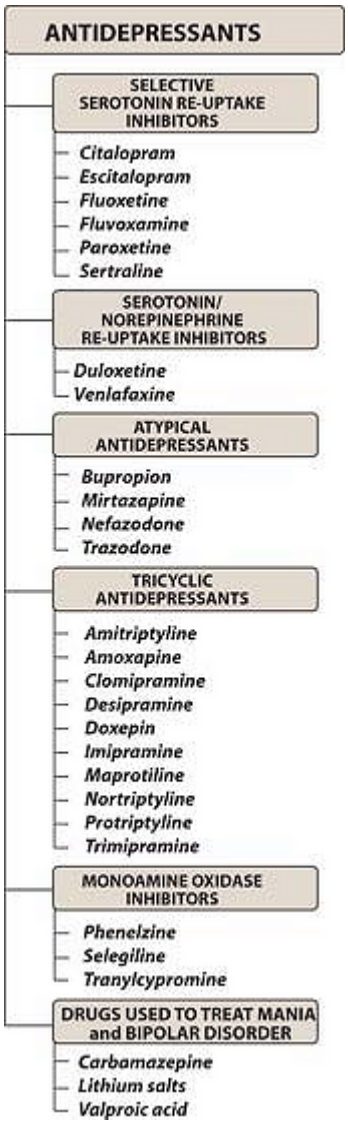

Figure 12.1 Summary of antidepressants.

II. Mechanism of Antidepressant Drugs

Most clinically useful antidepressant drugs potentiate, either directly or indirectly, the actions of norepinephrine and/or serotonin in the brain. (See Figure 12.1 for a summary of the antidepressant agents.) This, along with other evidence, led to the biogenic amine theory, which proposes that depression is due to a deficiency of monoamines, such as norepinephrine and serotonin, at certain key sites in the brain. Conversely, the theory envisions that mania is caused by an overproduction of these neurotransmitters. However, the amine theory of depression and mania is overly simplistic. It fails to explain why the pharmacologic effects of any of the antidepressant and antimania drugs on neurotransmission occur immediately, whereas the time course for a therapeutic response occurs over several weeks. Furthermore, the potency of the antidepressant drugs in blocking neurotransmitter uptake often does not correlate with clinically observed antidepressant effects. This suggests that decreased uptake of neurotransmitter is only an initial effect of the drugs, which may not be directly responsible for the antidepressant effects. It has been proposed that presynaptic inhibitory receptor densities in the brain decrease over a 2- to 4-week period with antidepressant drug use. This down-regulation of inhibitory receptors permits greater synthesis and release of

neurotransmitters into the synaptic cleft and enhanced signaling in the postsynaptic neurons, presumably leading to a therapeutic response (Figure 12.2).

III. Selective Serotonin Reuptake Inhibitors

The selective serotonin reuptake inhibitors (SSRIs) are a group of chemically diverse antidepressant drugs that specifically inhibit serotonin reuptake, having 300- to 3000-fold greater selectivity for the serotonin transporter as compared to the norepinephrine transporter. This contrasts with the tricyclic antidepressants (see p. 145) that nonselectively inhibit the uptake of norepinephrine and serotonin (Figure 12.3). Both of these antidepressant drug classes exhibit little ability to block the dopamine transporter. Moreover, the SSRIs have little blocking activity at muscarinic, Î±-adrenergic, and histaminic H_1 receptors. Therefore, common side effects associated with tricyclic antidepressants, such as orthostatic hypotension, sedation, dry mouth, and blurred vision, are not commonly seen with the SSRIs. Because they have fewer adverse effects and are relatively safe even in overdose, the SSRIs have largely replaced tricyclic antidepressants and monoamine oxidase inhibitors as the drugs of choice in treating depression. SSRIs include *fluoxetine* [floo-OX-e-teen] (the prototypic drug), *citalopram* [sye-TAL-oh-pram], *escitalopram* [es-sye-TAL-oh-pram], *fluvoxamine* [floo-VOX-e-meen], *paroxetine* [pa-ROX-e-teen], and *sertraline* [SER-tra-leen]. Both *citalopram* and *fluoxetine* are racemic mixtures, of which the respective S-enantiomers are the more potent inhibitors of the serotonin reuptake pump. *Escitalopram* is the pure S-enatiomer of *citalopram.*

A. Actions

The SSRIs block the reuptake of serotonin, leading to increased concentrations of the neurotransmitter in the synaptic cleft and, ultimately, to greater postsynaptic neuronal activity. Antidepressants, including SSRIs, typically take at least 2 weeks to produce significant improvement in mood, and maximum benefit may require up to 12 weeks or more (Figure 12.4). However, none of the antidepressants are uniformly effective. Approximately 40 percent of depressed patients treated with adequate doses for 4 to 8 weeks do not respond to the antidepressant agent. Patients that do not respond to one antidepressant may respond to another, and approximately 80 percent or more will respond to at least one antidepressant drug. [Note: These drugs do not usually produce central nervous system (CNS) stimulation or mood elevation in normal individuals.]

B. Therapeutic uses

The primary indication for SSRIs is depression, for which they are as effective as the tricyclic antidepressants. A number of other psychiatric disorders also respond favorably to SSRIs, including obsessive-compulsive disorder (the only approved indication for *fluvoxamine*), panic disorder, generalized anxiety disorder, posttraumatic stress disorder, social anxiety disorder, premenstrual dysphoric disorder, and bulimia nervosa (only *fluoxetine* is approved for this last indication).

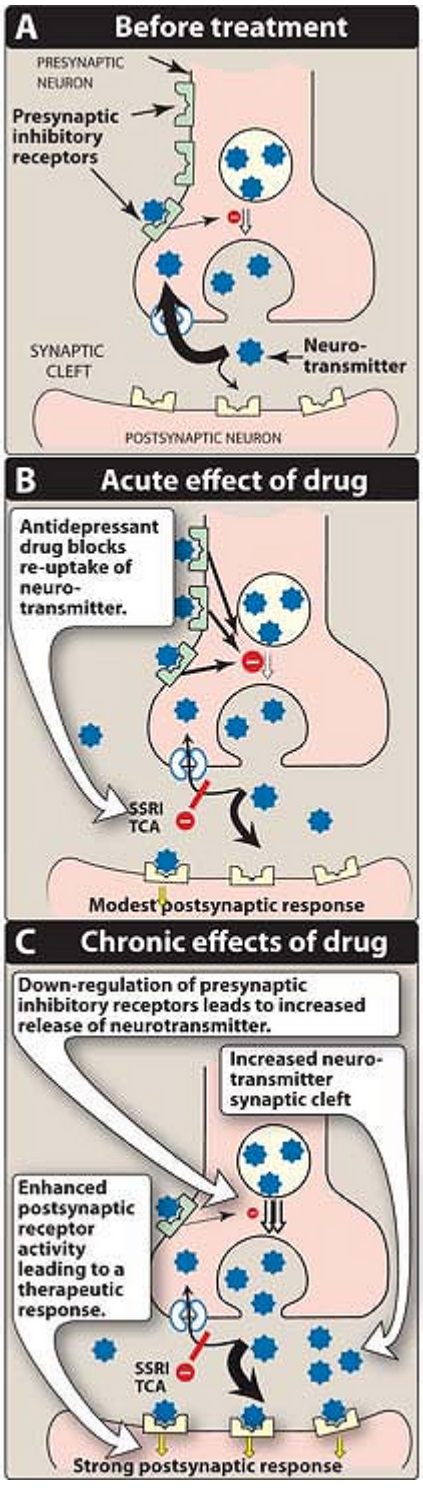

Figure 12.2 Proposed mechanism of action of selective serotonin re-uptake inhibitors (SSRI) and tricyclic antidepressant (TCA) drugs.

C. Pharmacokinetics

All of the SSRIs are well absorbed after oral administration. Peak levels are seen in approximately 2 to 8 hours on

average. Food has little effect on absorption (except with *sertraline*, for which food increases its absorption). Only *sertraline* undergoes significant first-pass metabolism. All of these agents are well distributed, having volumes of distribution far in excess of body weight (15â€“30 L/kg). The majority of SSRIs have plasma half-lives that range between 16 and 36 hours. Metabolism by P450-dependent enzymes and glucuronide or sulfate conjugation occur

extensively. [Note: These metabolites do not generally contribute to the pharmacologic activity.] *Fluoxetine* differs from the other members of the class in two respects. First, it has a much longer half-life (50 hours) and is available as a sustained-release preparation allowing once-weekly dosing. Second, the metabolite of the S-enantiomer, S-norfluoxetine, is as potent as the parent compound. The half-life of the metabolite is quite long, averaging 10 days. *Fluoxetine* and *paroxetine* are potent inhibitors of a hepatic cytochrome P450 isoenzyme (CYP2D6) responsible for the elimination of tricyclic antidepressant drugs, neuroleptic drugs, and some antiarrhythmic and Î²-adrenergicâ€“antagonist drugs. [Note: About seven percent of the Caucasian population lack this P450 enzyme and, therefore, metabolize *fluoxetine*, and other substrates of this enzyme, very slowly. These individuals may be referred to in the literature as poor metabolizers.] Other cytochrome enzymes (CYP2C9/19, CYP3A4, CYP1A2) are involved with SSRI metabolism and may also be inhibited to various degrees by the SSRIs and, thus, may affect the metabolism of multiple medications. Excretion of the SSRIs is primarily through the kidneys, except for *paroxetine* and *sertraline*, which also undergo fecal excretion (35 and 50 percent, respectively). Dosages of all of these drugs should be adjusted downward in patients with hepatic impairment.

DRUG	UPTAKE INHIBITION	
	Nor-epinephrine	Serotonin
Selective serotonin re-uptake inhibitor		
Fluoxetine	0	++++
Selective serotonin/ norepinephrine re-uptake inhibitors		
Venlafaxine	++*	++++
Duloxetine	++++	++++
Tricyclic antidepressant		
Imipramine	++++	+++

Figure 12.3 Relative receptor specificity of some antidepressant drugs. *Venlafaxine inhibits norepinephrine re-uptake only at high doses. ++++ = very strong affnity; +++ = strong affinity; ++ = moderate affinity; + = weak affinity; 0 = little or no affinity.

D. Adverse effects

Although the SSRIs are considered to have fewer and less severe adverse effects than the tricyclic antidepressants and monoamine oxidase inhibitors, the SSRIs are not without troublesome adverse effects, such as, headache, sweating, anxiety and agitation, gastrointestinal effects (nausea, vomiting, diarrhea), weakness and fatigue, sexual dysfunction, changes in weight, sleep disturbances (insomnia and somnolence), and the above-mentioned potential for drug-drug interactions (Figure 12.5).

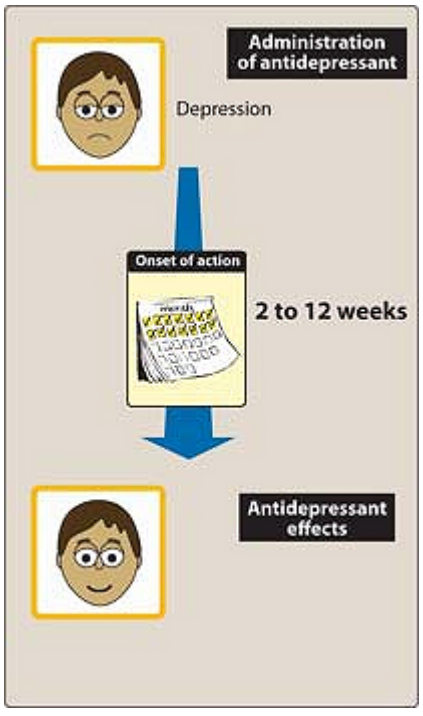

Figure 12.4 Onset of therapeutic effects of the major antidepressant drugs (tricyclic antidepressants, selective serotonin re-uptake inhibitors, and monoamine oxidase inhibitors) requires several weeks.

1. **Sleep disturbances:** *Paroxetine* and *fluvoxamine* are generally more sedating than activating, and they may be useful in patients who have difficulty sleeping. Conversely, patients who are fatigued or complaining of excessive somnolence may benefit from one of the more activating antidepressants, such as *fluoxetine or sertraline*.

2. **Sexual dysfunction:** Loss of libido, delayed ejaculation, and anorgasmia are underreported side effects often noted by clinicians but not prominently featured in the list of standard side effects. One option for managing SSRI-induced sexual dysfunction is to replace the offending antidepressant with an antidepressant having fewer sexual side effects, such as *bupropion* or *mirtazapine.* Alternatively, the dose of the drug may be reduced. In men with erectile dysfunction and depression, treatment with *sildenafil, vardenafil*, or *tadalafil* (see p. 341) may improve sexual function.

3. **Use in children and teenagers:** Antidepressants should be used cautiously in children and teenagers, because about 1 out of 50 children becomes more suicidal as a result of SSRI treatment. Pediatric patients should be observed for worsening depression and suicidal thinking whenever any antidepressant is started or its dose is increased or decreased.

4. **Overdoses:** Large intakes of SSRIs do not usually cause cardiac arrhythmias (compared to the arrhythmia risk for the tricyclic antidepressants), but seizures are a possibility because all antidepressants

may lower the seizure threshold. All SSRIs have the potential to cause a serotonin syndrome that may include the symptoms of hyperthermia, muscle rigidity, sweating, myoclonus (clonic muscle twitching), and changes in mental status and vital signs when used in the presence of a monoamine oxidase inhibitor or another highly serotonergic drug. Therefore, extended periods of washout for each drug class should occur prior to the administration of the other class of drugs.

5. **Discontinuation syndrome:** Whereas all of the SSRIs have the potential for causing a discontinuation syndrome

after their abrupt withdrawal, the agents with the shorter half-lives and having inactive metabolites have a higher risk for such an adverse reaction. *Fluoxetine* has the lowest risk of causing an SSRI discontinuation syndrome. Possible signs and symptoms of such a serotonin-related discontinuation syndrome include headache, malaise and flu-like symptoms, agitation and irritability, nervousness, and changes in sleep pattern.

IV. Serotonin-Norepinephrine Reuptake Inhibitors

Venlafaxine [VEN-la-fax-een] and *duloxetine* (doo-LOX-e-teen) selectively inhibit the re-uptake of both serotonin and norepinephrine (Figure 12.6). These agents, termed selective serotonin-norepinephrine reuptake inhibitors (SNRIs), may be effective in treating depression in patients in whom SSRIs are ineffective. Furthermore, depression is often accompanied by chronic painful symptoms, such as backache and muscle aches, against which SSRIs are also relatively ineffective. This pain is, in part, modulated by serotonin and norepinephrine pathways in the CNS. Both SNRIs and tricyclic antidepressants, with their dual actions of inhibiting both serotonin and norepinephrine reuptake are sometimes effective in relieving physical symptoms of neuropathic pain, such as diabetic peripheral neuropathy. However, the SNRIs, unlike the tricyclic antidepressants, have little activity at adrenergic, muscarinic, or histamine receptors and, thus, have fewer of these receptor-mediated adverse effects than the tricyclic antidepressants (see Figure 12.3). Both *venlafaxine* and *duloxetine* may precipitate a discontinuation syndrome if treatment is abruptly stopped.

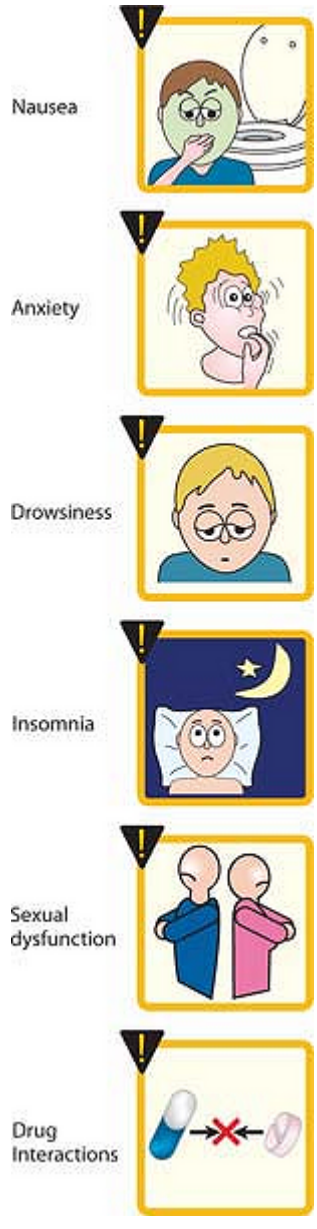

Figure 12.5 Some commonly observed adverse effects of selective serotonin re-uptake inhibitors.

A. Venlafaxine

Venlafaxine is a potent inhibitor of serotonin reuptake and, at medium to higher doses, is an inhibitor of norepinephrine re-uptake. It is also a mild inhibitor of dopamine reuptake at high doses. *Venlafaxine* has minimal inhibition of the cytochrome P450 isoenzymes and is a substrate of the CYP2D6 isoenzyme. The half-life of the parent compound plus its active metabolite is approximately 11 hours. *Venlafaxine* is only 27 percent bound to plasma protein and is not expected to be involved in protein displacement interactions. The most common side effects of *venlafaxine* are nausea, headache, sexual dysfunction, dizziness, insomnia, sedation, and constipation. At high doses, there may be an increase in blood pressure and heart rate.

B. Duloxetine

Duloxetine inhibits serotonin and norepinephrine reuptake at all doses. It is extensively metabolized in the liver to numerous metabolites. *Duloxetine* should not be administered to patients with hepatic insufficiency. Metabolites are excreted in the urine, and the use of *duloxetine* is not recommended in patients with end-stage renal disease.

Food delays the absorption of the drug. The half-life is approximately 12 hours. *Duloxetine* is highly bound to plasma protein. Gastrointestinal side effects are common with *duloxetine*, including nausea, dry mouth, and constipation. Diarrhea and vomiting are seen less often. Insomnia, dizziness, somnolence, and sweating are also seen. Sexual dysfunction also occurs along with the possible risk for an increase in either blood pressure or heart rate.

V. Atypical Antidepressants

The atypical antidepressants are a mixed group of agents that have actions at several different sites. This group includes *bupropion* [byoo-PROE-pee-on], *mirtazapine* [mir-TAZ-a-peen], *nefazodone* [nef-AY-zoe-done], and *trazodone* [TRAZ-oh-done]. They are not any more efficacious than the tricyclic antidepressants or SSRIs, but their side effect profiles are different.

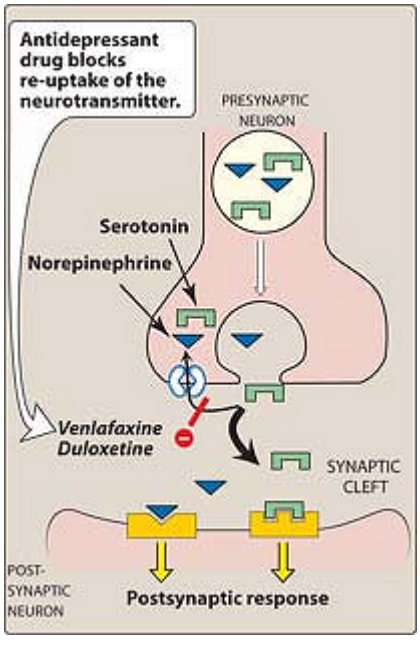

Figure 12.6 Proposed mechanism of action of selective serotonin/norepinephrine re-uptake inhibitor antidepressant drugs.

A. Bupropion

This drug acts as a weak dopamine and norepinephrine reuptake inhibitor to alleviate the symptoms of depression. Its short half-life may require more than once-a-day dosing or the administration of an extended-release formulation. *Bupropion* is unique in that it assists in decreasing the craving and attenuating the withdrawal symptoms for *nicotine* in tobacco users trying to quit smoking. Side effects may include dry mouth, sweating, nervousness, tremor, a very low incidence of sexual dysfunction, and an increased risk for seizures at high doses. *Bupropion* is metabolized by the CYP2D6 pathway and is considered to have a relatively low risk for drug-drug interactions.

B. Mirtazapine

This drug enhances serotonin and norepinephrine neurotransmission via mechanisms related to its ability to block presynaptic Î±$_2$ receptors. Additionally, it may owe at least some of its antidepressant activity to its ability to block 5-HT$_2$ receptors. It is a sedative because of its potent antihistaminic activity, but it does not cause the antimuscarinic side effects of the tricyclic antidepressants, or interfere with sexual functioning, as do the SSRIs. Increased appetite and weight gain frequently occur. *Mirtazapine* is markedly sedating, which may be used to advantage in depressed patients having difficulty sleeping.

C. Nefazodone and trazodone

These drugs are weak inhibitors of serotonin reuptake. Their therapeutic benefit appears to be related to their ability to block postsynaptic 5-HT$_{2A}$ receptors. With chronic use, these agents may desensitize 5-HT$_{1A}$ presynaptic autoreceptors and, thereby, increase serotonin release. Both agents are sedating, probably because of their potent H$_1$-blocking activity. *Trazodone* has been associated with causing priapism, and *nefazodone* has been associated with the risk for hepatotoxicity.

VI. Tricyclic Antidepressants

The tricyclic antidepressants (TCAs) block norepinephrine and serotonin reuptake into the neuron and, thus, if discovered today, may be referred to as SNRIs except for their differences in adverse effects relative to this newer class of antidepressants. The TCAs include the tertiary amines *imipramine* [ee-MIP-ra-meen] (the prototype drug), *amitriptyline* [aye-mee-TRIP-ti-leen], *clomipramine* [kloe-MIP-ra-meen], *doxepin* [DOX-e-pin] and *trimipramine*

[trye-MIP-ra-meen]. The TCAs also include the secondary amines *desipramine* [dess-IP-ra-meen] and *nortriptyline* [nor-TRIP-ti-leen] (the respective N-demethylated metabolites of *imipramine* and *amitriptyline*) and *protriptyline* [proe-TRIP-ti-leen]. *Maprotiline* [ma-PROE-ti-leen] and *amoxapine* [a-MOX-a-peen] are related â€œtetracyclicâ€ antidepressant agents and are commonly included in the general class of TCAs. All have similar therapeutic efficacy, and the choice of drug may depend on such issues as patient tolerance to side effects, prior response, preexisting medical conditions, and duration of action. Patients who do not respond to one TCA may benefit from a different drug in this group. These drugs are a valuable alternative for patients who do not respond to SSRIs.

A. Mechanism of action

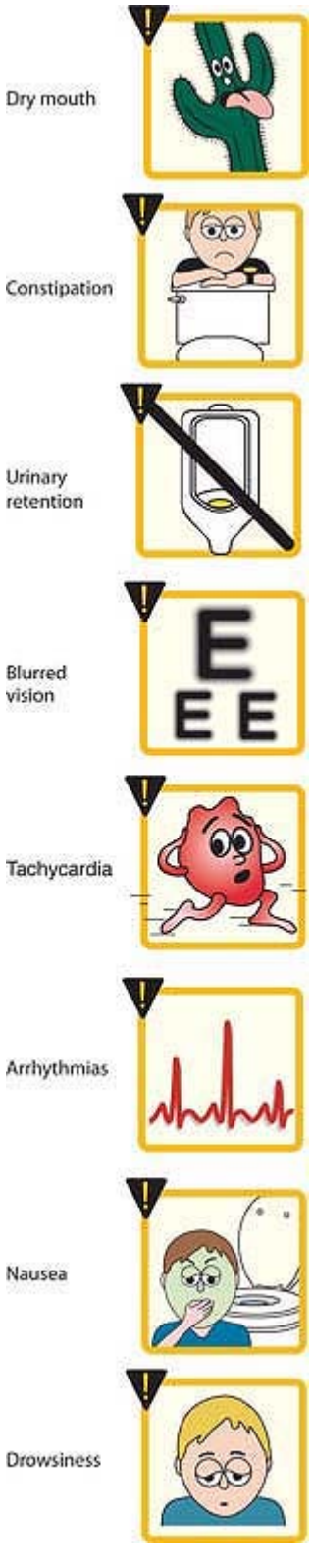

Figure 12.7 Some commonly observed adverse effects of tricyclic antidepressants.

1. **Inhibition of neurotransmitter reuptake:** TCAs and *amoxapine* are potent inhibitors of the neuronal reuptake

of norepinephrine and serotonin into presynaptic nerve terminals (see Figure 12.2). At therapeutic concentrations, they do not block dopamine transporters. By blocking the major route of neurotransmitter removal, the TCAs cause increased concentrations of monoamines in the synaptic cleft, ultimately resulting in antidepressant effects. *Maprotiline* and *desipramine* are selective inhibitors of norepinephrine reuptake.

2. **Blocking of receptors:** TCAs also block serotonergic, Î±-adrenergic, histaminic, and muscarinic receptors (see Figure 12.3). It is not known if any of these actions produce their therapeutic benefit. However, actions at these receptors are probably responsible for many of the untoward effects of the TCAs. *Amoxapine* also blocks the D_2 receptor.

B. Actions

The TCAs elevate mood, improve mental alertness, increase physical activity, and reduce morbid preoccupation in 50 to 70 percent of individuals with major depression. The onset of the mood elevation is slow, requiring 2 weeks or longer (see Figure 12.4). These drugs do not commonly produce CNS stimulation or mood elevation in normal individuals. Physical and psychological dependence has been rarely reported, however, this necessitates slow withdrawal to minimize discontinuation syndromes and cholinergic rebound effects. These drugs, like all of the antidepressants, can be used for prolonged treatment of depression.

C. Therapeutic uses

The TCAs are effective in treating moderate to severe major depression. Some patients with panic disorder also respond to TCAs. *Imipramine* has been used to control bed-wetting in children (older than 6 years) by causing contraction of the internal sphincter of the bladder. At present, it is used cautiously because of the inducement of cardiac arrhythmias and other serious cardiovascular problems. The TCAs, particularly *amitriptyline*, have been used to treat migraine headache and chronic pain syndromes (for example, â€œneuropathicâ€ pain) in a number of conditions for which the cause of the pain is unclear.

D. Pharmacokinetics

Tricyclic antidepressants are well absorbed upon oral administration. Because of their lipophilic nature, they are widely distributed and readily penetrate into the CNS. This lipid solubility also causes these drugs to have variable half-livesâ€”for example, 4 to 17 hours for *imipramine*.

As a result of their variable first-pass metabolism in the liver, TCAs have low and inconsistent bioavailability. Therefore, the patient's response and plasma levels can be used to adjust dosage. The initial treatment period is typically 4 to 8 weeks. The dosage can be gradually reduced to improve tolerability unless relapse occurs. These drugs are metabolized by the hepatic microsomal system (and, thus, may be sensitive to agents that induce or inhibit the CYP450 isoenzymes) and conjugated with glucuronic acid. Ultimately, the TCAs are excreted as inactive metabolites via the kidney.

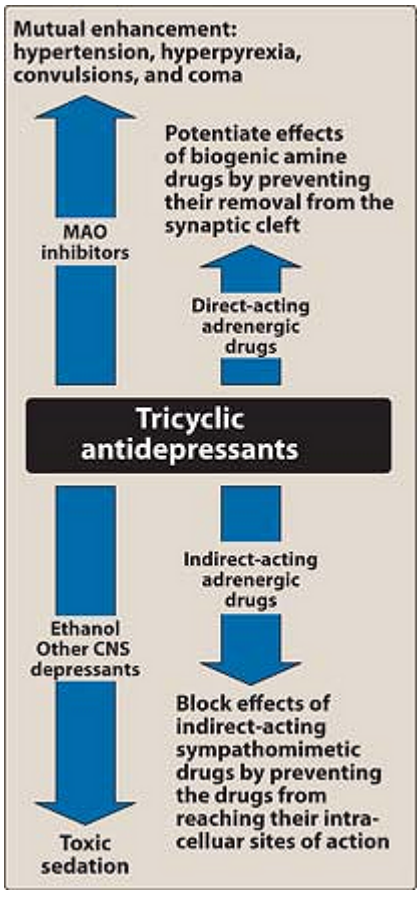

Figure 12.8 Drugs interacting with tricyclic antidepressants. CNS = central nervous system; MAO = monoamine oxidase.

E. Adverse effects

Blockade of muscarinic receptors leads to blurred vision, xerostomia (dry mouth), urinary retention, constipation, and aggravation of narrow-angle glaucoma (Figure 12.7). These agents slow cardiac conduction similarly to *quinidine,* which may precipitate life-threatening arrhythmias should an overdose of one of these drugs be taken. The TCAs also block Î±-adrenergic receptors, causing orthostatic hypotension, dizziness, and reflex tachycardia. In clinical practice, this is the most serious problem in the elderly. *Imipramine* is the most likely and *nortriptyline* the least likely to cause orthostatic hypotension. Sedation may be prominent, especially during the first several weeks of treatment, and is related to the ability of these drugs to block histamine H_1 receptors. Weight gain is a common adverse effect of the TCAs. Sexual dysfunction, as evidenced by erectile dysfunction in men and anorgasmia in women, occurs in a significant minority of patients, but the incidence is still considered to be lower than the incidence of sexual dysfunction associated with the SSRIs.

1. **Precautions:** TCAs (like all antidepressants) should be used with caution in known manic-depressive patients, even during their depressed state, because antidepressants may cause a switch to manic behavior. The TCAs have a narrow therapeutic index; for example, five- to six-fold the maximal daily dose of *imipramine* can be lethal. Depressed patients who are suicidal should be given only limited quantities of these drugs and be monitored closely. Drug interactions with the TCAs are shown in Figure 12.8. The TCAs may exacerbate certain medical conditions, such as unstable angina, benign prostatic hyperplasia, epilepsy, and patients with preexisting arrhythmias. Caution should be exercised with their use in very young or very old patients as well.

VII. Monoamine Oxidase Inhibitors

Monoamine oxidase (MAO) is a mitochondrial enzyme found in nerve and other tissues, such as the gut and liver. In the neuron, MAO functions as a â€œsafety valveâ€ to oxidatively deaminate and inactivate any excess neurotransmitter molecules (norepinephrine, dopamine, and serotonin) that may leak out of synaptic vesicles when the neuron is at rest. The MAO inhibitors may irreversibly or reversibly inactivate the enzyme, permitting neurotransmitter molecules to escape degradation and, therefore, to both accumulate within the presynaptic neuron and leak into the synaptic space. This is believed to cause activation of norepinephrine and serotonin receptors, and it may be responsible for the indirect antidepressant action of these drugs. Three MAO inhibitors are currently available for treatment of depression: *phenelzine* [FEN-el-zeen], *tranylcypromine* [tran-il-SIP-roe-meen] and the agent that was prior-approved for Parkinson's disease, but is now also

approved for depression, *selegiline,* which is the first antidepressant available in a transdermal delivery system. Use of MAO inhibitors is now limited due to the complicated dietary restrictions required of patients taking MAO inhibitors.

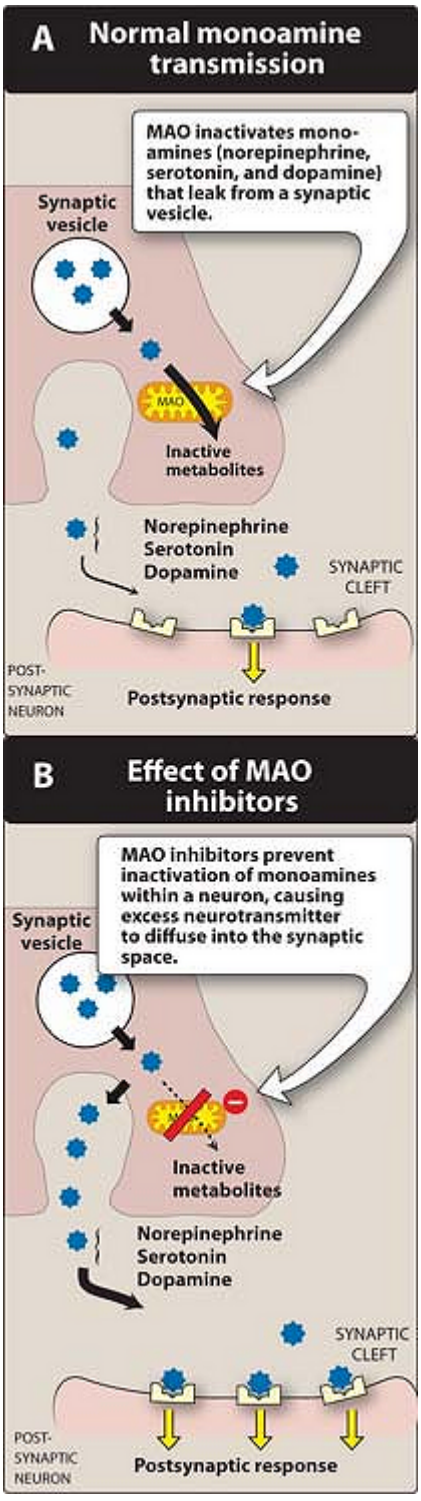

Figure 12.9 Mechanism of action of monoamine oxidase (MAO) inhibitors.

A. Mechanism of action

Most MAO inhibitors, such as *phenelzine*, form stable complexes with the enzyme, causing irreversible inactivation. This results in increased stores of norepinephrine, serotonin, and dopamine within the neuron and subsequent

diffusion of excess neurotransmitter into the synaptic space (Figure 12.9). These drugs inhibit not only MAO in the brain but also MAO in the liver and gut that catalyze oxidative deamination of drugs and potentially toxic substances, such as tyramine, which is found in certain foods. The MAO inhibitors therefore show a high incidence of drug-drug and drug-food interactions. *Selegiline* administered as the transdermal â€œpatchâ€ may produce less inhibition of hepatic MAO at low doses, because it avoids first-pass metabolism.

B. Actions

Although MAO is fully inhibited after several days of treatment, the antidepressant action of the MAO inhibitors, like that of the SSRIs and TCAs, is delayed several weeks. *Selegiline* and *tranylcypromine* have an amphetamine-like stimulant effect that may produce agitation or insomnia.

C. Therapeutic uses

The MAO inhibitors are indicated for depressed patients who are unresponsive or allergic to TCAs or who experience strong anxiety. Patients with low psychomotor activity may benefit from the stimulant properties of the MAO inhibitors. These drugs are also useful in the treatment of phobic states. A special subcategory of depression, called atypical depression, may respond to MAO inhibitors. Atypical depression is characterized by labile mood, rejection sensitivity, and appetite disorders. Despite their efficacy in treating depression, because of their risk for drug-drug and drug-food interactions, the MAO inhibitors are considered to be last-line agents in many treatment venues.

D. Pharmacokinetics

These drugs are well absorbed after oral administration, but antidepressant effects require at least 2 to 4 weeks of treatment. Enzyme regeneration, when irreversibly inactivated, varies, but it usually occurs several weeks after termination of the drug. Thus, when switching antidepressant agents, a minimum of 2 weeks of delay must be allowed after termination of MAO inhibitor therapy and the initiation of another antidepressant from any other class. MAO inhibitors are metabolized and excreted rapidly in the urine.

E. Adverse effects

Severe and often unpredictable side effects due to drug-food and drug-drug interactions limit the widespread use of MAO inhibitors. For example, tyramine, which is contained in certain foods, such as aged cheeses and meats, chicken liver, pickled or smoked fish such as anchovies or herring, and red wines, is normally inactivated by MAO in the gut. Individuals receiving an MAO inhibitor are unable to degrade tyramine obtained from the diet. Tyramine causes the release of large amounts of stored catecholamines from nerve terminals, resulting in occipital

headache, stiff neck, tachycardia, nausea, hypertension, cardiac arrhythmias, seizures, and possibly, stroke. Patients must therefore be educated to avoid tyramine-containing foods. *Phentolamine* or *prazosin* are helpful in the management of tyramine-induced hypertension. [Note: Treatment with MAO inhibitors may be dangerous in severely depressed patients with suicidal tendencies. Purposeful consumption of tyramine-containing foods is a possibility.] Other possible side effects of treatment with MAO inhibitors include drowsiness, orthostatic hypotension, blurred vision, dry mouth, dysuria, and constipation. The MAO inhibitors and SSRIs should not be coadministered due to the risk of the life-threatening â€œserotonin syndrome.â€ Both types of drugs require washout periods of at least 2 weeks before the other type is administered, with the exception of *fluoxetine,* which should be discontinued at least 6 weeks before a MAO inhibitor is initiated. Combination of MAO inhibitors and *bupropion* can produce seizures. Figure 12.10 summarizes the side effects of the antidepressant drugs.

VIII. Treatment of Mania and Bipolar Disorder

The treatment of bipolar disorder has increased in recent years, partly due to the increased recognition of the disorder and also due to the increase in the number of medications U.S. Food and Drug Administration (FDA)â€“approved for the treatment of mania. *Lithium salts* are used prophylactically for treating manic-depressive patients and in the treatment of manic episodes and, thus, is considered a â€œmood stabilizer.â€ *Lithium* is

effective in treating 60 to 80 percent of patients exhibiting mania and hypomania. Although many cellular processes are altered by treatment with *lithium salts*, the mode of action is unknown. [Note: *Lithium* is believed to attenuate signaling via receptors coupled to the phosphatidylinositol bisphosphate (PIP_2) second-messenger system. *Lithium* interferes with the resynthesis (recycling) of PIP_2, leading to its relative depletion in neuronal membranes of the CNS. PIP_2 levels in peripheral membranes are unaffected by *lithium*.] *Lithium* is given orally, and the ion is excreted by the kidney. *Lithium* salts can be toxic. Their safety factor and therapeutic index are extremely lowâ€"comparable to those of *digitalis*. Common adverse effects may include headache, dry mouth, polydipsia, polyuria, polyphagia, gastrointestinal distress (give *lithium* with food), fine hand tremor, dizziness, fatigue, dermatologic reactions, and sedation. Adverse effects due to higher plasma levels may include ataxia, slurred speech, coarse tremors, confusion, and convulsions. [Note: The diabetes insipidus that results from taking *lithium* can be treated with *amiloride*.] Thyroid function may be decreased and should be monitored. *Lithium* causes no noticeable effect on normal individuals. It is not a sedative, euphoriant, or depressant.

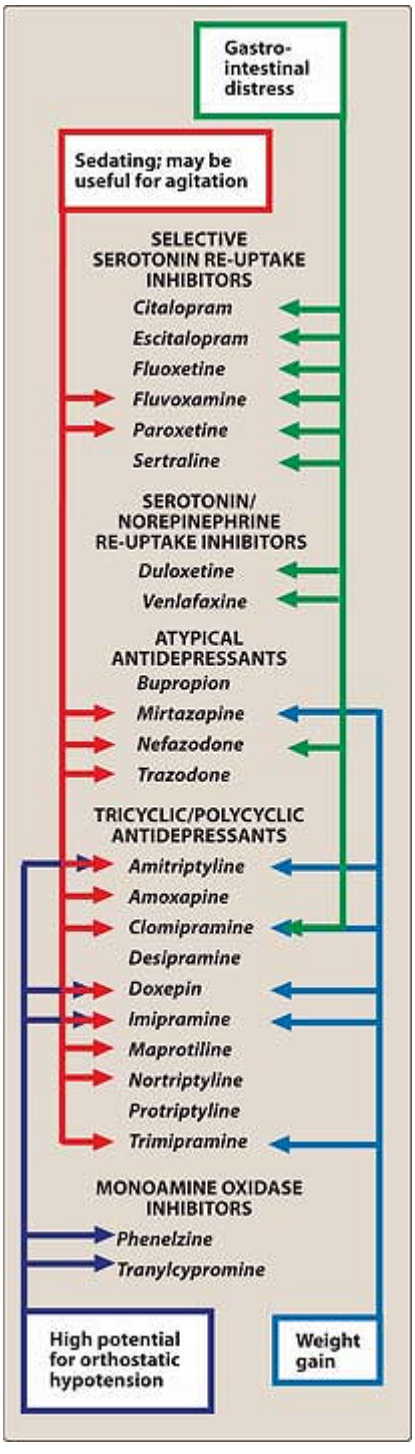

Figure 12.10 Side effects of some drugs used to treat depression.

Several antiepileptic drugs, including most notably *carbamazepine, valproic acid, and lamotrigine,* have been identified and FDA-approved as â€œmood stabilizersâ€ and have been successfully utilized in the treatment of bipolar disorder. Other agents that may improve manic symptoms include the older and newer antipsychotics. The atypical antipsychotics (*risperidone, olanzapine, ziprasidone, aripiprazole*, and *quetiapine*) have also received FDA approval for the management of mania. Benzodiazepines are also frequently used as adjunctive treatments for

the acute stabilization of patients with mania. (See the respective chapters on these psychotropics for a more detailed description).

Study Questions

Choose the ONE best answer.

12.1 A 55-year-old teacher began to experience changes in mood. He was losing interest in his work and lacked the desire to play his daily tennis match. He was preoccupied with feelings of guilt, worthlessness, and hopelessness. In addition to the psychiatric symptoms, the patient complained of muscle aches throughout his body. Physical and laboratory tests were unremarkable. After 6 weeks of therapy with fluoxetine, the patient's symptoms resolved. However, the patient complains of sexual dysfunction. Which of the following drugs might be useful in this patient?

A. Fluvoxamine.

B. Sertraline.

C. Citalopram.

D. Mirtazapine.

E. Lithium.

View Answer

12.2 A 25-year-old woman has a long history of depressive symptoms accompanied by body aches. Physical and laboratory tests are unremarkable. Which of the following drugs might be useful in this patient?

A. Fluoxetine.

B. Sertraline.

C. Phenelzine.

D. Mirtazapine.

E. Duloxetine.

View Answer

12.3 A 51-year-old woman with symptoms of major depression also has narrow-angle glaucoma. Which of the following antidepressants should be avoided in this patient?

A. Amitriptyline.

B. Sertraline.

C. Bupropion.

D. Mirtazepine.

E. Fluvoxamine.

View Answer

12.4 A 36-year-old man presents with symptoms of compulsive behavior. If anything is out of order, he feels that â€œwork will not be accomplished effectively or efficiently.â€ He realizes that his behavior is interfering with his ability to accomplish his daily tasks but cannot seem to stop himself. Which of the following drugs would be most helpful to this patient?

A. Imipramine.

B. Fluvoxamine.

C. Amitriptyline.

D. Tranylcypromine.

E. Lithium.

View Answer

Editors: **Finkel, Richard; Clark, Michelle A.; Cubeddu, Luigi X.**
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Chapter 13

Neuroleptics

I. Overview

The neuroleptic drugs (also called antipsychotic drugs, or major tranquilizers) are used primarily to treat schizophrenia, but they are also effective in other psychotic states, such as manic states with psychotic symptoms such as grandiosity or paranoia and hallucinations, and delirium. All currently available antipsychotic drugs that alleviate symptoms of schizophrenia decrease dopaminergic and/or serotonergic neurotransmission. The traditional or â€œtypicalâ€ neuroleptic drugs (also called conventional or first-generation antipsychotics) are competitive inhibitors at a variety of receptors, but their antipsychotic effects reflect competitive blocking of dopamine receptors. These drugs vary in potency. For example, *chlorpromazine* is a low-potency drug, and *fluphenazine* is a high-potency agent (Figure 13.1). No one drug is clinically more effective than another. In contrast, the newer antipsychotic drugs are referred to as â€œatypicalâ€ (or second-generation antipsychotics), because they have fewer extrapyramidal adverse effects than the older, traditional agents. These drugs appear to owe their unique activity to blockade of both serotonin and dopamine (and, perhaps, other) receptors. Current antipsychotic therapy commonly employs the use of the atypical agents to minimize the risk of debilitating movement disorders associated with the typical drugs that act primarily at the D_2 dopamine receptor. All of the atypical antipsychotics exhibit an efficacy that is equivalent to, or occasionally exceeds, that of the typical neuroleptic agents. However, consistent differences in therapeutic efficacy among the individual atypical neuroleptics have not been established, and individual patient response and comorbid conditions must often be used as a guide in drug selection. Neuroleptic drugs are not curative and do not eliminate the fundamental and chronic thought disorder, but they often decrease the intensity of hallucinations and delusions and permit the person with schizophrenia to function in a supportive environment.

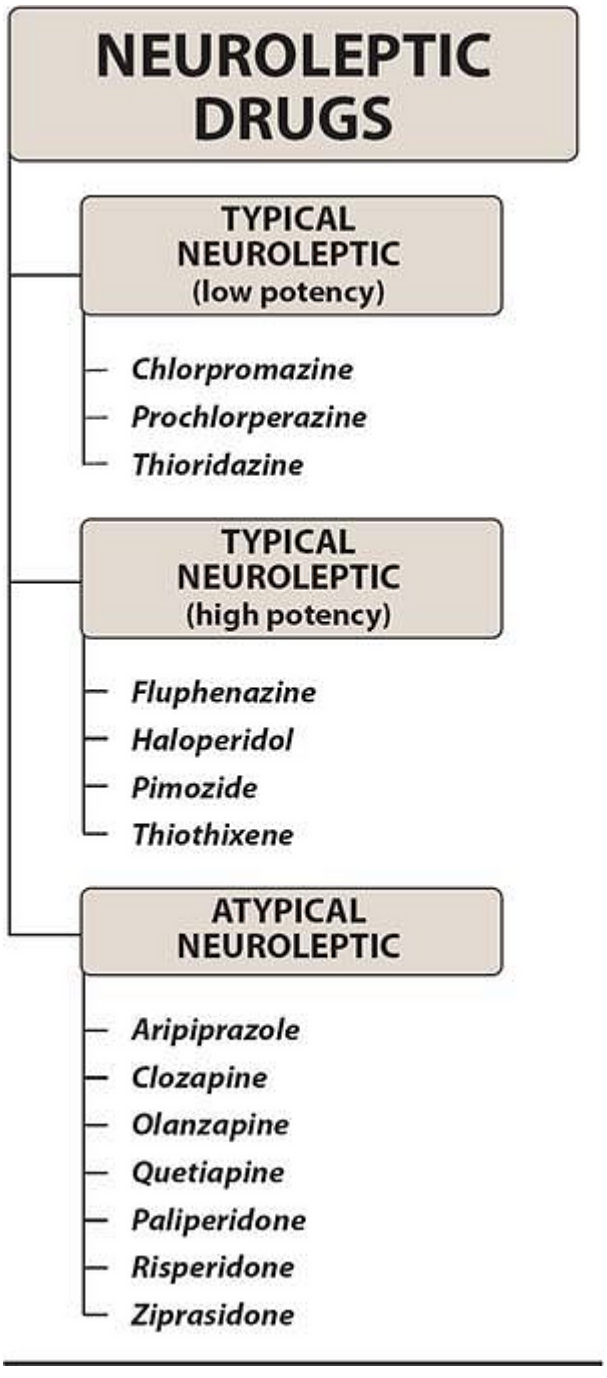

Figure 13.1 Summary of neuroleptic agents.

II. Schizophrenia

Schizophrenia is a particular type of psychosisâ€”that is, a mental disorder caused by some inherent dysfunction of the brain. It is characterized by delusions, hallucinations (often in the form of voices), and thinking or speech disturbances. This mental disorder is a common affliction, occurring among about one percent of the population. The illness often initially affects people during late adolescence or early adulthood and is a chronic and disabling disorder. Schizophrenia has a strong genetic component and probably reflects some fundamental biochemical

abnormality, possibly a dysfunction of the mesolimbic or mesocortical dopaminergic neurons.

III. Neuroleptic Drugs

The neuroleptic drugs represent several diverse, heterocyclic structures with markedly different potencies. The tricyclic phenothiazine derivative, *chlorpromazine* [klor-PROE-ma-zeen], was the first neuroleptic drug used to treat schizophrenia. Antipsychotic drugs developed subsequently, such as *haloperidol* [hal-oh-PER-i-dole], are more than 100-fold as potent as *chlorpromazine* but have an increased ability to induce parkinson-like and other extrapyramidal effects. Furthermore, these more potent traditional drugs are no more effective than *chlorpromazine*.

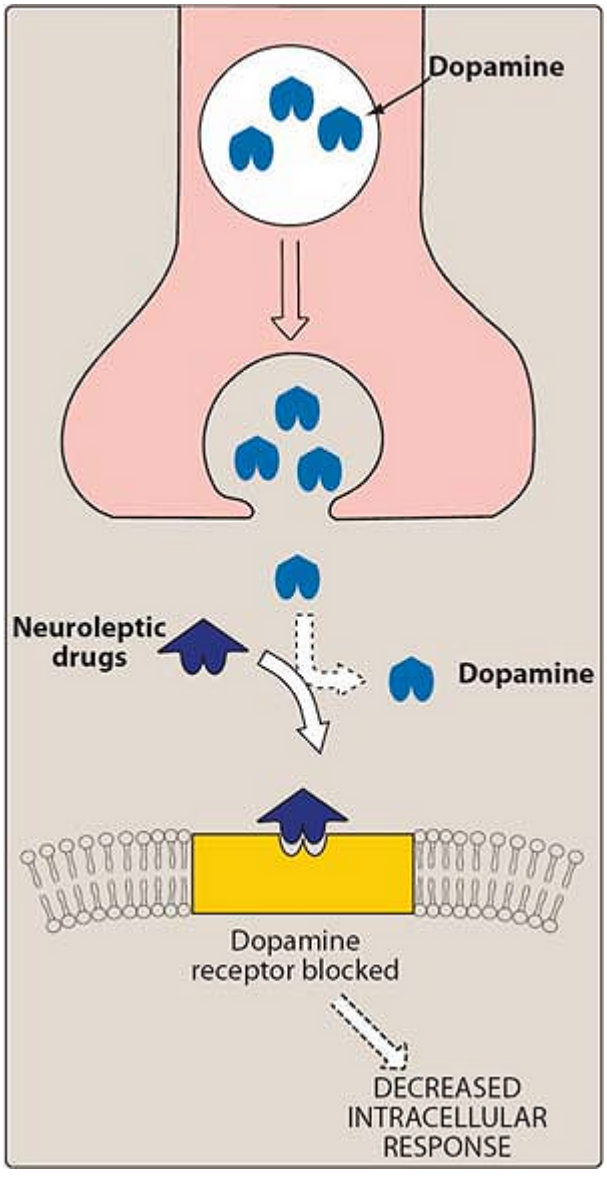

Figure 13.2 Dopamine-blocking actions of neuroleptic drugs.

A. Mechanism of action

1. **Dopamine receptorâ€“blocking activity in the brain:** All of the older and most of the newer neuroleptic drugs block dopamine receptors in the brain and the periphery (Figure 13.2). Five types of dopamine receptors have been identified. D_1 and D_5 receptors activate adenylyl cyclase, often exciting neurons, whereas D_2, D_3 and D_4 receptors inhibit adenylyl cyclase, or mediate membrane K^+ channel opening leading to neuronal hyperpolarization. The neuroleptic drugs bind to these receptors to varying degrees. However, the clinical efficacy of the typical neuroleptic drugs correlates closely with their relative ability to block D_2 receptors in the mesolimbic system of the brain. On the other hand, the atypical drug *clozapine* [KLOE-za-peen] has higher affinity for the D_4 receptor and lower affinity for the D_2 receptor, which may partially explain its minimal ability to cause extrapyramidal side effects (EPS). (Figure 13.3 summarizes the receptor-binding properties of *clozapine, chlorpromazine*, and *haloperidol.*) The actions of the neuroleptic drugs are antagonized by agents that raise synaptic dopamine concentrationsâ€"for example, *levodopa* and amphetaminesâ€"or mimic dopamine at post-synaptic binding sitesâ€"for example, *bromocriptine*.

2. **Serotonin receptorâ€“blocking activity in the brain:** Most of the newer atypical agents appear to exert part of their unique action through inhibition of serotonin receptors (5-HT), particularly 5-HT_{2A} receptors. Thus, *clozapine* has high affinity for D_1, D_4, 5-HT_2, muscarinic, and Î±-adrenergic receptors, but it is also a dopamine D_2-receptor antagonist. *Risperidone* [ris-PEER-i-dohn] blocks 5-HT_{2A} receptors to a greater extent than it does D_2 receptors, as does *olanzapine*. The atypical neuroleptic *aripiprazole* [a-rih-PIP-ra-zole] is a partial agonist at D_2 and 5-HT_{1A} receptors as well as a blocker of 5-HT_{2A} receptors. *Quetiapine* blocks D_2 receptors more potently than 5HT_{2A} receptors but is relatively weak at blocking either receptor, and its low risk for EPS may also be related to the relatively short period of time it binds to the D_2 receptor.

B. Actions

The antipsychotic actions of neuroleptic drugs appear to reflect a blockade at dopamine and/or serotonin receptors. However, many of these agents also block cholinergic, adrenergic, and histaminergic receptors (Figure 13.4). It is unknown what role, if any, these actions have in alleviating the symptoms of psychosis. The undesirable side effects of these agents, however, are often a result of actions at these other receptors.

1. **Antipsychotic actions:** All of the neuroleptic drugs can reduce the hallucinations and delusions associated with schizophrenia (the so-called

â€œpositiveâ€ symptoms) by blocking dopamine receptors in the mesolimbic system of the brain. The â€œnegativeâ€ symptoms, such as blunted affect, anhedonia (not getting pleasure from normally pleasurable stimuli), apathy, and impaired attention, as well as cognitive impairment are not as responsive to therapy, particularly with the typical neuroleptics. Many atypical agents, such as *clozapine*, ameliorate the negative symptoms to some extent. All of the drugs also have a calming effect and reduce spontaneous physical movement. In contrast to the central nervous system (CNS) depressants, such as barbiturates, the neuroleptics do not depress the intellectual functioning of the patient as much, and motor incoordination is minimal. The antipsychotic effects usually take several days to weeks to occur, suggesting that the therapeutic effects are related to secondary changes in the corticostriatal pathways.

2. **Extrapyramidal effects:** Dystonias (sustained contraction of muscles leading to twisting distorted postures), parkinson-like symptoms, akathisia (motor restlessness), and tardive dyskinesia (involuntary movements of the tongue, lips, neck, trunk, and limbs) occur with chronic treatment. Blocking of dopamine receptors in the nigrostriatal pathway probably causes these unwanted movement symptoms. The atypical neuroleptics exhibit a lower incidence of these symptoms.

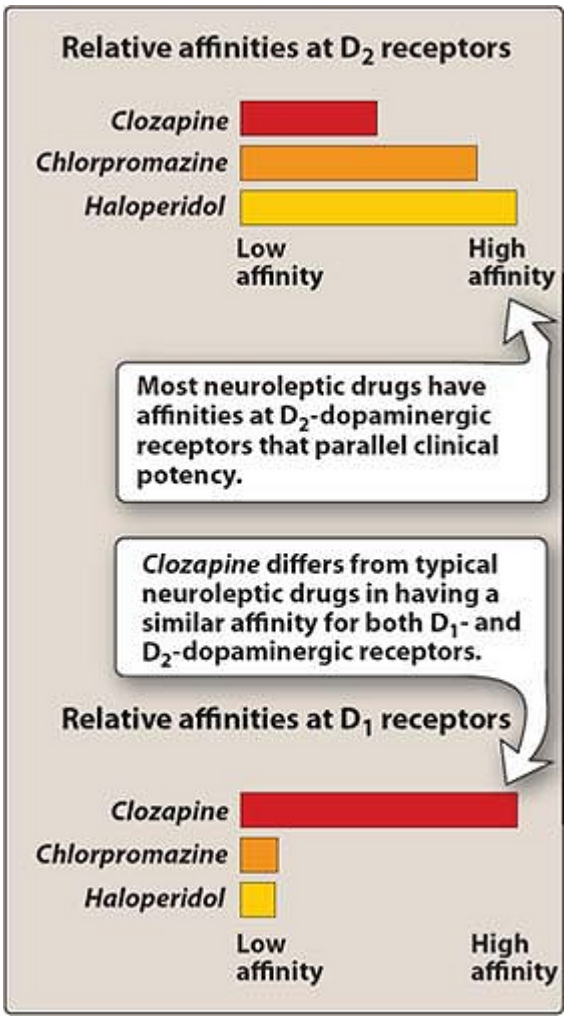

Figure 13.3 Relative affinity of *clozapine, chlorpromazine*, and *haloperidol* at D_1- and D_2-dopaminergic receptors.

3. **Antiemetic effects:** With the exceptions of *aripiprazole* and *thioridazine* [thye-oh-RID-a-zeen], most of the neuroleptic drugs have antiemetic effects that are mediated by blocking D_2-dopaminergic receptors of the chemoreceptor trigger zone of the medulla. (See p. 335 for a discussion of emesis.) Figure 13.5 summarizes the antiemetic uses of neuroleptic agents, along with the therapeutic applications of other drugs that combat nausea. [Note: The atypical antipsychotic drugs are not used as antiemetics.]

4. **Antimuscarinic effects:** Some of the neuroleptics, particularly *thioridazine, chlorpromazine, clozapine*, and *olanzapine* [oh-LAN-za-peen], produce anticholinergic effects, including blurred vision, dry

mouth (exception: *clozapine* increase salivation), confusion, and inhibition of gastrointestinal and urinary tract smooth muscle, leading to constipation and urinary retention. This anticholinergic property may actually assist in reducing the risk of EPS with these agents.

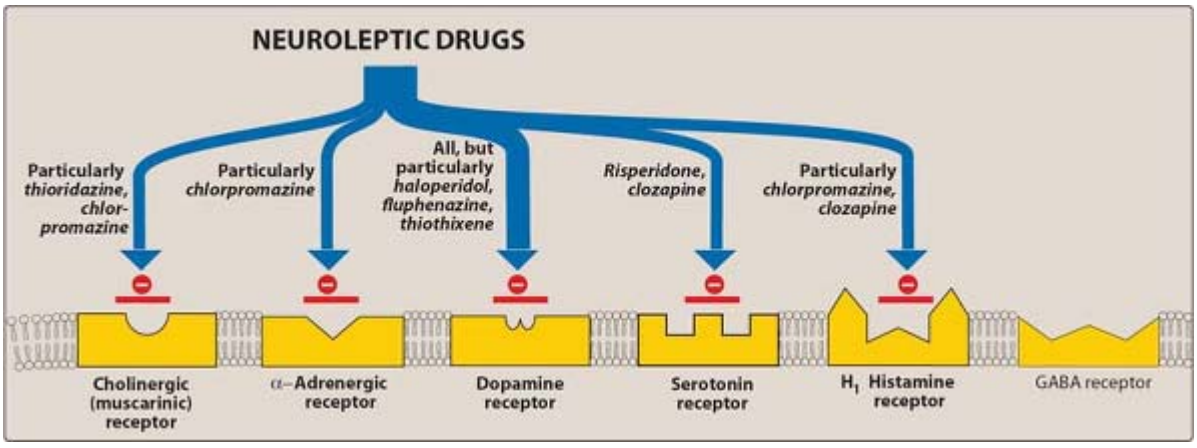

Figure 13.4 Neuroleptic drugs block at dopaminergic and serotonergic receptors as well as at adrenergic, cholinergic, and histamine-binding receptors. GABA = Î»-aminobutyric acid.

5. **Other effects:** Blockade of Î±-adrenergic receptors causes orthostatic hypotension and light-headedness. The neuroleptics also alter temperature-regulating mechanisms and can produce poikilothermia (body temperature varies with the environment). In the pituitary, neuroleptics block D_2 receptors, leading to an increase in prolactin release. Atypical neuroleptics are less likely to produce prolactin elevations. Sedation occurs with those drugs that are potent antagonists of the H_1-histamine receptor, including *chlorpromazine, olanzapine, quetiapine,* and *clozapine*. Sexual dysfunction may also occur with the antipsychotics due to various receptor-binding characteristics.

C. Therapeutic uses

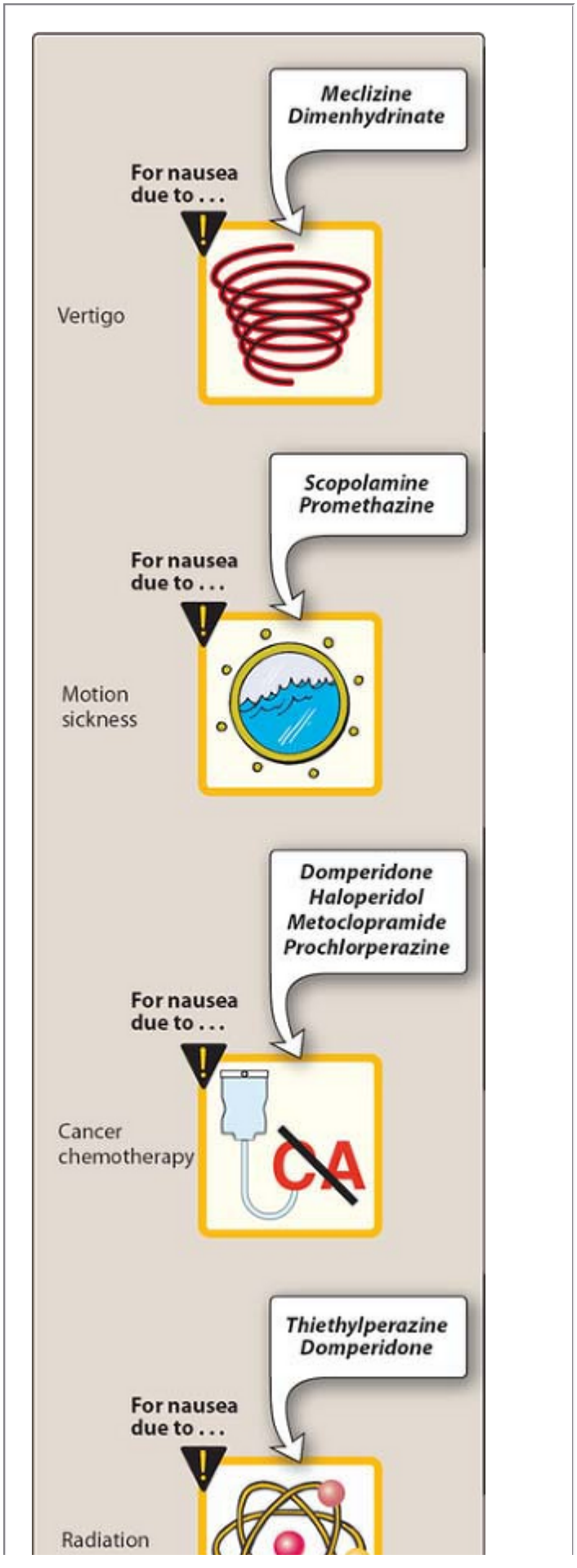
Meclizine
Dimenhydrinate
For nausea due to . . .
Vertigo
Scopolamine
Promethazine
For nausea due to . . .
Motion sickness
Domperidone
Haloperidol
Metoclopramide
Prochlorperazine
For nausea due to . . .
Cancer chemotherapy
CA
Thiethylperazine
Domperidone
For nausea due to . . .
Radiation

Figure 13.5 Therapeutic application of antiemetic agents.

1. **Treatment of schizophrenia:** The neuroleptics are considered to be the only efficacious treatment for schizophrenia. Not all patients respond, and complete normalization of behavior is seldom achieved. The traditional neuroleptics are most effective in treating positive symptoms of schizophrenia (delusions, hallucinations, thought processing, and agitation). The newer agents with 5-HT_{2A} receptorâ€"blocking activity may be effective in many patients who are resistant to the traditional agents, especially in treating the negative symptoms of schizophrenia (social withdrawal, blunted emotions, ambivalence, and reduced ability to relate to people). However, even the atypical antipsychotics do not consistently improve the negative symptoms of schizophrenia more than the older agents. [Note: *Clozapine* is reserved for the treatment of individuals who are unresponsive to other neuroleptics, because its use is associated with blood dyscrasias and other severe adverse effects].
2. **Prevention of severe nausea and vomiting:** The older neuroleptics (most commonly *prochlorperazine*) are useful in the treatment of drug-induced nausea (see p. 336). Nausea arising from motion should be treated with sedatives, antihistamines, and anticholinergics, however, rather than with the powerful neuroleptic drugs. [Note: Transdermal *scopolamine* is a drug of choice for treatment of motion sickness.]
3. **Other uses:** The neuroleptic drugs can be used as tranquilizers to manage agitated and disruptive behavior secondary to other disorders. Neuroleptics are used in combination with narcotic analgesics for treatment of chronic pain with severe anxiety. *Chlorpromazine* is used to treat intractable hiccups. *Promethazine* [proe-METH-a-zeen] is not a good antipsychotic drug; however, this agent is used in treating pruritus because of its antihistaminic properties. *Pimozide* [PI-moe-zide] is primarily indicated for treatment of the motor and phonic tics of Tourette's disorder. However, *risperidone* and *haloperidol* are also commonly prescribed for this tic disorder. Also, *risperidone* is now approved for the management of disruptive behavior and irritability secondary to autism.

D. Absorption and metabolism

After oral administration, the neuroleptics show variable absorption that is unaffected by food (except for *ziprasidone* and *paliperidone,* the absorption of which is increased with food). These agents readily pass into the brain, have a large volume of distribution, bind well to plasma proteins, and are metabolized to many different substances, usually by the cytochrome P450 system in the liver, particularly the CYP2D6, CYP1A2, and CYP3A4 isoenzymes. Some metabolites are active. *Fluphenazine decanoate, haloperidol decanoate*, and *risperidone* microspheres are slow-release (up to 2 to 4 weeks) injectable formulations of neuroleptics that are administered via deep gluteal intramuscular injection. These drugs are often used to treat outpatients and individuals who are noncompliant with oral medications. However, patients may still develop extrapyramidal symptoms (EPS), but the risk of EPS is lower with these long-acting, injectable formulations compared to their respective oral formulations. The neuroleptic drugs produce some tolerance but little physical dependence.

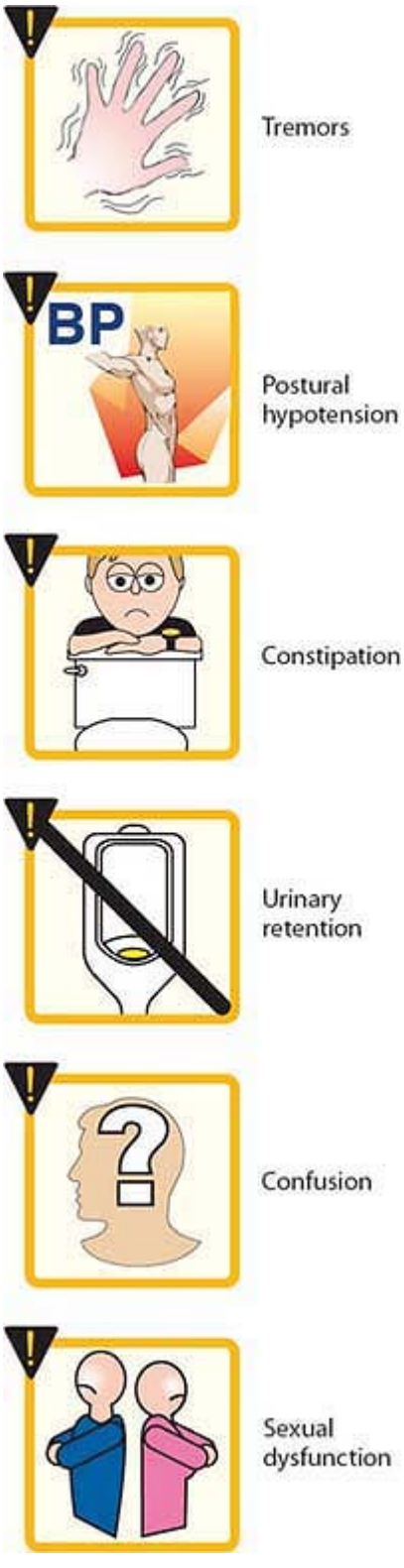

Figure 13.6 Adverse effects commonly observed in individuals treated with neuroleptic drugs.

E. Adverse effects

Adverse effects of the neuroleptic drugs can occur in practically all patients and are significant in about 80 percent (Figure 13.6). Although antipsychotic drugs have an array of adverse effects, their therapeutic index is high.

1. **Extrapyramidal side effects:** The inhibitory effects of dopaminergic neurons are normally balanced by the excitatory actions of cholinergic neurons in the striatum. Blocking dopamine receptors alters this balance, causing a relative excess of cholinergic influence, which results in extrapyramidal motor effects. The maximal risk of appearance of the movement disorders is time and dose dependent, with dystonias occurring within a few hours to days of treatment, followed by akathisias (the inability to remain seated due to motor restlessness) occurring within days to weeks. Parkinson-like symptoms of bradykinesia, rigidity, and tremor usually occur within weeks to months of initiating treatment. Tardive dyskinesia, which can be irreversible, may occur after months or years of treatment.

    a. **Effect of anticholinergic drugs:** If cholinergic activity is also blocked, a new, more nearly normal balance is restored, and extrapyramidal effects are minimized. This can be achieved by administration of an anticholinergic drug, such as *benztropine*. The therapeutic trade-off will be fewer extrapyramidal effects in exchange for the side effects of muscarinic receptor blockade. [Note: Sometimes, the parkinson-like actions persist despite the anticholinergic drugs.] Those drugs that exhibit strong anticholinergic activity, such as *thioridazine*, show fewer extrapyramidal disturbances, because the cholinergic activity is strongly dampened. This contrasts with *haloperidol* and *fluphenazine*, which have low anticholinergic activity and produce extrapyramidal effects more frequently because of the preferential blocking of dopaminergic transmission without the blocking of cholinergic activity.

    b. **Atypical antipsychotics (clozapine and risperidone):** These drugs exhibit a lower potential for causing extrapyramidal symptoms and lower risk of tardive dyskinesia, which has been

    attributed to their blockade of 5-HT_{2A} receptors. These two drugs appear to be superior to *haloperidol* and *chlorpromazine* in treating some of the symptoms of schizophrenia, especially the negative symptoms. *Risperidone* should be included among the first-line antipsychotic drugs, whereas *clozapine* should be reserved for severely schizophrenic patients who are refractory to traditional therapy. *Clozapine* can produce bone marrow suppression, seizures, and cardiovascular side effects. The risk of severe agranulocytosis necessitates frequent monitoring of white-blood-cell counts. Paliperidone, the major active metabolite of *risperidone*, exhibits neuroleptic activity similar to that of the parent drug. The other atypical antipsychotics (*olanzapine, quetiapine, ziprasidone*, and *aripiprazole*) have proven efficacy in treating psychotic symptoms, but their efficacy is not considered to be consistently superior to that of the older neurolepitcs. However, their lower incidence of EPS commonly places these newer agents ahead of the older neuroleptics when treating patients with schizophrenia.

2. **Tardive dyskinesia:** Long-term treatment with neuroleptics can cause this motor disorder. Patients display involuntary movements, including lateral jaw movements and â€œfly-catchingâ€ motions of the tongue. A prolonged holiday from neuroleptics may cause the symptoms to diminish or disappear within a few months. However, in many individuals, tardive dyskinesia is irreversible and persists after discontinuation of therapy. Tardive dyskinesia is postulated to result from an increased number of dopamine receptors that are synthesized as a compensatory response to long-term dopamine-receptor blockade. This makes the neuron supersensitive to the actions of dopamine, and it allows the dopaminergic input to this structure to overpower the cholinergic input, causing excess movement in the patient.

3. **Neuroleptic malignant syndrome:** This potentially fatal reaction to neuroleptic drugs is characterized by muscle rigidity, fever, altered mental status and stupor, unstable blood pressure, and myoglobinemia. Treatment necessitates discontinuation of the neuroleptic and supportive therapy. Administration of *dantrolene* or *bromocriptine* may be helpful.

4. **Other effects:** Drowsiness occurs due to CNS depression and antihistaminic effects, usually during the first few weeks of treatment. Confusion is sometimes encountered. Those neuroleptics with potent antimuscarinic activity often produce dry mouth, urinary retention, constipation, and loss of accommodation. Others may block

Î±-adrenergic receptors, resulting in lowered blood pressure and orthostatic hypotension. The neuroleptics depress the hypothalamus, affecting thermoregulation, and causing amenorrhea, galactorrhea, gynecomastia, infertility, and impotence. Significant weight gain is often a reason for noncompliance. It is also recommended that glucose and lipid profiles be monitored in patients taking antipsychotics due to the potential for the atypical agents to increase these laboratory parameters and the possible exacerbation of preexisting diabetes mellitus or hyperlipidemia.

5. **Cautions and contraindications:** Acute agitation accompanying withdrawal from alcohol or other drugs may be aggravated by the

neuroleptics. Stabilization with a simple sedative, such as a *benzodiazepine*, is the preferred treatment. All antipsychotics may lower the seizure threshold, and *chlorpromazine* and *clozapine* are contraindicated in patients with seizure disorders. Therefore, the neuroleptics can also aggravate preexisting epilepsy, and they should be used with caution in patients with epilepsy. The high incidence of agranulocytosis with *clozapine* may limit its use to patients who are resistant to other drugs. All of the atypical antipsychotics also carry the warning of increased risk for mortality when used in elderly patients with dementia-related behavioral disturbances and psychosis.

F. Maintenance treatment

Patients who have had two or more psychotic episodes secondary to schizophrenia should receive maintenance therapy for at least 5 years, and some experts prefer indefinite therapy. There has been a greater emphasis in research and practice on identifying and aggressively managing first-episode psychosis to determine the benefits of antipsychotic agents in this population. Low doses of antipsychotic drugs are not as effective as higher-dose maintenance therapy in preventing relapse (Figure 13.7).

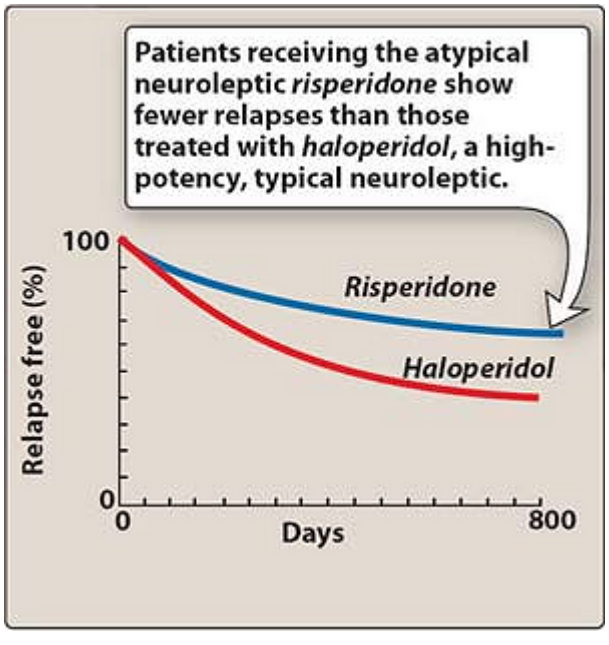

Figure 13.7 Rates of relapse among patients with schizophrenia after maintenance therapy with either *risperidone* or *haloperidol*.

Figure 13.8 summarizes the therapeutic uses of some of the neuroleptic drugs.

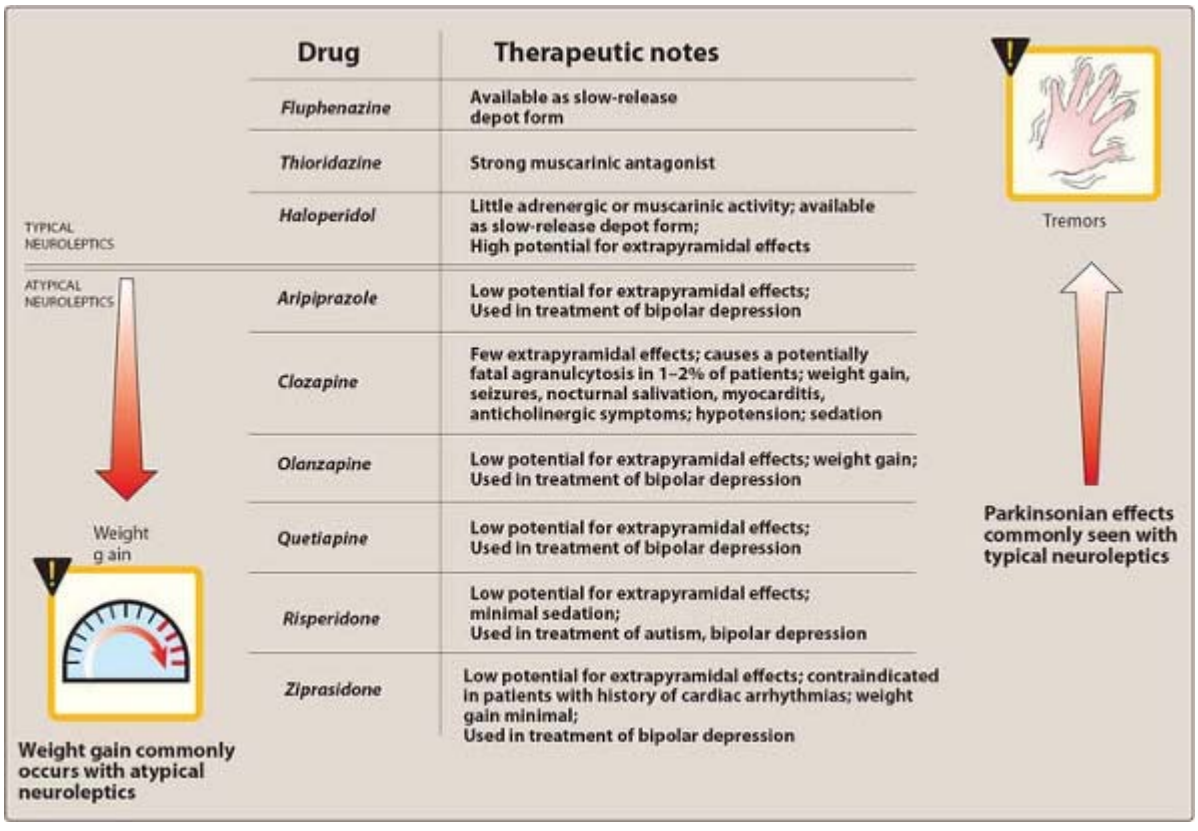

Figure 13.8 Summary of neuroleptic agents.

Study Questions

Choose the ONE best answer.

13.1 An adolescent male is newly diagnosed with schizophrenia. Which of the following neuroleptic agents may improve his apathy and blunted affect?

A. Chlorpromazine.

B. Fluphenazine.

C. Haloperidol.

D. Risperidone.

E. Thioridazine.

View Answer

13.2 Which one of the following neuroleptics has been shown to be a partial agonist at the D_2 receptor?

A. Aripiprazole.

B. Clozapine.

C. Haloperidol.

D. Risperidone.

E. Thioridazine.

View Answer

13.3 A 21-year-old male has recently begun pimozide therapy for Tourette's disorder. He is brought to the emergency department by his parents. They describe that he has been having â€œdifferent-appearing ticsâ€ than before, such as prolonged contraction of the facial muscles. While being examined, he experiences opisthotonus (spasm of the body where the head and heels are bent backward and the body is bowed forward. A type of extrapyramidal effect). Which of the following drugs would be beneficial in reducing these symptoms?

A. Benztropine.

B. Bromocriptine.

C. Lithium.

D. Prochlorperazine.

E. Risperidone.

View Answer

13.4 A 28-year-old woman with schizoid affective disorder and difficulty sleeping would be most benefited by which of the following drugs?

A. Aripiprazole.

B. Chlorpromazine.

C. Haloperidol.

D. Risperidone.

E. Ziprasidone.

View Answer

Editors: **Finkel, Richard; Clark, Michelle A.; Cubeddu, Luigi X.**
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Chapter 14

Opioids

I. Overview

Management of pain is one of clinical medicine's greatest challenges. Pain is defined as an unpleasant sensation that can be either acute or chronic and that is a consequence of complex neurochemical processes in the peripheral and central nervous system (CNS). It is subjective, and the physician must rely on the patient's perception and description of his or her pain. Alleviation of pain depends on its type. In many casesâ€"for example, with headaches or mild to moderate arthritic painâ€"nonsteroidal anti-inflammatory agents (NSAIDs, see Chapter 42) are effective. Neurogenic pain responds best to anticonvulsants (for example pregabalin, see p. 179), tricyclic antidepressants (for example, *amitriptyline,* see p. 145), or serotonin/norepinephrine reuptake inhibitors (for example, *duloxetine,* see p. 144) rather than NSAIDs or opioids. However, for severe or chronic malignant pain, opioids are usually the drugs of choice. Opioids are natural or synthetic compounds that produce *morphine*-like effects. [Note: The term â€œopiateâ€ is reserved for drugs, such as *morphine* and *codeine*, obtained from the juice of the opium poppy.] All drugs in this category act by binding to specific opioid receptors in the CNS to produce effects that mimic the action of endogenous peptide neurotransmitters (for example, endorphins, enkephalins, and dynorphins). Although the opioids have a broad range of effects, their primary use is to relieve intense pain and the anxiety that accompanies it, whether that pain is from surgery or a result of injury or disease, such as cancer. However, their widespread availability has led to abuse of those opioids with euphoric properties. [Note: Dependence is seldom a problem in patients being treated for severe pain with these agents, as in cancer or acute pain in terminally ill patients.] Antagonists that can reverse the actions of opioids are also very important clinically for use in cases of overdose. Figure 14.1 lists the opioid agonists and antagonists discussed in this chapter.

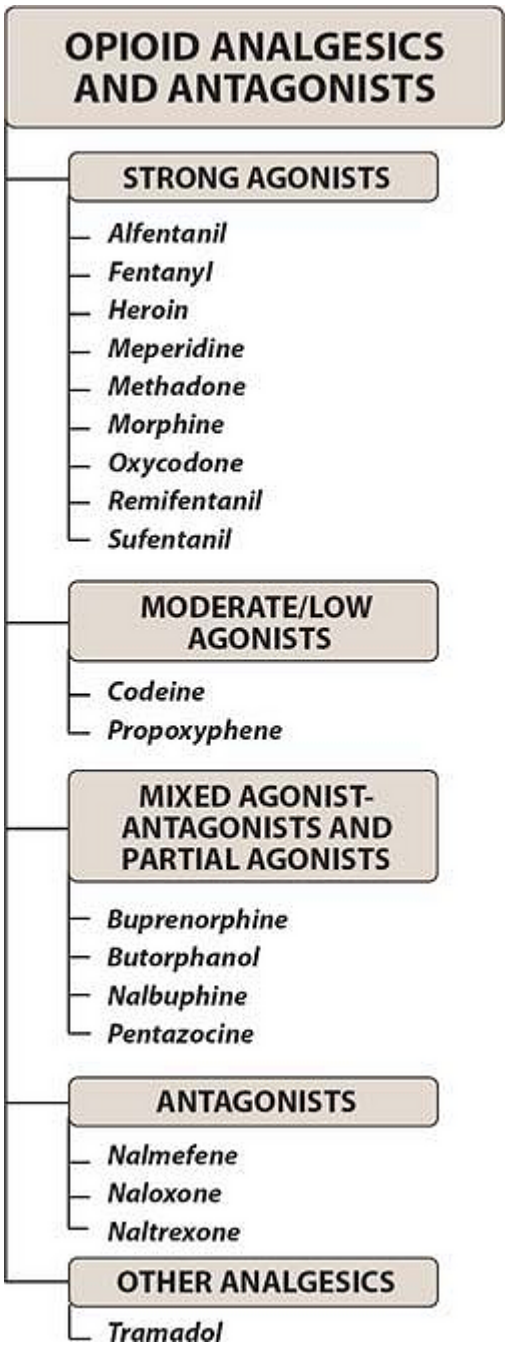

Figure 14.1 Summary of opioid analgesics and antagonists.

II. Opioid Receptors

Opioids interact stereospecifically with protein receptors on the membranes of certain cells in the CNS, on nerve terminals in the periphery, and on cells of the gastrointestinal tract and other anatomic regions. The major effects of the opioids are mediated by three major receptor families. These are designated by the Greek letters Âµ (mu), Îº (kappa), and Î´ (delta). Each receptor family exhibits a different specificity for the drug(s) it binds. The analgesic properties of the opioids are primarily mediated by the Âµ receptors; however, the Îº receptors in the dorsal horn also contribute. For example, *butorphanol* and *nalbuphine* primarily owe their analgesic effect

to K-receptor activation. The enkephalins interact more selectively with the Î´ receptors in the periphery. All three opioid receptors are members of the G proteinâ€“coupled receptor family and inhibit adenylyl cyclase.[1] They are also associated with ion channels, increasing postsynaptic K^+ efflux (hyperpolarization) or reducing presynaptic Ca^{2+} influx, thus impeding neuronal firing and transmitter release (Figure 14.2).

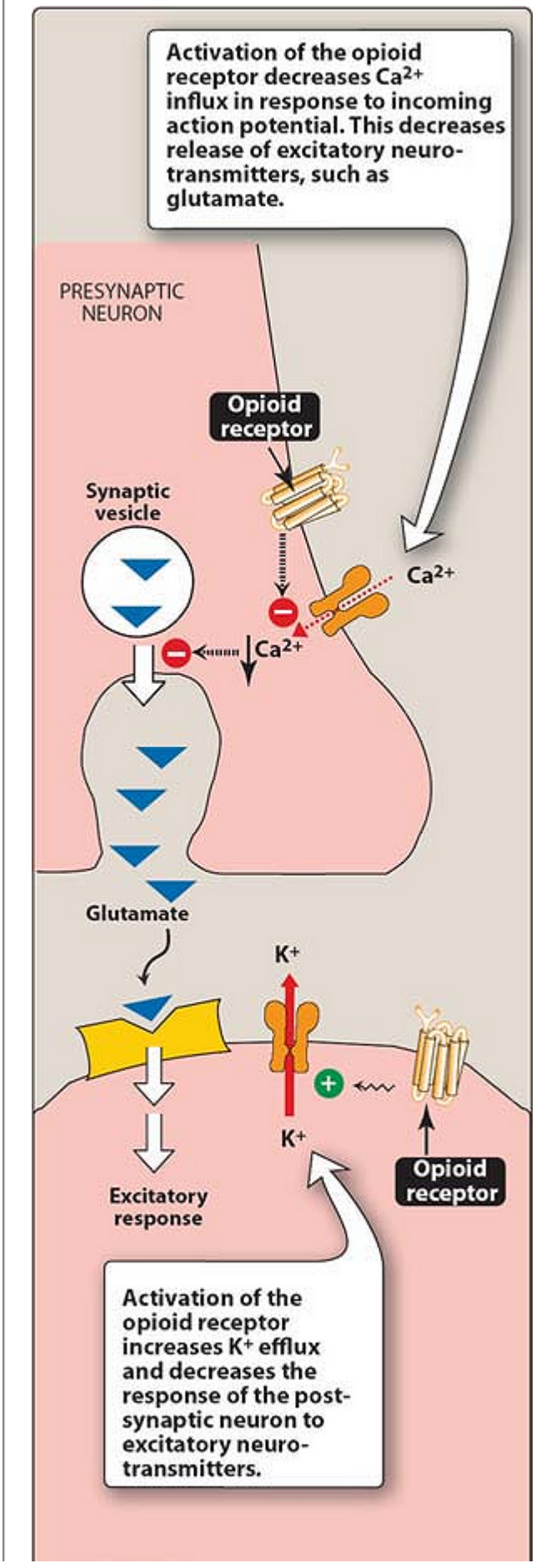
Activation of the opioid receptor decreases Ca^{2+} influx in response to incoming action potential. This decreases release of excitatory neuro-transmitters, such as glutamate.
PRESYNAPTIC NEURON
Opioid receptor
Synaptic vesicle
Ca^{2+}
Ca^{2+}
Glutamate
K^+
K^+
Opioid receptor
Excitatory response
Activation of the opioid receptor increases K^+ efflux and decreases the response of the post-synaptic neuron to excitatory neuro-transmitters.

Figure 14.2 Mechanism of action of Âμ-opioid receptor agonists in the spinal cord.

A. Distribution of receptors

High densities of opioid receptors known to be involved in integrating information about pain are present in five general areas of the CNS. They have also been identified on the peripheral sensory nerve fibers and their terminals and on immune cells. [Note: There is considerable overlap of receptor types in these various areas.]

1. **Brainstem:** Opioid receptors influence respiration, cough, nausea and vomiting, blood pressure, pupillary diameter, and control of stomach secretions.
2. **Medial thalamus:** This area mediates deep pain that is poorly localized and emotionally influenced.
3. **Spinal cord:** Receptors in the substantia gelatinosa are involved with the receipt and integration of incoming sensory information, leading to the attenuation of painful afferent stimuli.
4. **Hypothalamus:** Receptors here affect neuroendocrine secretion.
5. **Limbic system:** The greatest concentration of opiate receptors in the limbic system is located in the amygdala. These receptors probably do not exert analgesic action, but they may influence emotional behavior.
6. **Periphery:** Opioids also bind to peripheral sensory nerve fibers and their terminals. As in the CNS, they inhibit Ca^{2+}-dependent release of excitatory, proinflammatory substances (for example, substance P) from these nerve endings.
7. **Immune cells:** Opioid-binding sites have also been found on immune cells. The role of these receptors in nociception (response or sensitivity to painful stimuli) has not been determined.

III. Strong Agonists

Morphine [MOR-feen] is the major analgesic drug contained in crude opium and is the prototype strong agonist. *Codeine* is present in crude opium in lower concentrations and is inherently less potent. These drugs show a high affinity for Âμ receptors and varying affinities for Î´ and Îº receptors.

A. Morphine

1. **Mechanism of action:** Opioids exert their major effects by interacting with opioid receptors in the CNS and in other anatomic structures, such as the gastrointestinal tract and the urinary bladder. Opioids cause hyperpolarization of nerve

cells, inhibition of nerve firing, and presynaptic inhibition of transmitter release. *Morphine* acts at Îº receptors in Lamina I and II of the dorsal horn of the spinal cord, and it decreases the release of substance P, which modulates pain perception in the spinal cord. *Morphine* also appears to inhibit the release of many excitatory transmitters from nerve terminals carrying nociceptive (painful) stimuli.

2. **Actions:**

   a. **Analgesia:** *Morphine* causes analgesia (relief of pain without the loss of consciousness). Opioids relieve pain both by raising the pain threshold at the spinal cord level and, more importantly, by altering the brain's perception of pain. Patients treated with *morphine* are still aware of the presence of pain, but the sensation is not unpleasant. However, when given to an individual free of pain, its effects may be unpleasant and may cause nausea and vomiting. The maximum analgesic efficacy and the addiction potential for representative

agonists are shown in Figure 14.3.

b. **Euphoria:** *Morphine* produces a powerful sense of contentment and well-being. Euphoria may be caused by disinhibition of the ventral tegmentum.

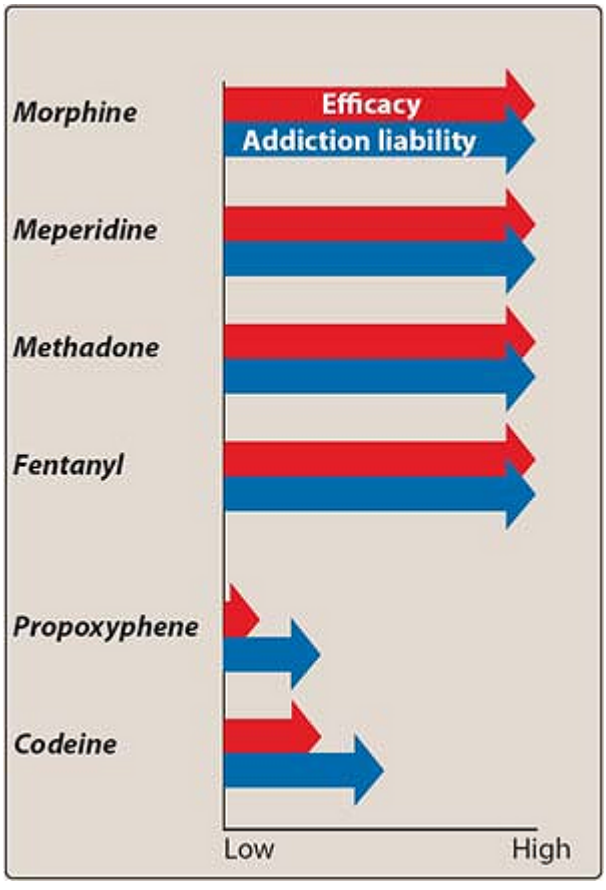

Figure 14.3 A comparison of the maximum efficacy and addiction/abuse liability of commonly used narcotic analgesics.

c. **Respiration:** *Morphine* causes respiratory depression by reduction of the sensitivity of respiratory center neurons to carbon dioxide. This occurs with ordinary doses of *morphine* and is accentuated as the dose increases until, ultimately, respiration ceases. Respiratory depression is the most common cause of death in acute opioid overdose.

d. **Depression of cough reflex:** Both *morphine* and *codeine* have antitussive properties. In general, cough suppression does not correlate closely with analgesic and respiratory depressant properties of opioid drugs. The receptors involved in the antitussive action appear to be different from those involved in analgesia.

e. **Miosis:** The pinpoint pupil, characteristic of *morphine* use, results from stimulation of Âμ and Îº receptors. *Morphine* excites the Edinger-Westphal nucleus of the oculomotor nerve, which causes enhanced parasympathetic stimulation to the eye (Figure 14.4). There is little tolerance to the effect, and all *morphine* abusers demonstrate pinpoint pupils. [Note: This is important diagnostically, because many other causes of coma and respiratory depression produce dilation of the pupil.]

f. **Emesis:** *Morphine* directly stimulates the chemoreceptor trigger zone in the area postrema that causes vomiting.

g. **Gastrointestinal tract:** *Morphine* relieves diarrhea and dysentery by decreasing the motility and increasing the tone of the intestinal circular smooth muscle. *Morphine* also increases the tone of the anal sphincter. Overall, *morphine* produces constipation, with little tolerance developing. It can also increase biliary tract pressure due to contraction of the gallbladder and constriction of the biliary sphincter.

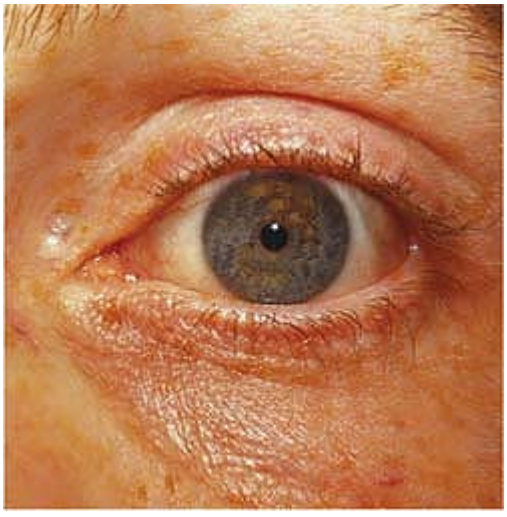

Figure 14.4 *Morphine* causes enhanced parasympathetic stimulation to the eye, resulting in pinpoint pupils.

h. **Cardiovascular:** *Morphine* has no major effects on the blood pressure or heart rate except at large doses, when hypotension and bradycardia may occur. Because of respiratory depression and carbon dioxide retention, cerebral vessels dilate and increase the cerebrospinal fluid (CSF) pressure. Therefore, *morphine* is usually contraindicated in individuals with severe brain injury.

i. **Histamine release:** *Morphine* releases histamine from mast cells, causing urticaria, sweating, and vasodilation. Because it can cause bronchoconstriction, asthmatics should not receive the drug.

j. **Hormonal actions:** *Morphine* inhibits release of gonadotropin-releasing hormone and corticotropin-releasing hormone, and it decreases the concentration of luteinizing hormone, follicle-stimulating hormone, adrenocorticotropic hormone, and Î²-endorphin. Testosterone and cortisol levels decrease. *Morphine* increases growth hormone release and enhances prolactin secretion. It increases antidiuretic hormone and, thus, leads to urinary retention. [Note: It also can inhibit the urinary bladder voiding reflex; thus, catheterization may be required.]

k. **Labor:** *Morphine* may prolong the second stage of labor by transiently decreasing the strength, duration, and frequency of uterine contractions.

3. **Therapeutic uses:**

a. **Analgesia:** Despite intensive research, few other drugs have been developed that are as effective as *morphine* in the relief of pain. Opioids induce sleep, and in clinical situations when pain is present and sleep is necessary, opiates may be used to supplement the sleep-inducing properties of benzodiazepines, such as *temazepam*. [Note: The sedative-hypnotic drugs are not usually analgesic, and they may have diminished sedative effect in the presence of pain.]

b. **Treatment of diarrhea:** *Morphine* decreases the motility and increases the tone of intestinal circular

smooth muscle. [Note: This can cause constipation.]

c. **Relief of cough:** *Morphine* suppresses the cough reflex; however, *codeine* or *dextromethorphan* are more widely used for this purpose. *Codeine* has greater antitussive action than *morphine*.

d. **Treatment of acute pulmonary edema:** Intravenous (IV) *morphine* dramatically relieves dyspnea caused by pulmonary edema associated with left ventricular failureâ€"possibly by its vasodilatory effect.

4. **Pharmacokinetics:**

a. **Administration:** Absorption of *morphine* from the gastrointestinal tract is slow and erratic. *Codeine*, by contrast, is well absorbed when given by mouth. Significant first-pass metabolism of *morphine* occurs in the liver; therefore, intramuscular, subcutaneous, or IV injections produce the most reliable responses. When used orally, *morphine* is commonly administered in an extended-release form to provide more consistent plasma levels. [Note: In

cases of chronic pain associated with neoplastic disease, it has become common practice to use either the extended-release tablets orally or pumps that allow the patient to control the pain through self-administration, as show in Figure 14.5.] Opiates have been taken for nonmedical purposes by inhaling powders or smoke from burning crude opium, which provide a rapid onset of drug action.

b. **Distribution:** *Morphine* rapidly enters all body tissues, including the fetuses of pregnant women, and should not be used for analgesia during labor. Infants born of addicted mothers show physical dependence on opiates and exhibit withdrawal symptoms if opioids are not administered. Only a small percentage of *morphine* crosses the blood-brain barrier, because *morphine* is the least lipophilic of the common opioids. This contrasts with the more fat-soluble opioids, such as *fentanyl, methadone*, and *heroin*, which readily penetrate into the brain.

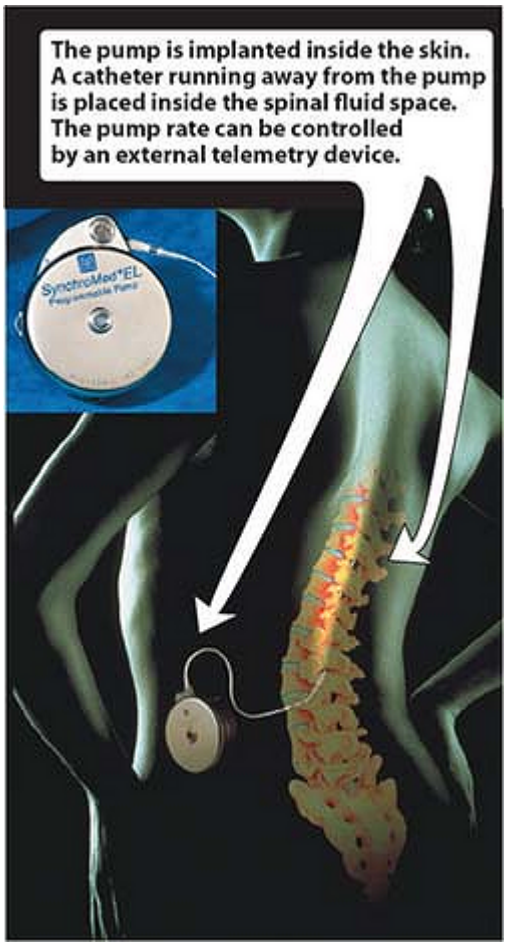

Figure 14.5 Implanted pump for delivery of morphine.

c. **Fate:** *Morphine* is conjugated in the liver to glucuronic acid. Morphine-6-glucuronide is a very potent analgesic, whereas the conjugate at position 3 is much less active. The conjugates are excreted primarily in the urine, with small quantities appearing in the bile. The duration of action of *morphine* is 4 to 6 hours when administered systemically to morphine-naÃ¯ve individuals but considerably longer when injected epidurally, because its low lipophilicity prevents redistribution from the epidural space. [Note: A patient's age can influence the response to *morphine*. Elderly patients are more sensitive to the analgesic effects of the drug, possibly due to decreased metabolism or other factors, such as decreased lean body mass, renal function, etc. They should be treated with lower doses. Neonates should not receive *morphine* because of their low conjugating capacity.]

5. **Adverse effects:** Severe respiratory depression occurs and can result in death from acute opioid poisoning. A serious effect of the drug is stoppage of respiratory exchange in patients with emphysema or cor pulmonale. [Note: If employed in such individuals, respiration must be carefully monitored.] Other effects include vomiting, dysphoria, and allergy-enhanced hypotensive effects (Figure 14.6). The elevation of intracranial pressure, particularly in head injury, can be serious. *Morphine* enhances cerebral and spinal ischemia. In benign prostatic hyperplasia, *morphine* may cause acute urinary retention. Patients with adrenal insufficiency or myxedema may experience extended and increased effects from the opioids. *Morphine* should be used with cautiously in patients with bronchial asthma or liver failure.

6. **Tolerance and physical dependence:** Repeated use produces tolerance to the respiratory depressant,

analgesic, euphoric, and sedative effects of *morphine*. However, tolerance usually does not develop to the pupil-constricting and constipating effects of the drug. Physical and psychological dependence readily occur with *morphine* and with some of the other agonists to be described (see Figure 14.3). Withdrawal produces a series of autonomic, motor, and psychological responses that incapacitate the individual and cause seriousâ€"almost unbearableâ€"symptoms. However, it is very rare that the

effects are so profound as to cause death. [Note: Detoxification of *heroin*- or *morphine*-dependent individuals is usually accomplished through the oral administration of *methadone, buprenorphine* (see below), or *clonidine*.]

7. **Drug interactions:** The depressant actions of *morphine* are enhanced by phenothiazines, monoamine oxidase inhibitors, and tricyclic antidepressants (Figure 14.7). Low doses of *amphetamine* inexplicably enhance analgesia, as does *hydroxyzine*.

B. Meperidine

Meperidine [me-PER-i-deen] is a synthetic opioid structurally unrelated to *morphine*. It is used for acute pain.

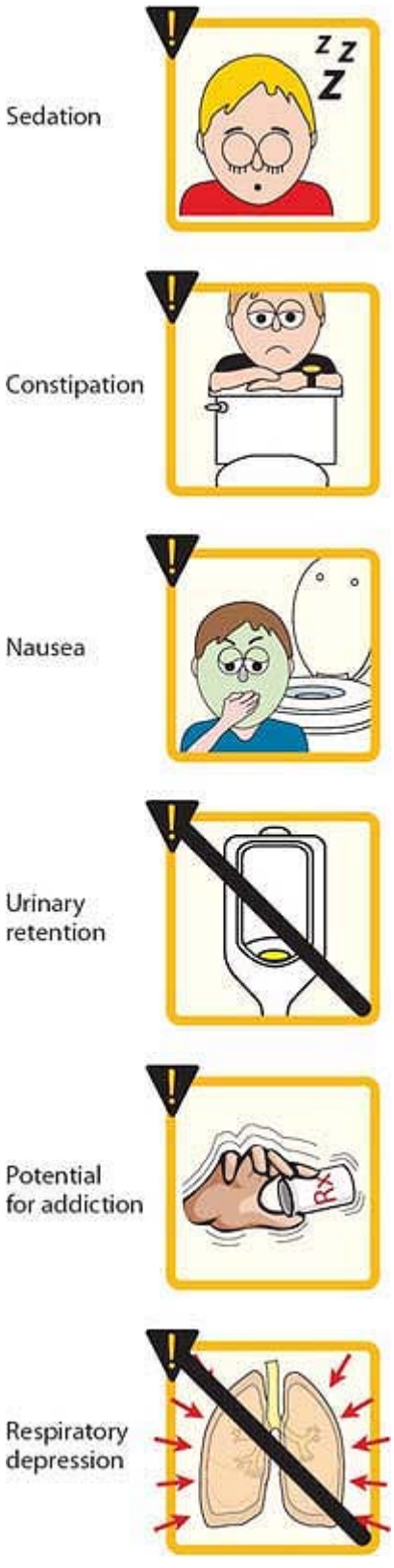

Figure 14.6 Adverse effects commonly observed in individuals treated with opioids.

1. **Mechanism of action:** *Meperidine* binds to opioid receptors, particularly Âμ receptors. However, it also binds

well to Îº receptors.

2. **Actions:** *Meperidine* causes a depression of respiration similar to that of *morphine*, but it has no significant cardiovascular action when given orally. On IV administration, *meperidine* produces a decrease in peripheral resistance and an increase in peripheral blood flow, and it may cause an increase in cardiac rate. As with *morphine, meperidine* dilates cerebral vessels, increases CSF pressure, and contracts smooth muscle (the latter to a lesser extent than does *morphine*). *Meperidine* does not cause pinpoint pupils but, rather, causes the pupils to dilate because of an *atropine*-like action.

3. **Therapeutic uses:** *Meperidine* provides analgesia for any type of severe pain. Unlike *morphine, meperidine* is not clinically useful in the treatment of diarrhea or cough. *Meperidine* produces less of an increase in urinary retention than does *morphine*. It has significantly less effects on uterine smooth muscle than morphine and is the opioid commonly employed in obstetrics (see below).

4. **Pharmacokinetics:** *Meperidine* is well absorbed from the gastrointestinal tract, and is useful when an orally administered, potent analgesic is needed. However, *meperidine* is most often administered parenterally. The drug has a duration of action of 2 to 4 hours, which is shorter than that of *morphine* (Figure 14.8). *Meperidine* is N-demethylated to normeperidine in the liver and is excreted in the urine. [Note: Because of its shorter action and different route of metabolism, *meperidine* is preferred over *morphine* for analgesia during labor.]

5. **Adverse effects:** Large or repetitive doses of *meperidine* can cause anxiety, tremors, muscle twitches, and rarely, convulsions due to the accumulation of a toxic metabolite, normeperidine. The drug differs from opioids in that when given in large doses, it dilates the pupil and causes hyperactive reflexes. Severe hypotension can occur when the drug is administered postoperatively. Due to its antimuscarinic action, patients may experience dry mouth and blurred vision. When used with major neuroleptics, depression is greatly enhanced. Administration to patients taking monoamine oxidase inhibitors can provoke severe reactions, such as convulsions and hyperthermia. *Meperidine* can cause dependence, and can substitute for *morphine* or *heroin* in opiate-dependent persons. Partial cross-tolerance with the other opioids occurs.

C. Methadone

Methadone [METH-a-done] is a synthetic, orally effective opioid that is approximately equal in potency to *morphine* but induces less euphoria and has a somewhat longer duration of action.

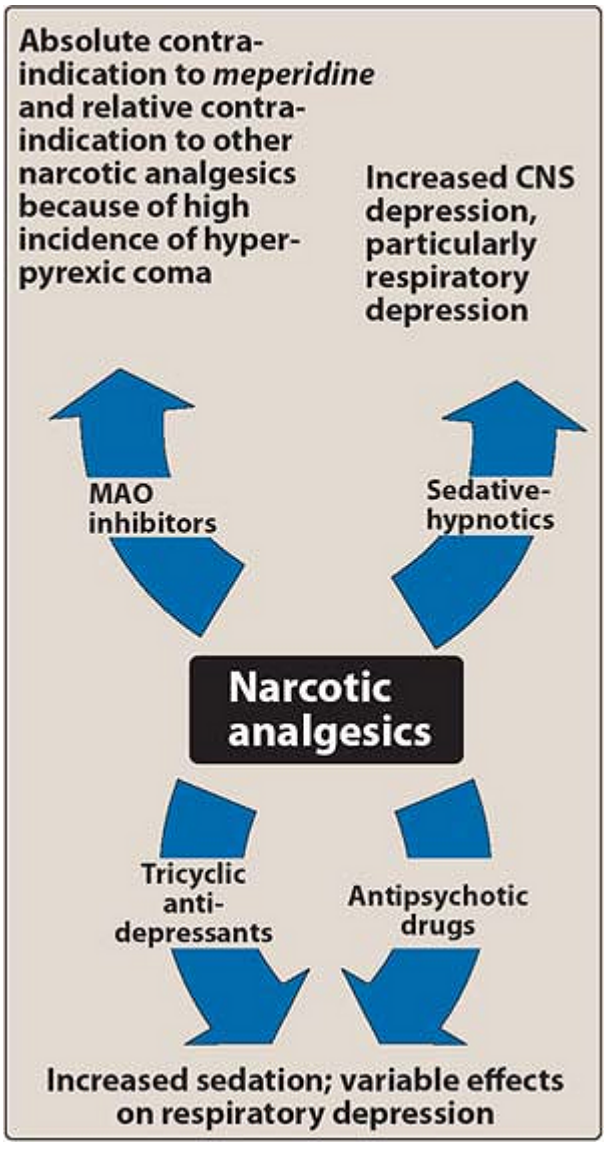

Figure 14.7 Drugs interacting with narcotic analgesics. CNS = central nervous system; MAO = monoamine oxidase.

1. **Mechanism of action:** The actions of *methadone* are mediated by the Âμ receptors.
2. **Actions:** The analgesic activity of *methadone* is equivalent to that of *morphine* (see Figure 14.3). *Methadone* is well-absorbed when administered orally, in contrast to *morphine*, which is only partially absorbed from the gastrointestinal tract. The miotic and respiratory-depressant actions of *methadone* have average half-lives of 24 hours. Like *morphine, methadone* increases biliary pressure and is also constipating.
3. **Therapeutic uses:** *Methadone* is used as an analgesic as well as in the controlled withdrawal of dependent abusers from *heroin* and *morphine*. Orally administered, *methadone* is substituted for the injected opioid. The patient is then slowly weaned from *methadone*. *Methadone* causes a withdrawal syndrome that is milder but more protracted (days to weeks) than that of other opioids.
4. **Pharmacokinetics:** *Methadone* is readily absorbed following oral administration. It accumulates in tissues, where it remains bound to protein, from which it is slowly released. The drug is biotransformed in the liver and

is excreted in the urine, mainly as inactive metabolites.

5. **Adverse effects:** *Methadone* can produce physical dependence like that of *morphine*.

D. Fentanyl

Fentanyl [FEN-ta-nil], which is chemically related to *meperidine*, has 100-fold the analgesic potency of *morphine* and is used in anesthesia. The drug is highly lipophilic and has a rapid onset and short duration of action (15 to 30 minutes). It is usually injected IV, epidurally, or intrathecally. Epidural *fentanyl* is used for analgesia postoperatively and during labor. An oral transmucosal preparation and a transdermal patch are also available. The transmucosal preparation is used in the treatment of cancer patients with breakthrough pain who are tolerant to opioids. The transdermal patch must be used with caution, because death resulting from hypoventilation has been known to occur. [Note: The transdermal patch creates a reservoir of the drug in the skin. Hence, the onset is delayed 12 hours, and the offset is prolonged.] *Fentanyl* is often used during cardiac surgery because of its negligible effects on myocardial contractility. Muscular rigidity, primarily of the abdomen and chest wall, is often observed with *fentanyl* use in anesthesia. *Fentanyl* is metabolized to inactive metabolites by the cytochrome P4503A4 system, and drugs that inhibit this isozyme can potentiate the effect of *fentanyl*. Most of the drug and metabolites are eliminated through the urine. Adverse effects of *fentanyl* are similar to those of other Âμ-receptor agonists. Because of life-threatening hypoventilation, the *fentanyl* patch is contraindicated in the management of acute and postoperative pain or pain that can be ameliorated with other analgesics. Unlike *meperidine*, it causes pupillary constriction.

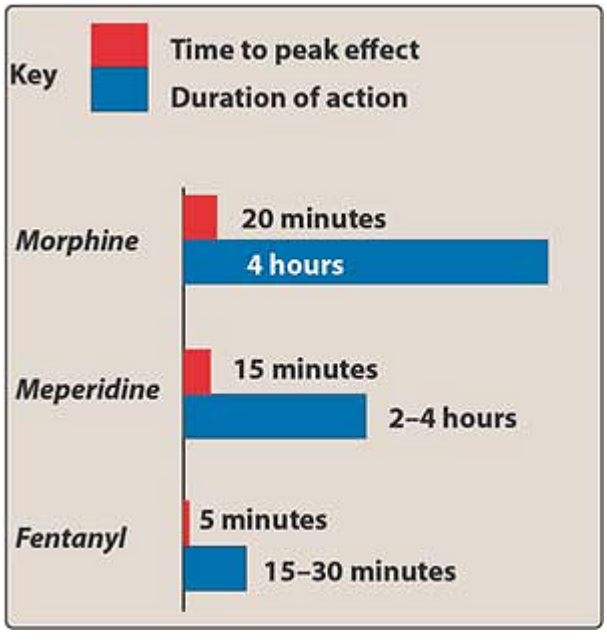

Figure 14.8 Time to peak effect and duration of action of several opioids administered intravenously.

E. Sufentanil, alfentanil, and remifentanil

Three drugs related to *fentanyl*â€"*sufentanil* [soo-FEN-ta-nil], *alfentanil* [al-FEN-ta-nil], and *remifentanil* [rem-i FEN-ta-nil]â€"differ in their potency and metabolic disposition. *Sufentanil* is even more potent than *fentanyl*, whereas the other two are less potent but much shorter-acting.

F. Heroin

Heroin [HAIR-o-in] does not occur naturally. It is produced by diacetylation of *morphine*, which leads to a three-fold increase in its potency. Its greater lipid solubility allows it to cross the blood-brain barrier more rapidly than *morphine*, causing a more exaggerated euphoria when the drug is taken by injection. *Heroin* is converted to *morphine* in the body, but its effects last about half as long. It has no accepted medical use in the United States.

G. Oxycodone

Oxycodone [ok-see-KOE-done] is a semisynthetic derivative of *morphine*. It is orally active and is sometimes formulated with *aspirin* or *acetaminophen*. It is used to treat moderate to severe pain and has many properties in common with *morphine*. *Oxycodone* is metabolized to products with lower analgesic activity. Excretion is via the kidney. Abuse of the sustained-release preparation (ingestion of crushed tablets) has been implicated in many deaths. It is important that the higher-dosage forms of the latter preparation be used only by patients who are tolerant to opioids.

IV. Moderate Agonists

A. Codeine

The analgesic actions of *codeine* [KOE-deen] are due to its conversion to morphine, whereas the drug's antitussive effects are due to *codeine* itself. Thus, *codeine* is a much less potent analgesic than *morphine*, but it has a higher oral effectiveness. *Codeine* shows good antitussive activity at doses that do not cause analgesia. At commonly used doses, the drug has a lower potential for abuse than *morphine*, and it rarely produces dependence. *Codeine* produces less euphoria than *morphine*. *Codeine* is often used in combination with *aspirin* or *acetaminophen*. [Note: In most nonprescription cough preparations, *codeine* has been replaced by drugs such as *dextromethorphan*â€”a synthetic cough depressant that has relatively no analgesic action and a relatively low potential for abuse in usual antitussive doses.] Figure 14.9 shows some of the actions of *codeine*.

Figure 14.9 Some actions of *codeine*.

B. Propoxyphene

Propoxyphene [proe-POX-i-feen] is a derivative of *methadone*. The dextro isomer is used as an analgesic to relieve mild to moderate pain. The levo isomer is not analgesic, but it has antitussive action. *Propoxyphene* is a weaker analgesic than *codeine*, requiring approximately twice the dose to achieve an effect equivalent to that of *codeine*. *Propoxyphene* is often used in combination with *acetaminophen* for an analgesia greater than that obtained with either drug alone. It is well absorbed orally, with peak plasma levels occurring in 1 hour, and it is metabolized in the liver. *Propoxyphene* can produce nausea, anorexia, and constipation. In toxic doses, it can cause respiratory depression, convulsions, hallucinations, and confusion. When toxic doses are taken, a very serious problem

can arise in some individuals, with resultant cardiotoxicity and pulmonary edema. [Note: When used with alcohol and sedatives, severe CNS depression is produced, and death by respiratory depression and cardiotoxicity can

result. Respiratory depression and sedation can be antagonized by *naloxone*, but the cardiotoxicity cannot.]

V. Mixed Agonist-Antagonists and Partial Agonists

Drugs that stimulate one receptor but block another are termed mixed agonist-antagonists. The effects of these drugs depend on previous exposure to opioids. In individuals who have not recently received opioids (naÃ¯ve patients), mixed agonist-antagonists show agonist activity and are used to relieve pain. In the patient with opioid dependence, the agonist-antagonist drugs may show primarily blocking effectsâ€”that is, produce withdrawal symptoms.

A. Pentazocine

Pentazocine [pen-TAZ-oh-seen] acts as an agonist on Îº receptors and is a weak antagonist at Âµ and Î´ receptors. *Pentazocine* promotes analgesia by activating receptors in the spinal cord, and it is used to relieve moderate pain. It may be administered either orally or parenterally. *Pentazocine* produces less euphoria compared to *morphine*. In higher doses, the drug causes respiratory depression and decreases the activity of the gastrointestinal tract. High doses increase blood pressure and can cause hallucinations, nightmares, dysphoria, tachycardia, and dizziness. The latter properties have led to its decreased use. In angina, *pentazocine* increases the mean aortic pressure and pulmonary arterial pressure and, thus, increases the work of the heart. The drug decreases renal plasma flow. Despite its antagonist action, *pentazocine* does not antagonize the respiratory depression of *morphine*, but it can precipitate a withdrawal syndrome in a *morphine* abuser. Tolerance and dependence develop on repeated use.

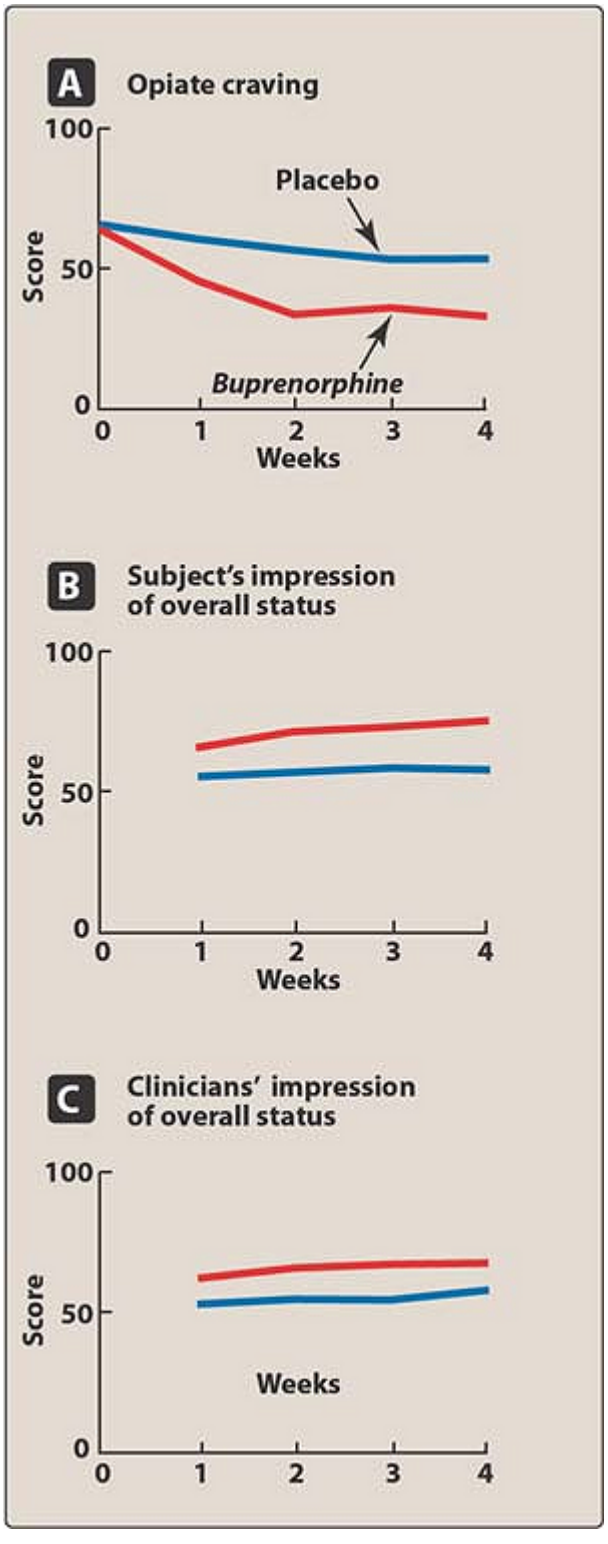

Figure 14.10 Scores for opiate craving and overall status in opioid-addicted patients assigned to office-based treatment with *buprenorphine* or placebo.

B. Buprenorphine

Buprenorphine [byoo-pre-NOR-feen] is classified as a partial agonist, acting at the Âμ receptor. It acts like *morphine* in naÃ¯ve patients, but it can also precipitate withdrawal in *morphine* users. A major use is in opiate detoxification, because it has a less severe and shorter duration of withdrawal symptoms compared to *methadone* (Figure 14.10). It causes little sedation, respiratory depression, and hypotension, even at high doses. In contrast to *methadone,* which is available only at specialized clinics, *buprenorphine* is approved for office-based detoxification or maintenance. *Buprenorphine* is administered sublingually or parenterally and has a long duration of action because of its tight binding to the Âμ receptor. The tablets are indicated for the treatment of opioid dependence. The injectable form is indicated for the relief of moderate to severe pain. It is metabolized by the liver and excreted in the bile and urine. Adverse effects include respiratory depression that cannot easily be reversed by *naloxone*, decreased (or, rarely, increased) blood pressure, nausea, and dizziness.

C. Nalbuphine and butorphanol

Nalbuphine [NAL byoo feen] and *butorphanol* [byoo-TOR-fa-nole], like *pentazocine*, play a limited role in the treatment of chronic pain. Neither is available for oral use. Their propensity to cause psychotomimetic

(actions mimics the symptoms of psychosis) effects is less than that of *pentazocine*. *Nalbuphine* does not affect the heart or increase blood pressure, in contrast to *pentazocine* and *butorphanol*. A benefit of all three medications is that they exhibit a ceiling effect for respiratory depression.

VI. Other Analgesics

A. Tramadol

Tramadol (TRA-ma-dole) is a centrally acting analgesic that binds to the Âμ-opioid receptor. In addition, it weakly inhibits reuptake of norepinephrine and serotonin. It is used to manage moderate to moderately severe pain. Its respiratory-depressant activity is less than that of *morphine*. *Naloxone* (see below) can only partially reverse the analgesia produced by *tramadol* or its active metabolite. The drug undergoes extensive metabolism, and one metabolite is active. Concurrent use with *carbamazepine* results in increased metabolism, presumably by induction of the cytochrome P450 2D6 system. [Note: *Quinidine*, which inhibits this isozyme, increases levels of *tramadol* when taken concurrently.] Anaphylactoid reactions have been reported. Of concern are the seizures that can occur, especially in patients taking selective serotonin reuptake inhibitors, tricyclic antidepressants, or in overdose. *Tramadol* should also be avoided in patients taking monoamine oxidase inhibitors.

VII. Antagonists

The opioid antagonists bind with high affinity to opioid receptors but fail to activate the receptor-mediated response. Administration of opioid antagonists produces no profound effects in normal individuals. However, in patients dependent on opioids, antagonists rapidly reverse the effect of agonists, such as *heroin*, and precipitate the symptoms of opiate withdrawal.

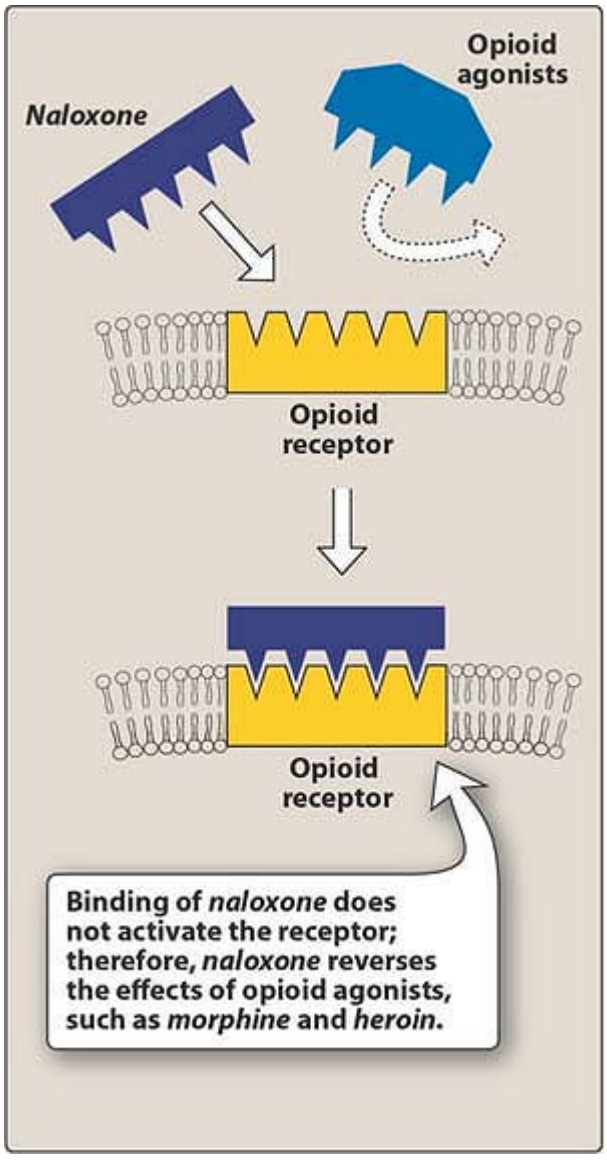

Figure 14.11 Competition of *naloxone* with opioid agonists.

A. Naloxone

Naloxone [nal-OX-own] is used to reverse the coma and respiratory depression of opioid overdose. It rapidly displaces all receptor-bound opioid molecules and, therefore, is able to reverse the effect of a *heroin* overdose (Figure 14.11). Within 30 seconds of IV injection of *naloxone*, the respiratory depression and coma characteristic of high doses of *heroin* are reversed, causing the patient to be revived and alert. *Naloxone* has a half-life of 60 to 100 minutes. [Note: Because of its relatively short duration of action, a depressed patient who has been treated and recovered may lapse back into respiratory depression.] *Naloxone* is a competitive antagonist at Âµ, Îº, and Î´, receptors, with a 10-fold higher affinity for Âµ than for Îº receptors. This may explain why *naloxone* readily reverses respiratory depression with only minimal reversal of the analgesia that results from agonist stimulation of Îº receptors in the spinal cord. *Naloxone* produces no pharmacologic effects in normal individuals, but it precipitates withdrawal symptoms in opioid abusers. Figure 14.12 summarizes some of the signs and symptoms of opiate withdrawal.

B. Naltrexone

Naltrexone [nal-TREX-own] has actions similar to those of *naloxone*. It has a longer duration of action than *naloxone*, and a single oral dose of *naltrexone* blocks the effect of injected *heroin* for up to 48 hours. *Naltrexone* in combination with *clonidine*â€"and, sometimes, with *buprenorphine*â€"is

employed for rapid opioid detoxification. It may also be beneficial in treating chronic alcoholism by an unknown mechanism; however, benzodiazepines and *clonidine* are preferred. *Naltrexone* is hepatotoxic.

C. Nalmefene

Nalmefene [NAL-meh-freen] is a parenteral opioid antagonist with actions similar to that of *naloxone* and *naltrexone*. It can be administered IV, intramuscularly, or subcutaneously. Its half-life of 8 to10 hours is significantly longer than that of *naloxone* and several opioid agonists.

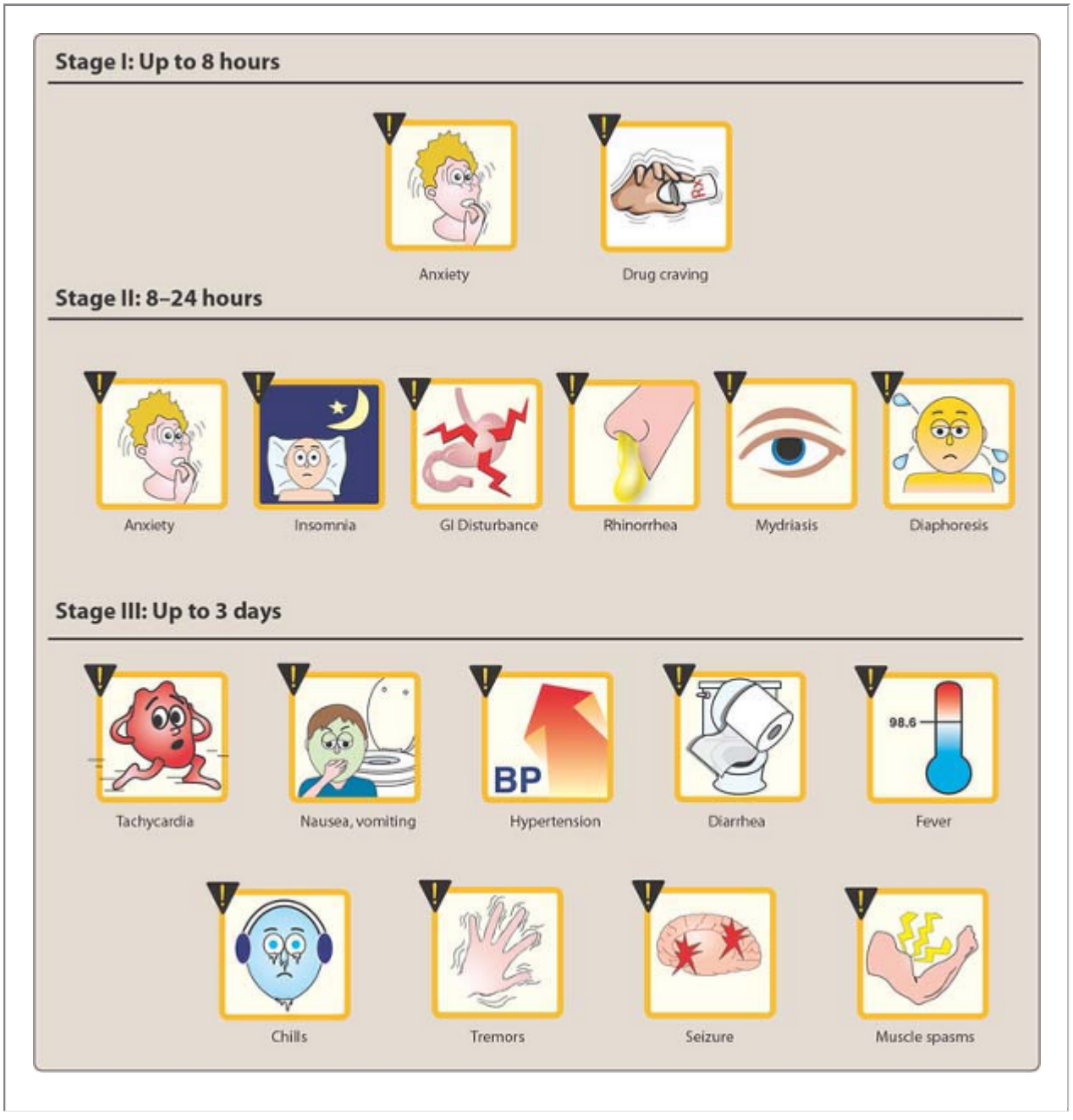

Figure 14.12 Opiate withdrawal syndrome.

Study Questions

Choose the ONE best answer.

14.1 A young man is brought into the emergency room. He is unconscious, and he has pupillary constriction and depressed respiration. You note needle marks on his legs. You administer naltrexone, and he awakens. This agent was effective because:

A. The patient was suffering from an overdose of a benzodiazepine.

B. Naltrexone antagonizes opiates at the receptor site.

C. Naltrexone is a stimulant of the CNS.

D. Naltrexone binds to the opioid and inactivates it.

E. The was was suffering from an overdose of meperidine.

View Answer

14.2 A heroin addict has entered a rehabilitation program that requires that she take methadone. Methadone is effective in this situation because it:

A. Is an antagonist at the morphine receptors.

B. Has less potent analgesic activity than heroin.

C. Is longer acting than heroin; hence, the withdrawal is milder than with the latter drug.

D. Does not cause constipation.

E. Is nonaddictive.

View Answer

14.3 Which of the following statements about morphine is correct?

A. It is used therapeutically to relieve pain caused by severe head injury.

B. Its withdrawal symptoms can be relieved by naloxone.

C. It causes diarrhea.

D. It is most effective by oral administration.

E. It rapidly enters all body tissues, including the fetus.

View Answer

14.4 The pain of a patient with bone cancer has been managed with a morphine pump. However, he has become tolerant to morphine. Which of the following might be indicated to ameliorate his pain?

A. Meperidine.

B. Codeine.

C. Fentanyl.

D. Methadone.

E. Buprenorphine.

View Answer

Editors: **Finkel, Richard; Clark, Michelle A.; Cubeddu, Luigi X.**
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Chapter 15

Epilepsy

I. Overview

Epilepsy affects approximately 3 percent of individuals by the time they are 80 years old. About 10 percent of the population will have at least one seizure in their lifetime. Globally epilepsy is the third most common neurologic disorder after cerebrovascular and Alzheimer's disease. Epilepsy is not a single entity but, instead, an assortment of different seizure types and syndromes originating from several mechanisms that have in common the sudden, excessive, and synchronous discharge of cerebral neurons. This abnormal electrical activity may result in a variety of events, including loss of consciousness, abnormal movements, atypical or odd behavior, or distorted perceptions that are of limited duration but recur if untreated. The site of origin of the abnormal neuronal firing determines the symptoms that are produced. For example, if the motor cortex is involved, the patient may experience abnormal movements or a generalized convulsion. Seizures originating in the parietal or occipital lobe may include visual, auditory, or olfactory hallucinations. Drug or vagal nerve stimulator therapy is the most widely effective mode for the treatment of patients with epilepsy. It is expected that seizures can be controlled completely in approximately 70 to 80 percent of patients with one medication. It is estimated that approximately 10 to 15 percent of patients will require more than one drug and perhaps 10 percent may not achieve complete seizure control. A summary of antiseizure drugs is shown in Figure 15.1.

Figure 15.1 Summary of agents used in the treatment of epilepsy.

II. Idiopathic and Symptomatic Seizures

In most cases, epilepsy has no identifiable cause. Focal areas that are functionally abnormal may be triggered into activity by changes in any of a variety of environmental factors, including alteration in blood gases, pH, electrolytes, blood glucose level, sleep deprivation, alcohol intake, and stress. The neuronal discharge in epilepsy results from the firing of a small population of neurons in some specific area of the brain that is referred to as the primary focus. Anatomically, this focal area may appear to be normal. However, advances in technology have improved ability to detect abnormalities, and in some patients, neuroimaging techniques, such as magnetic resonance imaging (MRI), positron-emission tomography (PET) scans and single-photon-emission coherence tomography (SPECT) can identify areas of concern (Figure 15.2). Epilepsy can be labeled idiopathic or symptomatic depending if the etiology is unknown, or is secondary to an identifiable condition. There are also multiple specific epilepsy syndromes that have been classified and include symptoms other than seizures.

A. Idiopathic epilepsy

When no specific anatomic cause for the seizure, such as trauma or neoplasm, is evident, a patient may be diagnosed with idiopathic or cryptogenic (primary) epilepsy. These seizures may result from an inherited abnormality in the central nervous system (CNS). Patients are treated chronically with antiseizure drugs or vagal nerve stimulation. Most cases of epilepsy are idiopathic.

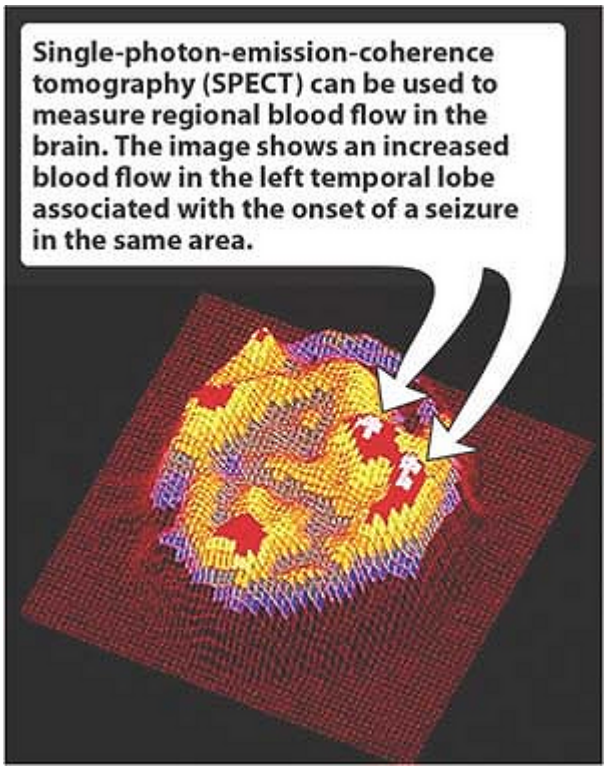

Figure 15.2 Region of the brain in an epileptic individual showing increased blood flow during a seizure.

B. Symptomatic epilepsy

A number of causes, such as illicit drug use, tumors, head injury, hypoglycemia, meningeal infection, or rapid withdrawal of alcohol from an alcoholic, can precipitate seizures. When two or more seizures occur, then the patient may be diagnosed with symptomatic (secondary) epilepsy. Chronic treatment with antiseizure medications, vagal nerve stimulation and surgery are all appropriate treatments and may be used alone or in combination. In some cases when the cause of a single seizure can be determined and corrected, therapy may not necessary. For example, a seizure that is caused by transient hypotension or is due to a drug reaction does not require chronic prophylactic therapy. In other situations, antiseizure drugs may be given until the primary cause of the seizures can be corrected.

III. Classification of Seizures

It is important to correctly classify seizures to determine appropriate treatment. Seizures have been categorized by site of origin, etiology, electrophysiologic correlation, and clinical presentation. The International League Against Epilepsy developed a nomenclature for describing seizures, and it is considered to be the standard way to document seizures and epilepsy syndromes (Figure 15.3). Seizures have been classified into two broad groups: partial (or focal), and generalized. A diagnosis may classify the seizure as partial or primary generalized epilepsy depending on the onset.

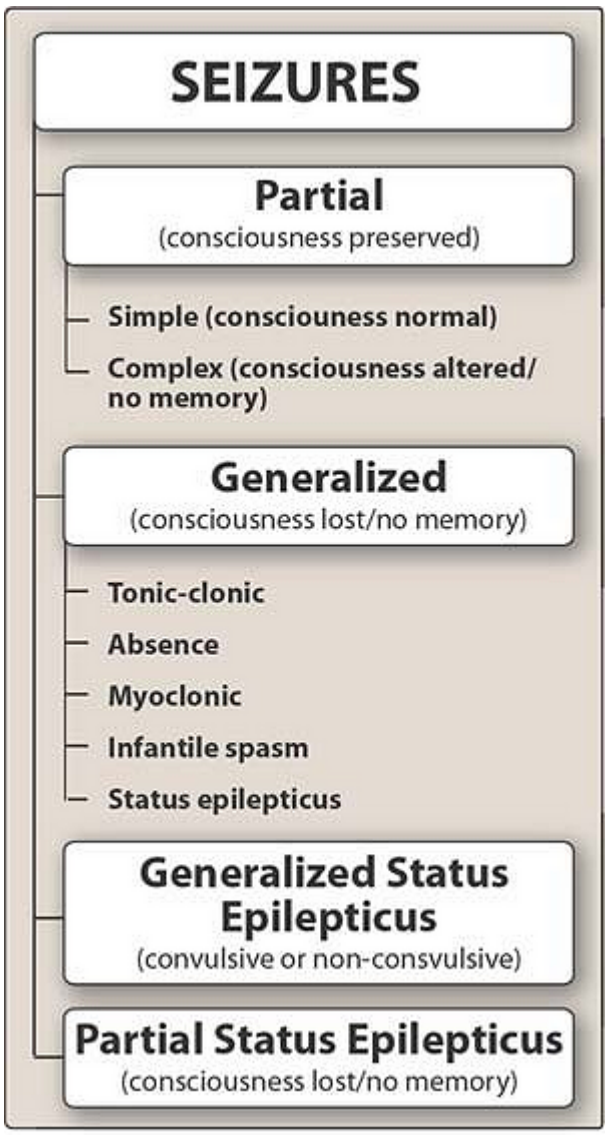

Figure 15.3 Classification of epilepsy.

A. Partial

Partial seizures involve only a portion of the brain, typically part of one lobe of one hemisphere. The symptoms of each seizure type depend on the site of neuronal discharge and on the extent to which the electrical activity spreads to other neurons in the brain. Consciousness is usually preserved. Partial seizures may progress, becoming generalized tonic-clonic seizures.

1. **Simple partial:** These seizures are caused by a group of hyperactive neurons exhibiting abnormal electrical activity, which are confined to a single locus in the brain. The electrical discharge does not spread, and the patient does not lose consciousness. The patient often exhibits abnormal activity of a single limb or muscle group that is controlled by the region of the brain experiencing the disturbance. The patient may also show sensory distortions. This activity may spread. Simple partial seizures may occur at any age.
2. **Complex partial:** These seizures exhibit complex sensory hallucinations, mental distortion, and loss of

consciousness. Motor dysfunction may involve chewing movements, diarrhea, and/or urination. Consciousness is altered. Simple partial seizure activity may spread and become complex and then spread to a secondarily generalized convulsion. Partial seizures may occur at any age.

P.173

B. Generalized

Generalized seizures may begin locally, producing abnormal electrical discharges throughout both hemispheres of the brain. Primary generalized seizures may be convulsive or nonconvulsive, and the patient usually has an immediate loss of consciousness

1. **Tonic-clonic:** Seizures result in loss of consciousness, followed by tonic (continuous contraction) and clonic (rapid contraction and relaxation) phases. The seizure may be followed by a period of confusion and exhaustion due to the depletion of glucose and energy stores.
2. **Absence:** These seizures involve a brief, abrupt, and self-limiting loss of consciousness. The onset generally occurs in patients at 3 to 5 years of age and lasts until puberty or beyond. The patient stares and exhibits rapid eye-blinking, which lasts for 3 to 5 seconds. This seizure has a very distinct three-per-second spike and wave discharge seen on electroencephalogram.

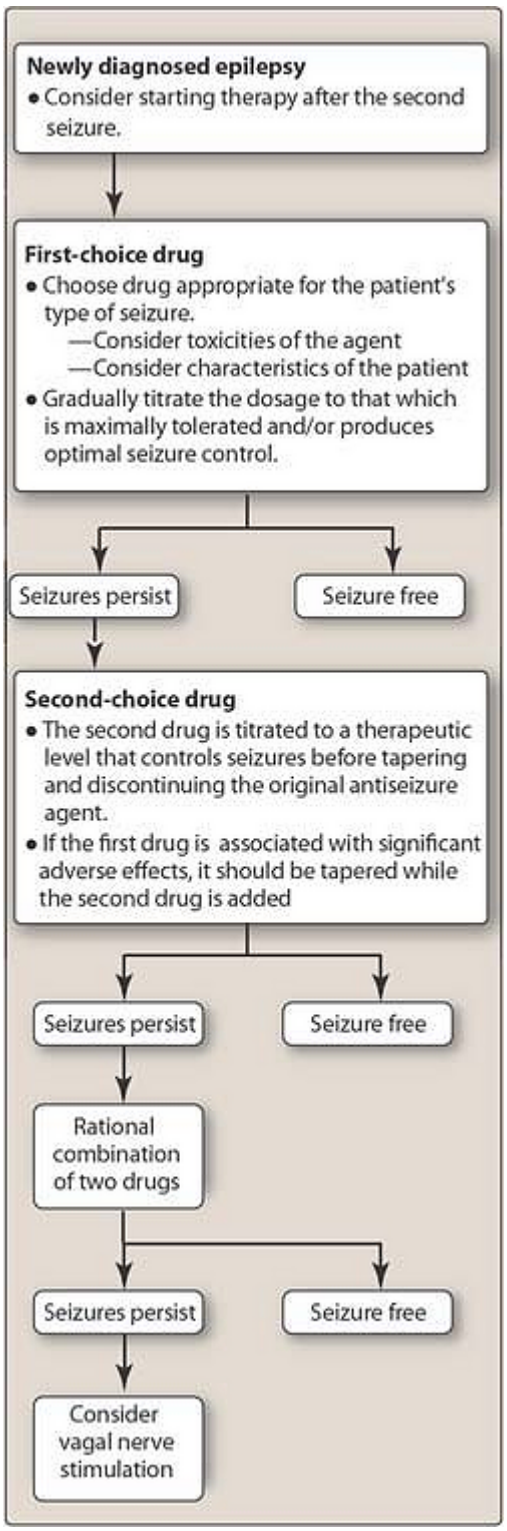

Figure 15.4 Therapeutic strategies for managing newly diagnosed epilepsy.

3. **Myoclonic:** These seizures consist of short episodes of muscle contractions that may reoccur for several minutes. They generally occur after wakening and exhibit as brief jerks of the limbs. Myoclonic seizures occur at any age but usually begin around puberty or early adulthood.

4. **Febrile seizures:** Young children may develop seizures with illness accompanied by high fever. This may occur in siblings. The febrile seizures consist of generalized tonic-clonic convulsions of short duration and do not necessarily lead to a diagnosis of epilepsy.

5. **Status epilepticus:** In status epilepticus, two or more seizures recur without recovery of full consciousness between them. These may be partial or primary generalized, convulsive or nonconvulsive. Status epilepticus is life-threatening and requires emergency treatment.

C. Mechanism of action of antiepileptic drugs

Drugs that are effective in seizure reduction accomplish this by a variety of mechanisms, including blockade of voltage-gated channels (Na^+ or Ca^{2+}), enhancement of inhibitory GABAergic impulses, or interference with excitatory glutamate transmission. Some antiepileptic drugs appear to have multiple targets within the CNS, whereas the mechanism of action for some agents is poorly defined. The antiepilepsy drugs suppress seizures but do not â€œcureâ€ or â€œpreventâ€ epilepsy.

IV. Drug Choice

Choice of drug treatment is based on the classification of the seizures being treated, patient specific variables (for example, age, comorbid medical conditions, lifestyle, and other preferences), and characteristics of the drug, including cost and interactions with other medications. For example, partial onset tonic-clonic seizures are treated differently than primary generalized seizures. Several drugs may be equally effective, and the toxicities of the agent and characteristics of the patient are major considerations in drug selection. In newly diagnosed patients, monotherapy is instituted with a single agent until seizures are controlled or toxicity occurs (Figure 15.4). Compared to those receiving combination therapy, patients receiving

monotherapy exhibit better adherence and fewer side effects. If seizures are not controlled with the first drug, monotherapy with an alternate antiepileptic drug(s), or vagal nerve stimulation should be considered (see Figure 15.5). An awareness of the antiepileptic drugs available, including their mechanisms of action, pharmacokinetics, potential for drug-drug interactions, and adverse effects, is essential for successful therapy.

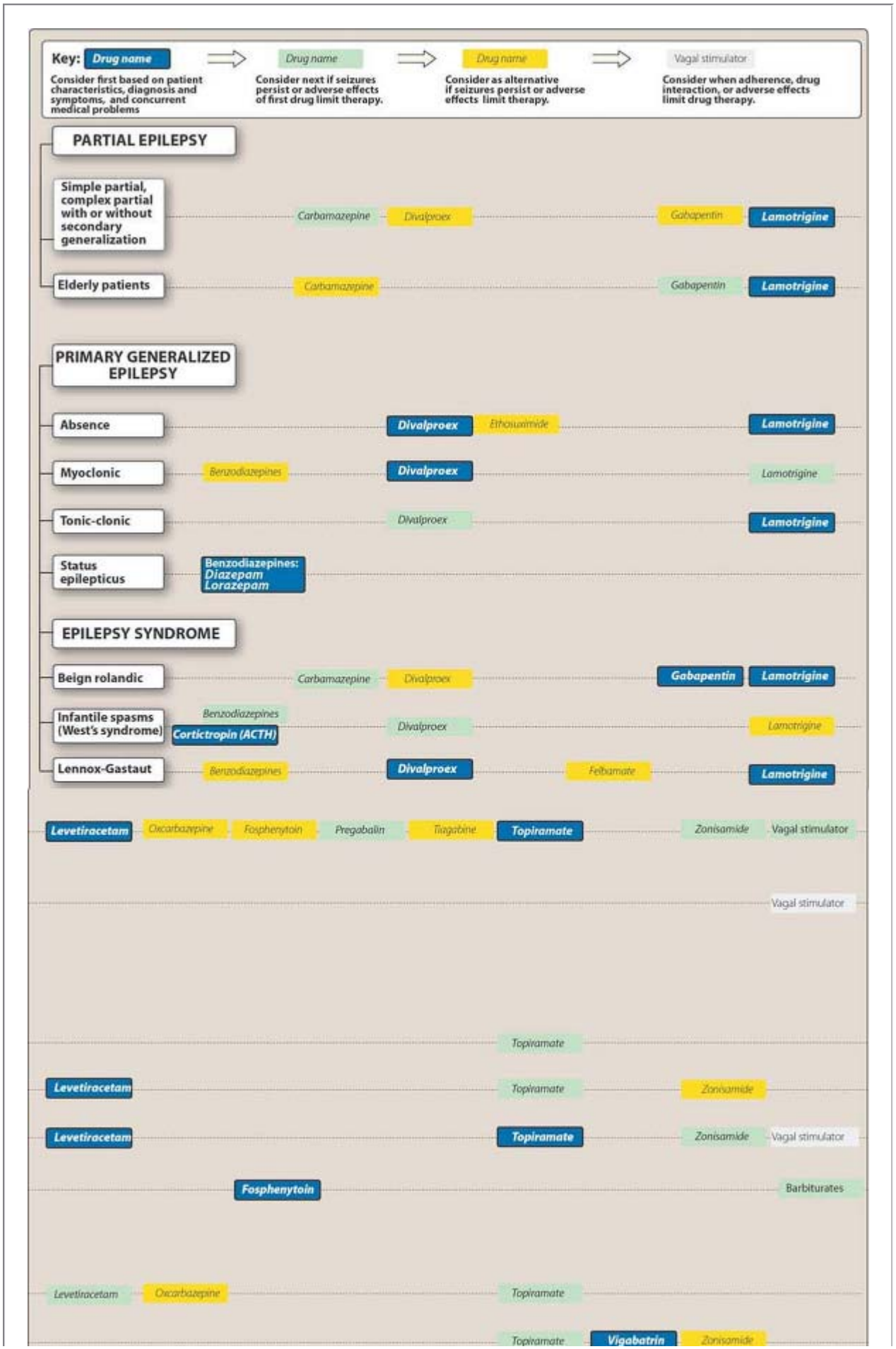
Key: Drug name
Consider first based on patient characteristics, diagnosis and symptoms, and concurrent medical problems
Drug name
Consider next if seizures persist or adverse effects of first drug limit therapy.
Drug name
Consider as alternative if seizures persist or adverse effects limit therapy.
Vagal stimulator
Consider when adherence, drug interaction, or adverse effects limit drug therapy.
PARTIAL EPILEPSY
Simple partial, complex partial with or without secondary generalization
Carbamazepine
Divalproex
Gabapentin
Lamotrigine
Elderly patients
Carbamazepine
Gabapentin
Lamotrigine
PRIMARY GENERALIZED EPILEPSY
Absence
Divalproex
Ethosuximide
Lamotrigine
Myoclonic
Benzodiazepines
Divalproex
Lamotrigine
Tonic-clonic
Divalproex
Lamotrigine
Status epilepticus
Benzodiazepines: Diazepam Lorazepam
EPILEPSY SYNDROME
Beign rolandic
Carbamazepine
Divalproex
Gabapentin
Lamotrigine
Infantile spasms (West's syndrome)
Benzodiazepines
Cortictropin (ACTH)
Divalproex
Lamotrigine
Lennox-Gastaut
Benzodiazepines
Divalproex
Felbamate
Lamotrigine
Levetiracetam
Oxcarbazepine
Fosphenytoin
Pregabalin
Tiagabine
Topiramate
Zonisamide
Vagal stimulator
Vagal stimulator
Topiramate
Levetiracetam
Topiramate
Zonisamide
Levetiracetam
Topiramate
Zonisamide
Vagal stimulator
Fosphenytoin
Barbiturates
Levetiracetam
Oxcarbazepine
Topiramate
Topiramate
Vigabatrin
Zonisamide

Figure 15.5 Therapeutic indications for the anticonvulsant agents.

V. Primary Antiepileptic Drugs

During the past 15 years, new antiepileptic drugs have been introduced, some of which have potential advantages in terms of pharmacokinetics, tolerability, and lesser risk for drug-drug interactions when compared with the

older agents used to treat epilepsy. These new drugs, which include *gabapentin, lamotrigine, topiramate, levetiracetam, oxcarbazepine, zonisamide*, are labeled â€œsecond generationâ€ when compared with older antiepileptics, such as *phenobarbital, phenytoin, carbamazepine, ethosuximide, divalproex* and *valproic acid*. However, clinical studies have not shown that the second-generation drugs as a group are significantly better with respect to efficacy and in some cases, adverse effects than the older agents. For that reason, the authors have chosen to present the antiepileptic drugs in alphabetic order, rather than attempting to rank them by efficacy. Figure 15.6 shows the commonly encountered adverse effect of the antiepileptic drugs. In addition, an increased risk of suicidal behavior and suicidal ideation has been observed with many of the antiepileptic drugs.

A. Benzodiazepines

Benzodiazepines bind to GABA inhibitory receptors to reduce firing rate. *Diazepam*, and *lorazepam* are most often used as an adjunctive therapy for myoclonic as well as for partial and generalized tonic-clonic seizures. *Lorazepam* (see p. 108) has a shorter pharmacokinetic half-life but stays in the brain longer than *diazepam*. *Diazepam* is available for rectal administration to avoid or interrupt prolonged generalized tonic-clonic seizures or clusters. Other benzodiazepines may be used in the treatment of various epilepsies but should be considered for use only after trials with monotherapy or combinations of most other medications for treatment of seizures fail.

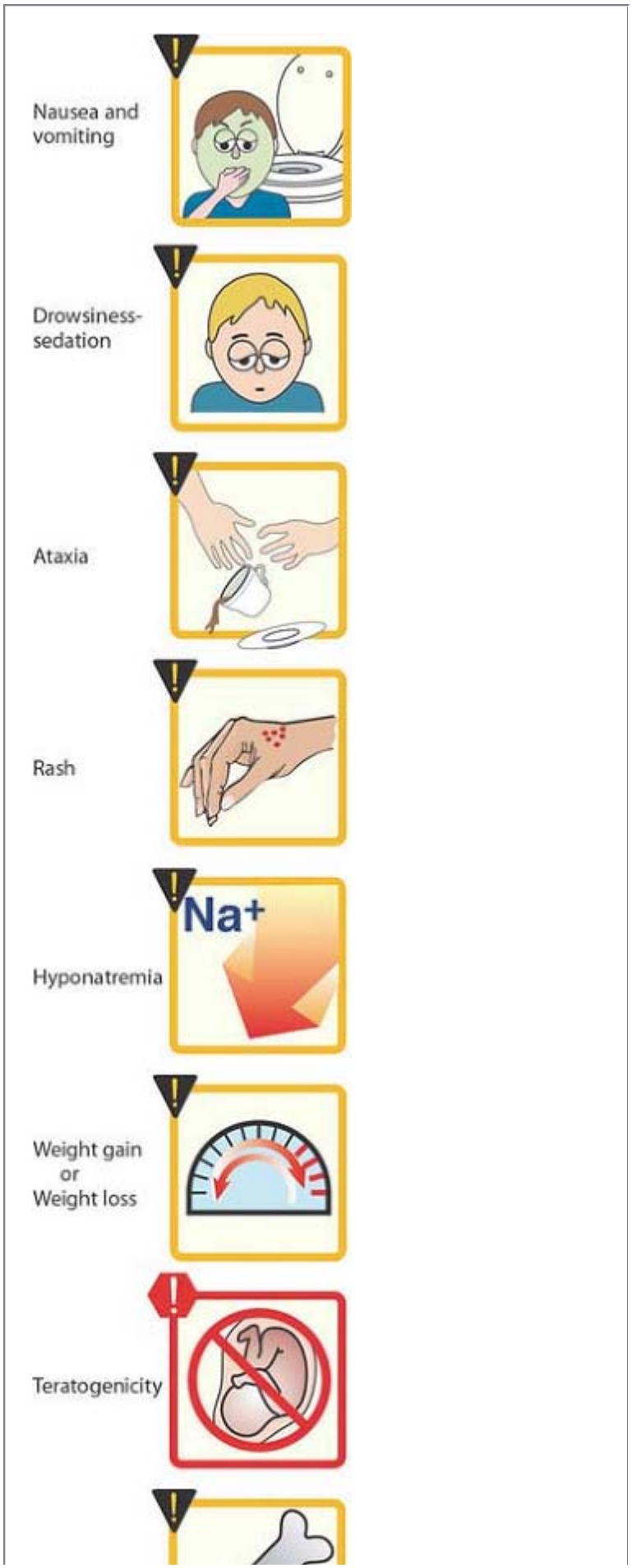
Nausea and vomiting
Drowsiness-sedation
Ataxia
Rash
Na+
Hyponatremia
Weight gain or Weight loss
Teratogenicity

Figure 15.6 Notable adverse effects of antiseizure medications.

B. Carbamazepine

Carbamazepine [kar-ba-MAZ-a peen] reduces the propagation of abnormal impulses in the brain by blocking sodium channels, thereby inhibiting the generation of repetitive action potentials in the epileptic focus and preventing their spread. *Carbamazepine* is effective for treatment of partial seizures and secondarily generalized tonic-clonic seizures. It is also used to treat trigeminal neuralgia and in bipolar disease. *Carbamazepine* is absorbed slowly and erratically following oral administration and may vary from generic to generic, resulting in large variations in serum concentrations of the drug. It induces its own drug metabolism and has an active metabolite. It is a substrate for CYP3A4 with minor metabolism by CYP1A2 and CYC2C8. The epoxide metabolite accounts for 25 percent of the dose, is active, and can be inhibited by drugs that inhibit UDP glucouronosyltransferase (UGT), leading to toxicity (Figure 15.7). *Carbamazepine* is an inducer of the isozyme families CYP1A2, CYP2C, and CYP3A and UGT enzymes which may increase the clearance and reduce the efficacy of drugs that are metabolized by these enzymes. It is not as well tolerated by the elderly as other available antiseizure medications. Hyponatremia may be noted in some patients, especially the elderly, and could indicate a need for change of therapy. The 10,11-epoxide metabolite of the drug has been implicated in causing blood dyscrasias. A characteristic rash may develop early in therapy but may not require a change in treatment. *Carbamazepine* should not be prescribed for patients with absence seizures because it may cause an increase in seizures.

C. Divalproex

Divalproex sodium is a combination of *sodium valproate* and *valproic acid* and is reduced to *valproate* when it reaches the gastrointestinal tract. It was developed to improve gastrointestinal tolerance of *valproic acid*. All of the available salt forms are equivalent in efficacy (*valproic acid* and *valproate sodium*). Commercial products are available in multiple-salt, dosage forms and extended-release formulations. Therefore the risk for medication errors is high, and it is essential to be familiar with all preparations. Proposed mechanisms of action include sodium channel blockade, blockade of GABA transaminase, and action at the T-type calcium channels. These many mechanisms provide a broad spectrum of activity against seizures. It is effective for the treatment of partial and primary generalized epilepsies. *Valproate* inhibits metabolism of the CYP2C9, UGT and epoxide hydrolase systems. *Valproate* is bound to albumin (greater than 90 percent), which can cause significant interactions with other highly protein bound drugs. Rare hepatic toxicity may cause a rise in hepatic enzymes in plasma, which should be monitored

frequently. Teratogenicity is of great concern. Therefore all women of child-bearing age should be placed on other therapies and counseled about the potential for birth defects, including neural tube defects.

D. Ethosuximide

Ethosuximide [eth-oh-SUX-i-mide] reduces propagation of abnormal electrical activity in the brain, most likely by inhibiting T-type calcium channels. It is effective in treating only primary generalized absence seizures (see Figure 15.5). Use of *ethosuximide* is limited because of this very narrow spectrum.

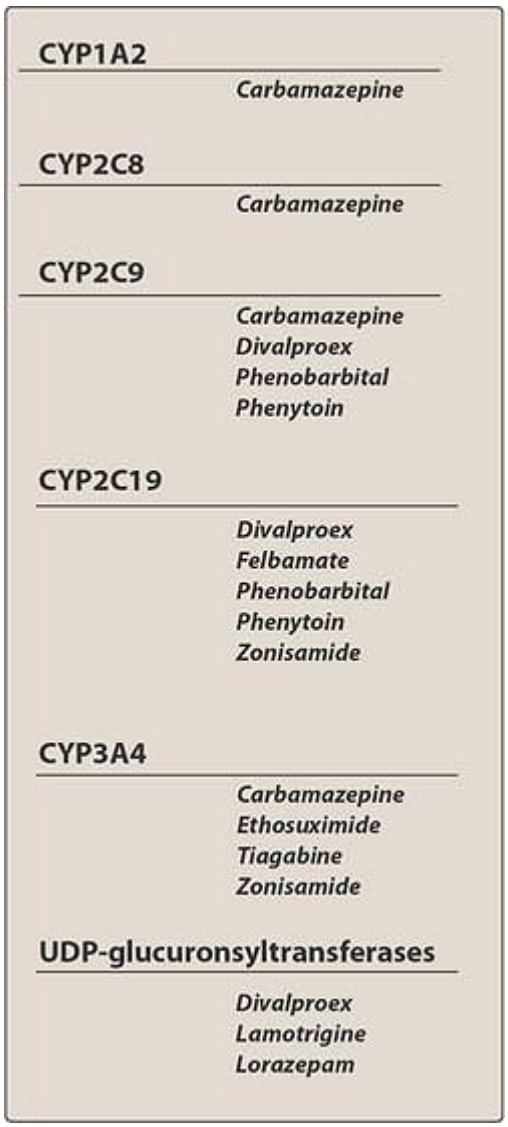

Figure 15.7 Metabolism of the antiepeliptic drugs.

E. Felbamate

Felbamate [FEL-ba-mate] has a broad spectrum of anticonvulsant action. The drug has multiple proposed mechanisms including 1) blocking voltage-dependent sodium channels, 2) competing with the glycine-coagonist binding site on the N-methyl-D-aspartate (NMDA) glutamate receptor, 3) blocking calcium channels, and 5) potentiation of GABA actions. It is an inhibitor of drugs metabolized by CYP2C19 and b-oxidation. It induces drugs metabolized by CYP3A4. It is reserved for use in refractory epilepsies (particularly Lennox-Gastaut syndrome) because of the risk of aplastic anemia (about 1:4000) and hepatic failure.

F. Gabapentin

Gabapentin [GA-ba-pen-tin] is an analog of GABA. However, it does not act at GABA receptors nor enhance GABA actions, nor is it converted to GABA. Its precise mechanism of action is not known. It is approved as adjunct therapy for partial seizures and for treatment of postherpetic neuralgia. *Gabapentin* exhibits nonlinear pharmacokinetics

due to its uptake by a saturable transport system from the gut. *Gabapentin* does not bind to plasma proteins and is excreted unchanged through the kidneys. Reduced dosing is required in renal disease. *Gabapentin* has been shown to be well tolerated by the elderly population with partial seizures due to the relatively mild adverse effects and a good choice due to limited or no reported pharmacokinetic drug interactions.

G. Lamotrigine

Lamotrigine [la-MOE-tri-jeen] blocks sodium channels as well as high voltageâ€“dependent calcium channels. *Lamotrigine* is effective in a wide variety of seizure disorders, including partial seizures, generalized seizures, typical absence seizures, and the Lennox-Gastaut syndrome. It is approved for use in bipolar disorder as well. *Lamotrigine* is metabolized primarily to the N-2 glucuronide through the UGT pathway. The half-life of *lamotrigine* (24â€“35 hours) is decreased by enzyme-inducing drugs (for example, *carbamazepine* and *phenytoin*) and increased by greater than 50 percent with addition of *valproate*. *Lamotrigine* dosages should be reduced when adding *valproate* to therapy unless the *valproate* is being added in a small dose to provide a boost to the *lamotrigine* serum concentration. Rapid titration to high serum concentrations of *lamotrigine* have been reported to cause a rash, which in some patients may progress to a serious, life-threatening reaction. *Lamotrigine* has also been shown to be well tolerated by the elderly population with partial seizures due to the relatively minor adverse effects when titrated slowly.

H. Levetiracetam

Levetiracetam [lee-ve-tye-RA-se-tam] is approved for adjunct therapy of partial onset seizures, myoclonic seizures, and primary generalized tonic-clonic seizures in adults and children. The exact mechanism of anticonvulsant action is unknown. It demonstrates high affinity for a synaptic vesicle protein (SV2A). In mice, this was associated with potent antiseizure action. The drug is well absorbed orally, and excretion is urinary, with most of the drug (66 percent) being unchanged. The drug does not interact with CYP or UGT metabolism systems. Side effects most often reported include dizziness, sleep disturbances, headache, and weakness.

I. Oxcarbazepine

Oxcarbazepine [ox-kar-BAY-zeh-peen] is a prodrug that is rapidly reduced to the 10-monohydroxy (MHD) metabolite which is responsible for its anticonvulsant activity. MHD blocks sodium channels preventing the spread of the abnormal discharge. Modulation of calcium channels is also a hypothesis. It is approved for use in adults and children with partial onset seizures. *Oxcarbazepine* is a less potent inducer of CYP3A4 and UGT than *carbamazepine.* The adverse effects profile is similar to that of other antiepileptic drugs with respect to nausea, vomiting, headache, and visual disturbance.

J. Phenobarbital

Phenobarbital [fee-noe-BAR-bih-tal] was synthesized in 1902 and brought to the market in 1912 by Bayer. The primary mechanism of action is the enhancement of inhibitory effects of GABA-mediated neurons (see p. 111). The primary use for *phenobarbital* in epilepsy is in treatment of status epilepticus. Due to interaction with the cytochrome P450 enzymes as an inducer, and adverse effects of sedation, cognitive impairment, and potential for osteoporosis, this drug should only be considered for chronic therapy once a patient is found to be refractory to many other drugs, and the benefits of therapy outweigh the multiple risks.

K. Phenytoin and fosphenytoin

Phenytoin [FEN-i-toin] blocks voltage-gated sodium channels by selectively binding to the channel in the inactive state and slowing its rate of recovery. At very high concentrations, *phenytoin* can block voltage-dependent calcium channels and interfere with the release of monoaminergic neurotransmitters. *Phenytoin* is effective for treatment of partial seizures and generalized tonic-clonic seizures and in the treatment of status epilepticus (see Figure 15.5). The drug is 90 percent bound to plasma albumin. *Phenytoin* is an inducer of drugs metabolized by the CYP2C, and

CYP3A families and the UGT enzyme system. *Phenytoin* exhibits saturable enzyme metabolism at a low serum concentration; thus knowledge of zero- order pharmacokinetics and population parameters is important for dosing adjustment. Small increases in a daily dose can produce large increases in the plasma concentration, resulting in drug-induced toxicity (Figure 15.8). Depression of the CNS occurs particularly in the cerebellum and vestibular system, causing nystagmus and ataxia. The elderly are highly susceptible to this effect. Gingival hyperplasia may cause the gums to grow over the teeth. Long-term use may lead to development of peripheral neuropathies and osteoporosis.

Fosphenytoin [FOS-phen-i-toin] is a prodrug and is rapidly converted to *phenytoin* in the blood, providing high levels of *phenytoin* within minutes. *Fosphenytoin* may also be administered intramuscularly (IM). *Phenytoin sodium* should never be given IM because it can cause tissue damage and necrosis. *Fosphenytoin* is the drug of choice and standard of care for IV and IM administration. Due to sound-alike and look-alike names, there is a risk for medication error to occur. The trade name of *fosphenytoin* is CerebyxÂ®, which is easily confused with CelebrexÂ®, the cyclooxygenase-2 inhibitor, and CelexaÂ®, the antidepressant.

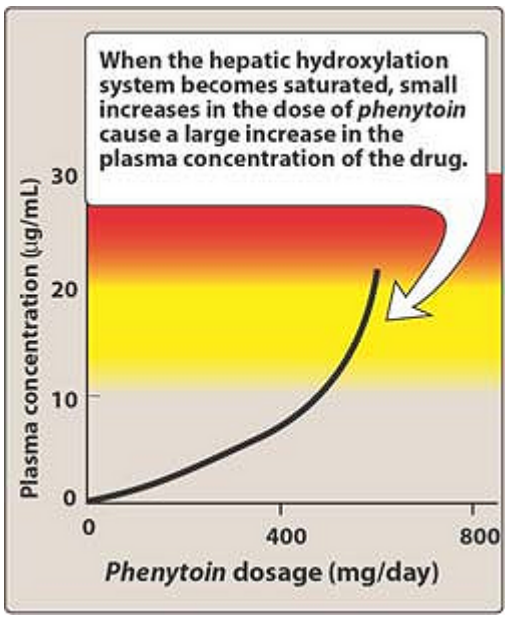

Figure 15.8 Nonlinear effect of *phenytoin* dosage on the plasma concentration of the drug.

L. Pregabalin

Pregabalin [pree-GABA-lin] binds to the a_2-d site, an auxiliary subunit of voltage-gated calcium channels in the CNS, inhibiting excitatory neurotransmitter release. The exact role this plays in treatment is not known, but the drug has proven effects on partial onset seizures, neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, and fibromyalgia. *Pregabalin* is greater than 90 percent eliminated renally, with no indication of CYP involvement. Drowsiness, blurred vision, weight gain, and peripheral edema have been reported.

M. Primidone

Primidone [PRIM-i-done] has two active metabolites, *phenobarbital* and phenylethylmalonamide, which have longer half-lives than the parent drug. Due to the nature of the long term adverse effects associated with *phenobarbital*, this drug should be considered for use only in those patients with refractory epilepsy.

N. Tiagabine

Tiagabine [ty-AG-a-been] blocks GABA uptake into presynaptic neurons, permitting more GABA to be available for receptor binding, thus, there is thought to be enhanced inhibitory activity. *Tiagabine* is effective in decreasing the number of seizures in patients with partial onset epilepsy. Binding to albumin and a_1-acid glycoprotein is greater than 95 percent, and metabolism is mainly completed by the CYP3A family of enzymes. Adverse effects include tiredness, dizziness, and gastrointestinal upset. There is some indication in postmarketing surveillance that seizures have occurred in patients who did not have epilepsy when the drug was used. *Tiagabine* has not been approved for use for any other indication.

O. Topiramate

Topiramate [toe-PEER-a-mate] possesses several actions that are believed to contribute to its broad spectrum of antiseizure activity. *Topiramate* blocks voltage-dependent sodium channels; it has been shown to increase the frequency of chloride channel opening by binding to the $GABA_A$ receptor. High-voltage calcium currents (L type) are reduced by *topiramate*. It is a carbonic anhydrase inhibitor and may act at glutamate (NMDA) sites. *Topiramate* is effective and approved for use in partial and primary generalized epilepsies. It is also approved for treatment of migraine. *Topiramate* is renally eliminated to a high degree, but it also has inactive metabolites. It inhibits CYP2C19 and is induced by *phenytoin*, and *carbamazepine. Lamotrigine* is reported to cause an increase in *topiramate* concentration. Coadministration of *topiramate* reduces *ethinyl estradiol*. Adverse effects include somnolence, weight loss, and paresthesias; renal stones are reported to occur at a higher

incidence than in a nontreated population. Glaucoma, oligohidrosis, and hyperthermia have also been reported. The latter are specifically related to the carbonic anhydrase activity.

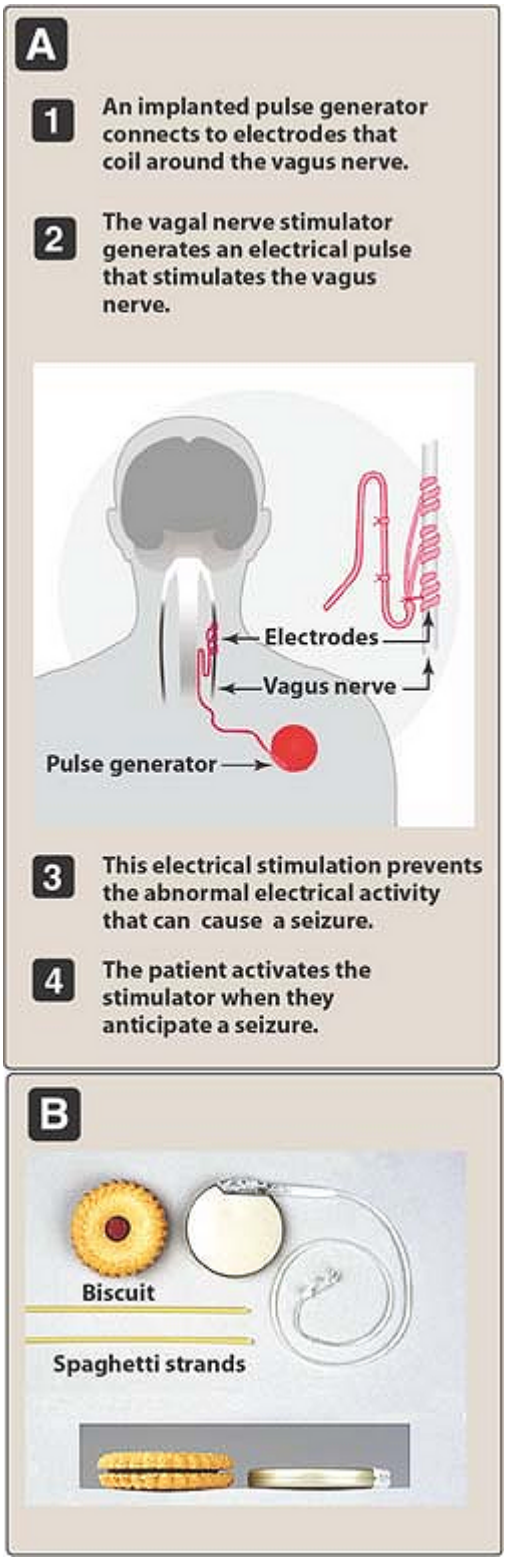

Figure 15.9 Vagal nerve stimulation. A. Location of implanted stimulator. B. Size of device.

P. Zonisamide

Zonisamide [zoe-NIS-a-mide] is a sulfonamide derivative that has a broad spectrum of action. The compound has multiple effects on neuronal systems thought to be involved in seizure generation. These include blockade of both voltage-gated sodium channels and T-type calcium currents. It has a limited amount of carbonic anhydrase activity. Cross reactivity with other sulfonamides should be reviewed and its use monitored in patients with reported allergies. *Zonisamide* is approved for use in patients with partial epilepsy. It is metabolized by the CYP3A4 isozyme and may, to a lesser extent, be affected by CYP3A5 and CYP2C19. In addition to the typical CNS adverse effects, *zonisamide* may cause kidney stones. Oligohidrosis has been reported, and patients should be monitored for increased body temperature and decreased sweating.

VI. Vagal Nerve Stimulation

Vagal nerve stimulation requires surgical implant of a small pulse generator with a battery and a lead wire for stimulus (Figure 15.9). The device is implanted and lead wires wrapped around the patient's vagal nerve. This device and treatment were approved in 1997. The device is also approved for treatment of depression. The mechanism of action is unknown. Because it has diffuse involvement with the neuronal circuits, there are a variety of mechanisms by which it may exert its affect on seizure control. Vagal nerve stimulation has been effective in treatment of partial onset seizures and has enabled reduction of drug therapy in some cases. It is an alternative for patients who have been refractory to multiple drugs, who are sensitive to the many adverse effects of antiseizure drugs, and who have difficulty adhering to medication schedules. Vagal nerve stimulation requires invasive procedure and is expensive.

VII. Epilepsy in Pregnancy

Women with epilepsy are often very concerned about pregnancy and what the medications will do to the development of the baby. Planning is the most important component. All women should be on high doses of folic acid prior to conception. *Divalproex* and barbiturates should be avoided. Switching women to other drugs before pregnancy should be accomplished when possible. When seizures are controlled, maintenance medication should be reduced, if possible, to the lowest dose that provides control. If seizures are not controlled, medications and dosages should be adjusted. The frequency and severity of seizures may change during pregnancy. Women should be monitored regularly by the obstetrician as well as the neurologist. All women with epilepsy should register with the AED (Antiepileptic drug) Pregnancy Registry.

Figure 15.10 summarizes the antiepileptic drugs,

DRUG	MECHANISM OF ACTION	ADVERSE EFFECTS AND COMMENTS
Carbamazepine	Blocks Na^+ channels	Hyponatremia, drowsiness, fatigue, dizziness, and blurred vision. Drug use has as been associated with Stevens-Johnson Syndrome. Blood dyscrasias: neutropenia, leukopenia, thrombocytopenia, pancytopenia, and anemias.
Divalproex	Multiple mechanisms of action	Weight gain, easy bruising, nausea, tremor, hair loss, weight gain, GI upset, liver damage, alopecia, and sedation. Hepatic failure, pancreatitis, and teratogenic effects such have been observed. Broad spectrum of antiseizure activity.
Ethosuximide	Blocks Ca^{2+} channels	Drowsiness, hyperactivity, nausea, sedation, GI upset, weight gain, lethargy, SLE, and rash. Blood dyscrasias can occur; periodic CBCs should be done. Abrupt discontinuance of drug may causes seizures.
Felbamate	Multiple mechanisms of action	Insomnia, dizziness, headache, ataxia, weight gain, and irritability. Aplastic anemia; hepatic failure. Broad spectrum of antiseizure activity. Requires patient to sign informed consent at dispensing.
Gabapentin	Unknown	Mild drowsiness, dizziness, ataxia, weight gain, and diarrhea. Few drug interactions. One-hundred percent renal elimination.
Lamotrigine	Multiple mechanisms of action	Nausea, drowsiness, dizziness, headache, and diplopia. Rash (Stevens-Johnson syndrome—potentially life-threatening). Broad spectrum of antiseizure activity.
Levetiracetam	Multiple mechanisms of action	Sedation, dizziness, headache, anorexia, fatigue, infections, and behavioral symptoms. Few drug interactions. Broad spectrum of antiseizure activity.
Oxcarbazepine	Blocks Na^+ channels	Nausea, rash, hyponatremia, headache, sedation, dizziness, vertigo, ataxia, and diplopia.
Fosphenytoin	Blocks Na^+ channels	Gingival hyperplasia, confusion, slurred speech, double vision, ataxia, sedation, dizziness, and hirsutism. Stevens-Johnson syndrome—potentially life-threatening. Not recommended for chronic use. Primary treatment for status epilepticus.
Pregabalin	Multiple mechanisms of action	Weight gain, somnolence, dizziness, headache, weight gain, diplopia, and ataxia. One hundred percent renal elimination.
Primidone	GABA receptor	Sedation, lethargy, behavioral changes, ataxia, hyperactivity, and nausea. Not recommended for chronic use.
Tiagabine	GABA receptor	Sedation, weight gain, fatigue, headache, tremor, dizziness, and anorexia. Multiple drug interactions.
Topiramate	Multiple mechanisms of action	Paresthesia, weight loss, nervousness, depression, anorexia, anxiety, tremor, cognitive complaints, headache, and oligohidrosis. Few drug interactions. Broad spectrum of antiseizure activity.
Zonisamide	Multiple mechanisms of action	Nausea, anorexia, ataxia, confusion, difficulty concentrating, sedation, paresthesia and oligohidrosis. Broad spectrum of antiseizure activity.

Figure 15.10 Summary of antiepileptic drugs. CBC = complete blood count; GABA = Î³-aminobutyrc acid; GI = gastrointestinal; SLE = systemic lupus erythematosus

Study Questions

Choose the ONE best answer.

15.1 A nine-year-old boy is sent for neurologic evaluation because of episodes of confusion. Over the past

year, the child has experienced episodes during which he develops a blank look on his face and fails to respond to questions. However, it appears to take several minutes before the boy recovers from the episodes. Which one the following best describes this patient's seizures?

A. Simple partial.

B. Complex partial.

C. Tonic-clonic.

D. Absence.

E. Myoclonic.

View Answer

15.2 Which one of the following therapies would be appropriate for the patient described in the above question?

A. Ethosuximide.

B. Carbamazepine.

C. Diazepam.

D. Carbamazepine plus primidone.

E. Watchful waiting.

View Answer

15.3 The patient described in Question 15.1 was treated for six months with carbamazepine but, recently, has been experiencing breakthrough seizures on a more frequent basis. You are considering adding a second drug to this patient's antiseizure regimen. Which of the following drugs is least likely to have a pharmacokinetic interaction with carbamazepine?

A. Topiramate.

B. Tiagabine.

C. Levetiracetam.

D. Lamotrigine.

E. Zonisamide.

View Answer