09 - 29.9 Benzodiazepines and Drugs Acting on GABA

29.9 Benzodiazepines and Drugs Acting on GABA Receptors

addition, the carrier can impair macrophage function and cause hematologic and lipid abnormalities and anaphylactic reactions. Etomidate Etomidate is a carboxylated imidazole that acts at the β2 and β3 subunits of the GABAA receptor. It has a rapid onset (1 minute) and short duration (less than 5 minutes) of action. The propylene glycol vehicle has been linked to hyperosmolar metabolic acidosis. It has both proconvulsant and anticonvulsant properties, and it inhibits cortisol release, with possible adverse consequences after long-term use. REFERENCES Dubovsky SL. Barbiturates and similarly acting substances. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 9th ed. Vol. 2. Philadelphia: Lippincott Williams & Wilkins; 2009:3038. Bigal ME, Lipton RB. Excessive acute migraine medication use and migraine progression. Neurology. 2008;71:1821. Chen HI, Malhotra NR, Oddo M, Heuer GG, Levine JM, Le Roux PD. Barbiturate infusion for intractable intracranial hypertension and its effect on brain oxygenation. Neurosurgery. 2008;63:880. Flomenbaum NE, Goldfrank LR, Hoffman RS, Howland MA, Lewin NA. Goldfrank's Toxicologic Emergencies. 8th ed. New York: McGraw-Hill; 2006. Hutto B, Fairchild A, Bright R. γ-Hydroxybutyrate withdrawal and chloral hydrate. Am J Psychiatry. 2000;157:1706. Koerner IK, Brambrink AM. Brain protection by anesthetic agents. Curr Opin Anaesthesiol. 2006;19:481. McCarron MM, Schulze BW, Walberg CB, Thompson GA, Ansari A. Short acting barbiturate overdosage: Correlation of intoxication score with serum barbiturate concentration. JAMA. 1982;248:55. Rosa MA, Rosa MO, Marcolin MA, Fregni F. Cardiovascular effects of anesthesia in ECT: A randomized, double-blind comparison of etomidate, propofol and thiopental. J ECT. 2007;23:6. Silberstein SD, McCrory DC. Butalbital in the treatment of headache: History, pharmacology, and efficacy. Headache. 2001;41:953. Smith MC, Riskin BJ. The clinical use of barbiturates in neurological disorders. Drugs. 1991;42:365. Wheeler DS, Jensen RA, Poss WB. A randomized, blinded comparison of chloral hydrate and midazolam sedation in children undergoing echocardiography. Clin Pediatr. 2001;40:381.

Receptors The first benzodiazepine to be introduced was chlordiazepoxide (Librium), in 1959. In 1963, diazepam (Valium) became available. Over the next three decades, superior safety and tolerability helped the benzodiazepines replace the older antianxiety and hypnotic medications, such as the barbiturates and meprobamate (Miltown). Dozens of benzodiazepines and drugs acting on benzodiazepine receptors have been synthesized and marketed worldwide. Many of these agents are not in the United States, and some benzodiazepines have been discontinued because of lack of use. Table 29.9-1 lists agents currently available in the United States.

Table 29.9-1 Preparations and Doses of Medications Acting on the Benzodiazepine Receptor Available in the United States The benzodiazepines derive their name from their molecular structure. They share a common effect on receptors that have been termed benzodiazepine receptors, which in turn modulate γ-aminobutyric acid (GABA) activity. Nonbenzodiazepine agonists, such as zolpidem (Ambien), zaleplon (Sonata), and eszopiclone (Lunesta)—the so-called "Z drugs"—are discussed in this chapter because their clinical effects result from binding domains located close to benzodiazepine receptors. Flumazenil (Romazicon), a benzodiazepine receptor antagonist used to reverse benzodiazepine-induced sedation and in emergency care of benzodiazepine overdosage, is also covered here. Because benzodiazepines have a rapid anxiolytic sedative effect, they are most commonly used for acute treatment of insomnia, anxiety, agitation, or anxiety associated with any psychiatric disorder. In addition, the benzodiazepines are used as anesthetics, anticonvulsants, and muscle relaxants and as the preferred treatment for catatonia. Because of the risk of psychological and physical dependence associated with long-term use of benzodiazepines, ongoing assessment should be made as to the continued clinical need for these drugs in treating patients. In most patients, given the nature of their disorders, it is often best if benzodiazepine agents are used in conjunction with psychotherapy and when alternative agents have been tried and proven ineffective or poorly tolerated. In many forms of chronic anxiety disorders, antidepressant drugs such as the selective serotonin reuptake inhibitor (SSRI) and serotonin–norepinephrine reuptake inhibitors (SNRIs) are now used as primary

treatments, with benzodiazepines used as adjuncts. Benzodiazepine abuse is rare, usually found in patients who abuse multiple prescription and recreational drugs. PHARMACOLOGIC ACTIONS All benzodiazepines except clorazepate (Tranxene) are completely absorbed after oral administration and reach peak serum levels within 30 minutes to 2 hours. Metabolism of clorazepate in the stomach converts it to desmethyldiazepam, which is then completely absorbed. The absorption, the attainment of peak concentrations, and the onset of action are quickest for diazepam (Valium), lorazepam (Ativan), alprazolam (Xanax), triazolam (Halcion), and estazolam (ProSom). The rapid onset of effects is important to persons who take a single dose of a benzodiazepine to calm an episodic burst of anxiety or to fall asleep rapidly. Several benzodiazepines are effective after intravenous (IV) injection, but only lorazepam and midazolam (Versed) have rapid and reliable absorption after intramuscular (IM) administration. Diazepam, chlordiazepoxide, clonazepam (Klonopin), clorazepate, flurazepam (Dalmane), and quazepam (Doral) have plasma half-lives of 30 hours to more than 100 hours and are technically described as long-acting benzodiazepines. The plasma halflives of these compounds can be as high as 200 hours in persons whose metabolism is genetically slow. Because the attainment of steady-state plasma concentrations of the drugs can take up to 2 weeks, persons may experience symptoms and signs of toxicity after only 7 to 10 days of treatment with a dosage that seemed initially to be in the therapeutic range. Clinically, half-life alone does not necessarily determine the duration of therapeutic action for most benzodiazepines.

The fact that all benzodiazepines are lipid soluble to varying degrees means that benzodiazepines and their active metabolites bind to plasma proteins. The extent of this binding is proportional to their lipid solubility. The amount of protein binding varies from 70 to 99 percent. Distribution, onset, and termination of action after a single dose are thus largely determined by benzodiazepine lipid solubility, not elimination half-life. Preparations with high lipid solubility, such as diazepam and alprazolam, are absorbed rapidly from the GI tract and distribute rapidly to the brain by passive diffusion along a concentration gradient, resulting in a rapid onset of action. However, as the concentration of the medication increases in the brain and decreases in the bloodstream, the concentration gradient reverses itself, and these medications leave the brain rapidly, resulting in fast cessation of drug effect. Drugs with longer elimination half-lives, such as diazepam, may remain in the bloodstream for a substantially longer period of time than their actual pharmacologic action at benzodiazepine receptors because the concentration in the brain decreases rapidly below the level necessary for a noticeable effect. In contrast, lorazepam, which has a shorter elimination half-life than diazepam but is less lipid soluble, has a slower onset of action after a single dose because the drug is absorbed and enters the brain more slowly. However, the duration of action after a single dose is longer because it takes longer for

lorazepam to leave the brain and for brain levels to decrease below the concentration that produces an effect. In chronic dosing, some of these differences are not as apparent because brain levels are in equilibrium with higher and more consistent steady-state blood levels, but additional doses still produce a more rapid but briefer action with diazepam than with lorazepam. Benzodiazepines are distributed widely in adipose tissue. As a result, medications may persist in the body after discontinuation longer than would be predicted from their elimination half-lives. In addition, the dynamic half-life (i.e., duration of action on the receptor) may be longer than the elimination half-life. The advantages of long–half-life drugs over short–half-life drugs include less frequent dosing, less variation in plasma concentration, and less severe withdrawal phenomena. The disadvantages include drug accumulation, increased risk of daytime psychomotor impairment, and increased daytime sedation. The half-lives of lorazepam, oxazepam (Serax), temazepam (Restoril), and estazolam are between 8 and 30 hours. Alprazolam has a half-life of 10 to 15 hours, and triazolam has the shortest half-life (2 to 3 hours) of all the orally administered benzodiazepines. Rebound insomnia and anterograde amnesia are thought to be more of a problem with the short–half-life drugs than with the long–half-life drugs. Because administration of medications more frequently than the elimination half-life leads to drug accumulation, medications such as diazepam and flurazepam accumulate with daily dosing, eventually resulting in increased daytime sedation. Some benzodiazepines (e.g., oxazepam) are conjugated directly by glucuronidation and are excreted. Most benzodiazepines are oxidized first by CYP3A4 and CYP2C19, often to active metabolites. These metabolites may then be hydroxylated to another active metabolite. For example, diazepam is oxidized to desmethyldiazepam, which, in turn, is hydroxylated to produce oxazepam. These products undergo glucuronidation to inactive metabolites. A number of benzodiazepines (e.g., diazepam, chlordiazepoxide) have the same active metabolite (desmethyldiazepam), which has an elimination halflife of more than 120 hours. Flurazepam (Dalmane), a lipid-soluble benzodiazepine used as a hypnotic that has a short elimination half-life, has an active metabolite (desalkylflurazepam) with a half-life greater than 100 hours. This is another reason that the duration of action of a benzodiazepine may not correspond to the half-life of the parent drug. Zaleplon, zolpidem, and eszopiclone are structurally distinct and vary in their binding to the GABA receptor subunits. Benzodiazepines activate all three specific

GABA– benzodiazepine (GABA–BZ) binding sites of the GABAA-receptor, which opens chloride channels and reduces the rate of neuronal and muscle firing. Zolpidem, zaleplon, and eszopiclone have selectivity for certain subunits of the GABA receptor. This may account for their selective sedative effects and relative lack of muscle relaxant and anticonvulsant effects. Zolpidem, zaleplon, and eszopiclone are rapidly and well absorbed after oral administration, although absorption can be delayed by as long as 1 hour if they are taken with food. Zolpidem reaches peak plasma concentrations in 1.6 hours and has a

half-life of 2.6 hours. Zaleplon reaches peak plasma concentrations in 1 hour and has a half-life of 1 hour. If taken immediately after a high-fat or heavy meal, the peak is delayed by approximately 1 hour, reducing the effects of eszopiclone on sleep onset. The terminal-phase elimination half-life is approximately 6 hours in healthy adults. Eszopiclone is weakly bound to plasma protein (52 to 59 percent). The rapid metabolism and lack of active metabolites of zolpidem, zaleplon, and eszopiclone avoid the accumulation of plasma concentrations compared with the longterm use of benzodiazepines. THERAPEUTIC INDICATIONS Insomnia Because insomnia may be a symptom of a physical or psychiatric disorder, hypnotics should not be used for more than 7 to 10 consecutive days without a thorough investigation of the cause of the insomnia. However, many patients have long-standing sleep difficulties and benefit greatly from long-term use of hypnotic agents. Temazepam, flurazepam, and triazolam are benzodiazepines with a sole indication for insomnia. Zolpidem, zaleplon, and eszopiclone are also indicated only for insomnia. Although these “Z drugs” are not usually associated with rebound insomnia after the discontinuation of their use for short periods, some patients experience increased sleep difficulties the first few nights after discontinuing their use. Use of zolpidem, zaleplon, and eszopiclone for periods longer than 1 month is not associated with the delayed emergence of adverse effects. No development of tolerance to any parameter of sleep measurement was observed over 6 months in clinical trials of eszopiclone. Flurazepam, temazepam, quazepam, estazolam, and triazolam are the benzodiazepines approved for use as hypnotics. The benzodiazepine hypnotics differ principally in their half-lives; flurazepam has the longest half-life, and triazolam has the shortest. Flurazepam may be associated with minor cognitive impairment on the day after its administration, and triazolam may be associated with mild rebound anxiety and anterograde amnesia. Quazepam may be associated with daytime impairment when used for a long time. Temazepam or estazolam may be a reasonable compromise for most adults. Estazolam produces rapid onset of sleep and a hypnotic effect for 6 to 8 hours. γ-Hydroxybutyrate (GHB, Xyrem), which is approved for the treatment of narcolepsy and improves slow-wave sleep, is also an agonist at the GABAA receptor, where it binds to specific GHB receptors. GHB has the capacity both to reduce drug craving and to induce dependence, abuse, and absence seizures as a result of complex actions on tegmental dopaminergic systems. Anxiety Disorders Generalized Anxiety Disorder. Benzodiazepines are highly effective for the relief of anxiety associated with generalized anxiety disorder (GAD). Most persons

should be treated for a predetermined, specific, and relatively brief period. However, because GAD is a chronic disorder with a high rate of recurrence, some persons with GAD may warrant long-term maintenance treatment with benzodiazepines. Panic Disorder. Alprazolam and clonazepam, both high-potency benzodiazepines, are commonly used medications for panic disorder with or without agoraphobia. Although the SSRIs are also indicated for treatment of panic disorder, the benzodiazepines have the advantage of working quickly and not causing significant sexual dysfunction and weight gain. However, the SSRIs are still often preferred because they target

common comorbid conditions, such as depression or obsessive-compulsive disorder (OCD). Benzodiazepines and SSRIs can be initiated together to treat acute panic symptoms; use of the benzodiazepine can be tapered after 3 to 4 weeks after the therapeutic benefits of the SSRI have emerged. Social Phobia. Clonazepam has been shown to be an effective treatment for social phobia. In addition, several other benzodiazepines (e.g., diazepam) have been used as adjunctive medications for treatment of social phobia. Other Anxiety Disorders. Benzodiazepines are used adjunctively for treatment of adjustment disorder with anxiety, pathological anxiety associated with life events (e.g., after an accident), OCD, and posttraumatic stress disorder. Anxiety Associated with Depression. Depressed patients often experience significant anxiety, and antidepressant drugs may cause initial exacerbation of these symptoms. Accordingly, benzodiazepines are indicated for the treatment of anxiety associated with depression. Bipolar I and II Disorders Clonazepam, lorazepam, and alprazolam are effective in the management of acute manic episodes and as an adjuvant to maintenance therapy in lieu of antipsychotics. As an adjuvant to lithium (Eskalith) or lamotrigine (Lamictal), clonazepam may result in an increased time between cycles and fewer depressive episodes. Benzodiazepines may help patients with bipolar disorder sleep better. Catatonia Lorazepam, sometimes in low doses (less than 5 mg per day) and sometimes in very high doses (12 mg per day or more), is regularly used to treat acute catatonia, which is more frequently associated with bipolar disorder than with schizophrenia. Other benzodiazepines have also been said to be helpful. However, there are no valid controlled trials of benzodiazepines in catatonia. Chronic catatonia does not respond as well to benzodiazepines. The definitive treatment for catatonia is electroconvulsive therapy.

Akathisia The first-line drug for akathisia is most commonly a β-adrenergic receptor antagonist. However, benzodiazepines are also effective in treating some patients with akathisia. Parkinson’s Disease A small number of persons with idiopathic Parkinson’s disease respond to long-term use of zolpidem with reduced bradykinesia and rigidity. Zolpidem dosages of 10 mg four times daily may be tolerated without sedation for several years. Other Psychiatric Indications Chlordiazepoxide (Librium) and clorazepate (Tranxene) are used to manage the symptoms of alcohol withdrawal. The benzodiazepines (especially IM lorazepam) are used to manage substance induced and psychotic agitation in the emergency department. Benzodiazepines have been used instead of amobarbital (Amytal) for drugassisted interviewing. Flumazenil for Benzodiazepine Overdosage Flumazenil is used to reverse the adverse psychomotor, amnestic, and sedative effects of benzodiazepine receptor agonists, including benzodiazepines, zolpidem, and zaleplon. Flumazenil is administered IV and has a half-life of 7 to 15 minutes. The most common adverse effects of flumazenil are nausea, vomiting, dizziness, agitation, emotional lability, cutaneous vasodilation, injection-site pain, fatigue, impaired vision, and headache. The most common serious adverse effect associated with the use of flumazenil is the precipitation of seizures, which is especially likely to occur in persons with seizure disorders, those who are physically dependent on benzodiazepines, and those who have ingested large quantities of benzodiazepines. Flumazenil alone may impair memory retrieval. In mixed-drug overdosage, the toxic effects (e.g., seizures and cardiac arrhythmias) of other drugs (e.g., tricyclic antidepressants) may emerge with the reversal of the benzodiazepine effects of flumazenil. For example, seizures caused by an overdosage of tricyclic antidepressants may have been partially treated in a person who had also taken an overdosage of benzodiazepines. With flumazenil treatment, the tricyclicinduced seizures or cardiac arrhythmias may appear and result in a fatal outcome. Flumazenil does not reverse the effects of ethanol, barbiturates, or opioids. For the initial management of a known or suspected benzodiazepine overdosage, the

recommended initial dosage of flumazenil is 0.2 mg (2 mL) administered IV over 30 seconds. If the desired consciousness is not obtained after 30 seconds, a further dose of 0.3 mg (3 mL) can be administered over 30 seconds. Further doses of 0.5 mg (5 mL) can be administered over 30 seconds at 1-minute intervals up to a cumulative dose of 3.0 mg. The clinician should not rush the administration of flumazenil. A secure airway and

IV access should be established before the administration of the drug. Persons should be awakened gradually. Most persons with a benzodiazepine overdosage respond to a cumulative dose of 1 to 3 mg of flumazenil; doses above 3 mg of flumazenil do not reliably produce additional effects. If a person has not responded 5 minutes after receiving a cumulative dose of 5 mg of flumazenil, the major cause of sedation is probably not benzodiazepine receptor agonists, and additional flumazenil is unlikely to have an effect. Sedation can return in 1 to 3 percent of persons treated with flumazenil. It can be prevented or treated by giving repeated dosages of flumazenil at 20-minute intervals. For repeat treatment, no more than 1 mg (given as 0.5 mg a minute) should be given at any one time, and no more than 3 mg should be given in any 1 hour. PRECAUTIONS AND ADVERSE REACTIONS The most common adverse effect of the benzodiazepines is drowsiness, which occurs in about 10 percent of all persons. Because of this adverse effect, persons should be advised to be careful while driving or using dangerous machinery when taking the drugs. Drowsiness can be present during the day after the use of a benzodiazepine for insomnia the previous night, the so-called residual daytime sedation. Some persons also experience ataxia (fewer than 2 percent) and dizziness (less than 1 percent). These symptoms can result in falls and hip fractures, especially in elderly persons. The most serious adverse effects of the benzodiazepines occur when other sedative substances, such as alcohol, are taken concurrently. These combinations can result in marked drowsiness, disinhibition, or even respiratory depression. Infrequently, benzodiazepine receptor agonists cause mild cognitive deficits that may impair job performance. Persons taking benzodiazepine receptor agonists should be advised to exercise additional caution when driving or operating dangerous machinery. High-potency benzodiazepines, especially triazolam, can cause anterograde amnesia. A paradoxical increase in aggression has been reported in persons with preexisting brain damage. Allergic reactions to the drugs are rare, but a few studies report maculopapular rashes and generalized itching. The symptoms of benzodiazepine intoxication include confusion, slurred speech, ataxia, drowsiness, dyspnea, and hyporeflexia. Triazolam has received significant attention in the media because of an alleged association with serious aggressive behavioral manifestations. Therefore, the manufacturer recommends that the drug be used for no more than 10 days for treatment of insomnia and that physicians carefully evaluate the emergence of any abnormal thinking or behavioral changes in persons treated with triazolam, giving appropriate consideration to all potential causes. Triazolam was banned in Great Britain in 1991. Zolpidem (Ambien) has also been associated with automatic behavior and amnesia. Persons with hepatic disease and elderly persons are particularly likely to have adverse effects and toxicity from the benzodiazepines, including hepatic coma, especially when the drugs are administered repeatedly or in high dosages.

Benzodiazepines can produce clinically significant impairment of respiration in persons with chronic obstructive pulmonary disease and sleep apnea. Alprazolam may exert a direct appetite stimulant effect and may cause weight gain. The benzodiazepines should be used with caution by persons with a history of substance abuse, cognitive disorders, renal disease, hepatic disease, porphyria, central nervous system (CNS) depression, or myasthenia gravis. Some data indicate that

benzodiazepines are teratogenic; therefore, their use during pregnancy is not advised. Moreover, the use of benzodiazepines in the third trimester can precipitate a withdrawal syndrome in newborns. The drugs are secreted in the breast milk in sufficient concentrations to affect newborns. Benzodiazepines may cause dyspnea, bradycardia, and drowsiness in nursing babies. Zolpidem and zaleplon are generally well tolerated. At zolpidem dosages of 10 mg per day and zaleplon dosages above 10 mg per day, a small number of persons will experience dizziness, drowsiness, dyspepsia, or diarrhea. Zolpidem and zaleplon are secreted in breast milk and are therefore contraindicated for use by nursing mothers. The dosage of zolpidem and zaleplon should be reduced in elderly persons and persons with hepatic impairment. In rare cases, zolpidem may cause hallucinations and behavioral changes. The coadministration of zolpidem and SSRIs may extend the duration of hallucinations in susceptible patients. Eszopiclone exhibits a dose–response relationship in elderly adults for the side effects of pain, dry mouth, and unpleasant taste. Tolerance, Dependence, and Withdrawal When benzodiazepines are used for short periods (1 to 2 weeks) in moderate dosages, they usually cause no significant tolerance, dependence, or withdrawal effects. The short-acting benzodiazepines (e.g., triazolam) may be an exception to this rule because some persons have reported increased anxiety the day after taking a single dose of the drug and then stopping its use. Some persons also report a tolerance for the anxiolytic effects of benzodiazepines and require increased doses to maintain the clinical remission of symptoms. The appearance of a withdrawal syndrome, also called a discontinuation syndrome, depends on the length of time the person has been taking a benzodiazepine, the dosage the person has been taking, the rate at which the drug is tapered, and the half-life of the compound. Benzodiazepine withdrawal syndrome consists of anxiety, nervousness, diaphoresis, restlessness, irritability, fatigue, lightheadedness, tremor, insomnia, and weakness (Table 29.9-2). Abrupt discontinuation of benzodiazepines, particularly those with short half-lives, is associated with severe withdrawal symptoms, which may include depression, paranoia, delirium, and seizures. These severe symptoms are more likely to occur if flumazenil is used for rapid reversal of the benzodiazepine receptor agonist effects. Some features of the syndrome may occur in as many as 90 percent of persons treated with the drugs. The development of a severe withdrawal syndrome is seen only

in persons who have taken high dosages for long periods. The appearance of the syndrome may be delayed for 1 or 2 weeks in persons who had been taking benzodiazepines with long half-lives. Alprazolam seems to be particularly associated with an immediate and severe withdrawal syndrome and should be tapered gradually. Table 29.9-2 Signs and Symptoms of Benzodiazepine Withdrawal When the medication is to be discontinued, the drug must be tapered slowly (25 percent a week); otherwise, recurrence or rebound of symptoms is likely. Monitoring of any withdrawal symptoms (possibly with a standardized rating scale) and psychological support of the person are helpful in the successful accomplishment of benzodiazepine discontinuation. Concurrent use of carbamazepine (Tegretol) during benzodiazepine discontinuation has been reported to permit a more rapid and better tolerated withdrawal than does a gradual taper alone. The dosage range of carbamazepine used to facilitate withdrawal is 400 to 500 mg a day. Some clinicians report particular difficulty in tapering and discontinuing alprazolam, especially in persons who have been receiving high dosages for long periods. There have been reports of successful discontinuation of alprazolam by switching to clonazepam, which is then gradually withdrawn. Zolpidem and zaleplon can produce a mild withdrawal syndrome lasting 1 day after prolonged use at higher therapeutic dosages. Rarely, a person taking zolpidem has selftitrated up the daily dosage to 30 to 40 mg a day. Abrupt discontinuation of such a high dosage of zolpidem may cause

withdrawal symptoms for 4 or more days. Tolerance does not develop to the sedative effects of zolpidem and zaleplon. DRUG INTERACTIONS The most common and potentially serious benzodiazepine receptor agonist interaction is excessive sedation and respiratory depression occurring when benzodiazepines, zolpidem, or zaleplon are administered concomitantly with other CNS depressants, such as alcohol, barbiturates, tricyclic and tetracyclic drugs, dopamine receptor antagonists, opioids, and antihistamines. Ataxia and dysarthria may be likely to occur when lithium, antipsychotics, and clonazepam are combined. The combination of benzodiazepines and clozapine (Clozaril) has been reported to cause delirium and should be avoided. Cimetidine (Tagamet), disulfiram (Antabuse), isoniazid, estrogen, and oral contraceptives increase the plasma concentration of diazepam, chlordiazepoxide, clorazepate, and flurazepam. Cimetidine increases the plasma concentrations of zaleplon. However, antacids may reduce the GI absorption of benzodiazepines. The

plasma concentrations of triazolam and alprazolam are increased to potentially toxic concentrations by nefazodone (Serzone) and fluvoxamine (Luvox). The manufacturer of nefazodone recommends that the dosage of triazolam be lowered by 75 percent and the dosage of alprazolam be lowered by 50 percent when given concomitantly with nefazodone. Over-the-counter preparations of kava plant, advertised as a “natural tranquilizer,” can potentiate the action of benzodiazepine receptor agonists through synergistic overactivation of GABA receptors. Carbamazepine can lower the plasma concentration of alprazolam. Antacids and food may decrease the plasma concentrations of benzodiazepines, and smoking may increase the metabolism of benzodiazepines. Rifampin (Rifadin), phenytoin (Dilantin), carbamazepine, and phenobarbital (Solfoton, Luminal) significantly increase the metabolism of zaleplon. The benzodiazepines may increase the plasma concentrations of phenytoin and digoxin (Lanoxin). The SSRIs may prolong and exacerbate the severity of zolpidem-induced hallucinations. Deaths have been reported when parental lorazepam is given with parental olanzapine. The CYP3A4 and CYP2E1 enzymes are involved in the metabolism of eszopiclone. Eszopiclone did not show any inhibitory potential on CYP450 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 in cryopreserved human hepatocytes. Coadministration of 3 mg of eszopiclone to subjects receiving 400 mg of ketoconazole, a potent inhibitor of CYP3A4, resulted in a 2.2-fold increase in exposure to eszopiclone. LABORATORY INTERFERENCES No known laboratory interferences are associated with the use of the benzodiazepines, zolpidem, and zaleplon. DOSAGE AND CLINICAL GUIDELINES The clinical decision to treat an anxious person with a benzodiazepine should be carefully considered. Medical causes of anxiety (e.g., thyroid dysfunction, caffeinism, and prescription medications) should be ruled out. Benzodiazepine use should be started at a low dosage, and the person should be instructed regarding the drug’s sedative properties and abuse potential. An estimated length of therapy should be decided at the beginning of therapy, and the need for continued therapy should be reevaluated at least monthly because of the problems associated with long-term use. However, certain persons with anxiety disorders are unresponsive to treatments other than benzodiazepines in long-term use. Benzodiazepines are available in a wide range of formulations. Clonazepam is available in a wafer formulation that facilitates its use in patients who have trouble swallowing pills. Alprazolam is available in an extended-release form, which reduces the frequency of dosing. Some benzodiazepines are more potent than others in that one compound requires a relatively smaller dosage than another compound to achieve the same effect. For example, clonazepam requires 0.25 mg to achieve the same effect as 5 mg of diazepam; thus, clonazepam is considered a high-potency benzodiazepine.

Revision #1
Created 2026-01-04 19:51:43 UTC by Omar Ayman
Updated 2026-01-04 19:51:43 UTC by Omar Ayman