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20.8 Sedative-, Hypnotic-, or Anxiolytic-Related Disorders

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20.8 Sedative-, Hypnotic-, or Anxiolytic-Related Disorders The drugs discussed in this section are referred to as anxiolytic or sedative-hypnotic drugs. Their sedative or calming effects are on a continuum with their hypnotic or sleepinducing effects. In addition to their psychiatric indications, these drugs are also used as antiepileptics, muscle relaxants, anesthetics, and anesthetic adjuvants. Alcohol and all drugs of this class are cross-tolerant, and their effects are additive. Physical and psychological dependence develops to these drugs, and all are associated with withdrawal symptoms. In the practice of psychiatry and addiction medicine, the drug class that is most important clinically is the benzodiazepines. The three major groups of drugs associated with this class of substance-related disorders are benzodiazepines, barbiturates, and barbiturate-like substances. Each group is discussed below.

BENZODIAZEPINES Many benzodiazepines, differing primarily in their half-lives, are available in the United States. Examples of benzodiazepines are diazepam, flurazepam (Dalmane), oxazepam (Serax), and chlordiazepoxide (Librium). Benzodiazepines are used primarily as anxiolytics, hypnotics, antiepileptics, and anesthetics, as well as for alcohol withdrawal. After their introduction in the United States in the 1960s, benzodiazepines rapidly became the most prescribed drugs; about 15 percent of all persons in the United States have had a benzodiazepine prescribed by a physician. Increasing awareness of the risks for dependence on benzodiazepines and increased regulatory requirements, however, have decreased the number of benzodiazepine prescriptions. The Drug Enforcement Agency (DEA) classifies all benzodiazepines as Schedule IV controlled substances. Flunitrazepam (Rohypnol), a

benzodiazepine used in Mexico, South America, and Europe but not available in the United States, has become a drug of abuse. When taken with alcohol, it has been associated with promiscuous sexual behavior and rape. It is illegal to bring flunitrazepam into the United States. Although misused in the United States, it remains a standard anxiolytic in many countries. Non-benzodiazepine sedatives such as zolpidem (Ambien) zaleplon (Sonata), and

eszopiclone (Lunesta)—the so called Z drugs—have clinical effects similar to the benzodiazepines and are also subject to misuse and dependence. **BARBITURATES** Before the introduction of benzodiazepines, barbiturates were frequently prescribed, but because of their high abuse potential, their use is much rarer today. Secobarbital (popularly known as “reds,” “red devils,” “seggies,” and “downers”), pentobarbital (Nembutal) (known as “yellow jackets,” “yellows,” and “nembies”), and a secobarbital- amobarbital combination (known as “reds and blues,” “rainbows,” “double-trouble,” and “tooies”) are easily available on the street from drug dealers. Pentobarbital, secobarbital, and amobarbital (Amytal) are now under the same federal legal controls as morphine. The first barbiturate, barbitol (Veronal), was introduced in the United States in 1903. Barbitol and phenobarbital (Solfoton, Luminal), which was introduced shortly thereafter, are long-acting drugs with half-lives of 12 to 24 hours. Amobarbital is an intermediate-acting barbiturate with a half-life of 6 to 12 hours. Pentobarbital and secobarbital are short-acting barbiturates with half-lives of 3 to 6 hours. Although barbiturates are useful and effective sedatives, they are highly lethal with only ten times the normal dose producing coma and death. **BARBITURATE-LIKE SUBSTANCES** The most commonly abused barbiturate-like substance is methaqualone, which is no longer manufactured in the United States. It is often used by young persons who believe that the substance heightens the pleasure of sexual activity. Abusers of methaqualone commonly take one or two standard tablets (usually 300 mg per tablet) to obtain the desired effects. The street names for methaqualone include “mandrakes” (from the United Kingdom preparation Mandrax) and “soapers” (from the brand name Sopor). “Luding out” (from the brand name Quaalude) means getting high on methaqualone, which is often combined with excessive alcohol intake. Other barbiturate-like substances include meprobamate (Equanil), a carbamate derivative that has weak efficacy as an antianxiety agent but has muscle-relaxant effects and is used for that purpose; chloral hydrate, a hypnotic that is highly toxic to the gastrointestinal (GI) system and, when combined with alcohol, is known as a “mickey finn”; and ethchlorvynol, a rapidly acting sedative agent with anticonvulsant and muscle-relaxant properties. All are subject to abuse. **EPIDEMIOLOGY** About 6 percent of individuals have used either sedatives or tranquilizers illicitly, including 0.3 percent who reported illicit use of sedatives in the prior year and 0.1 percent who reported use of sedatives in the prior month. The age group with the highest lifetime prevalence of sedative (3 percent) or tranquilizer (6 percent) use was 26

to 34 years of age, and those aged 18 to 25 were most likely to have used sedatives or tranquilizers in the prior year. About one fourth to one third of all substance-related emergency room visits involve substances of this class. The patients have a female-to-male ratio of 3:1 and a white-to-black ratio of 2:1. Some persons use benzodiazepines alone, but persons who use cocaine often use benzodiazepines to reduce withdrawal symptoms, and opioid abusers use them to enhance the euphoric effects of opioids. Because they are easily obtained, benzodiazepines are also used by abusers of stimulants, hallucinogens, and phencyclidine (PCP) to help reduce the anxiety that can be caused by those substances. Whereas barbiturate abuse is common among mature adults who have long histories of abuse of these substances, benzodiazepines are abused

by a younger age group, usually those under 40 years of age. This group may have a slight male predominance and has a white-to-black ratio of about 2:1. Benzodiazepines are probably not abused as frequently as other substances for the purpose of getting “high,” or inducing a euphoric feeling. Rather, they are used when a person wishes to experience a general relaxed feeling.

NEUROPHARMACOLOGY The benzodiazepines, barbiturates, and barbiturate-like substances all have their primary effects on the γ -aminobutyric acid (GABA) type A (GABAA) receptor complex, which contains a chloride ion channel, a binding site for GABA, and a well-defined binding site for benzodiazepines. The barbiturates and barbiturate-like substances are also believed to bind somewhere on the GABAA receptor complex. When a benzodiazepine, barbiturate, or barbiturate-like substance does bind to the complex, the effect is to increase the affinity of the receptor for its endogenous neurotransmitter, GABA, and to increase the flow of chloride ions through the channel into the neuron. The influx of negatively charged chloride ions into the neuron is inhibitory, and hyperpolarizes the neuron relative to the extracellular space. Although all the substances in this class induce tolerance and physical dependence, the mechanisms behind these effects are best understood for the benzodiazepines. After long-term benzodiazepine use, the receptor effects caused by the agonist are attenuated. Specifically, GABA stimulation of the GABAA receptors results in less chloride influx than was caused by GABA stimulation before the benzodiazepine administration. This downregulation of receptor response is not caused by a decrease in receptor number or by decreased affinity of the receptor for GABA. The basis for the downregulation seems to be in the coupling between the GABA binding site and the activation of the chloride ion channel. This decreased efficiency in coupling may be regulated within the GABAA receptor complex itself or by other neuronal mechanisms.

DIAGNOSIS

Sedative, Hypnotic, or Anxiolytic Use Disorder Sedative, hypnotic, or anxiolytic use disorder is diagnosed according to the general criteria in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) for substance use disorder (see page 621).

Sedative, Hypnotic, or Anxiolytic Intoxication The intoxication syndromes induced by all these drugs are similar, and include incoordination, dysarthria, nystagmus, impaired memory, gait disturbance, and in severe cases stupor, coma, or death. The diagnosis of intoxication by one of this class of substances is best confirmed by obtaining a blood sample for substance screening.

Benzodiazepines. Benzodiazepine intoxication can be associated with behavioral disinhibition, potentially resulting in hostile or aggressive behavior in some persons. The effect is perhaps most common when benzodiazepines are taken in combination with alcohol. Benzodiazepine intoxication is associated with less euphoria than is intoxication by other drugs in this class. This characteristic is the basis for the lower abuse and dependence potential of benzodiazepines than of barbiturates.

Barbiturates and Barbiturate-like Substances. When barbiturates and barbiturate-like substances are taken in relatively low doses, the clinical syndrome of intoxication is indistinguishable from that associated with alcohol intoxication. The symptoms include sluggishness, incoordination, difficulty thinking, poor memory, slow speech and comprehension, faulty judgment, disinhibited sexual aggressive impulses, narrowed range of attention, emotional lability, and exaggerated basic personality traits. The sluggishness usually resolves after a few hours, but depending primarily on the half-life of the abused substance, impaired judgment, distorted mood, and impaired motor skills may remain for 12 to 24 hours. Other potential symptoms are hostility, argumentativeness, moroseness, and, occasionally, paranoid and suicidal ideation. The neurological effects include nystagmus, diplopia, strabismus, ataxic gait, positive Romberg’s sign, hypotonia, and decreased superficial reflexes.

Sedative, Hypnotic, or Anxiolytic Withdrawal Benzodiazepines. The severity of

the withdrawal syndrome associated with the benzodiazepines varies significantly depending on the average dose and the duration of use, but a mild withdrawal syndrome can follow even short-term use of relatively low doses of benzodiazepines. A significant withdrawal syndrome is likely to occur at cessation of dosages in the range of 40 mg a day for diazepam, for example, although 10 to 20 mg a day, taken for a month, can also result in a withdrawal syndrome when drug administration is stopped. The onset of withdrawal symptoms usually occurs 2 to 3 days after the cessation of use, but with long-acting drugs, such as diazepam, the latency before onset can be 5 or 6 days. The symptoms include anxiety, dysphoria, intolerance

for bright lights and loud noises, nausea, sweating, muscle twitching, and sometimes seizures (generally at dosages of 50 mg a day or more of diazepam). Table 20.8-1 lists the signs and symptoms of benzodiazepine withdrawal. Table 20.8-1 Signs and Symptoms of the Benzodiazepine Discontinuation Syndrome Barbiturates and Barbiturate-like Substances. The withdrawal syndrome for barbiturate and barbiturate-like substances ranges from mild symptoms (e.g., anxiety, weakness, sweating, and insomnia) to severe symptoms (e.g., seizures, delirium, cardiovascular collapse, and death). Persons who have been abusing phenobarbital in the range of 400 mg a day may experience mild withdrawal symptoms; those who have been abusing the substance in the range of 800 mg a day can experience orthostatic hypotension, weakness, tremor, and severe anxiety. About 75 percent of these persons have withdrawal-related seizures. Users of dosages higher than 800 mg a day may experience anorexia, delirium, hallucinations, and repeated seizures. Most symptoms appear in the first 3 days of abstinence, and seizures generally occur on the second or third day, when the symptoms are worst. If seizures do occur, they always precede the development of delirium. The symptoms rarely occur more than a week after stopping the substance. A psychotic disorder, if it develops, starts on the third to eighth day. The various associated symptoms generally run their course within 2 to 3 days, but can last as long as 2 weeks. The first episode of the syndrome usually occurs after 5 to 15 years of heavy substance use. Other Sedative-, Hypnotic-, or Anxiolytic-Induced Disorders Delirium. Delirium that is indistinguishable from delirium tremens associated with alcohol withdrawal is seen more commonly with barbiturate withdrawal than with benzodiazepine withdrawal. Delirium associated with intoxication can be seen with either barbiturates or benzodiazepines if the dosages are sufficiently high. Persisting Dementia. The existence of the sedative/hypnotic-induced persisting

dementia is controversial, because uncertainty exists whether a persisting dementia is caused by the substance use itself or by associated features of the substance use. Persisting Amnestic Disorder. Amnestic disorders associated with sedatives and hypnotics may be underdiagnosed. One exception is the increased number of reports of amnestic episodes associated with short-term use of benzodiazepines with short half-lives (e.g., triazolam [Halcion]). Psychotic Disorders. The psychotic symptoms of barbiturate withdrawal can be indistinguishable from those of alcohol-associated delirium tremens. Agitation, delusions, and hallucinations are usually visual, but sometimes tactile or auditory features develop after about 1 week of abstinence. Psychotic symptoms associated with intoxication or withdrawal are more common with barbiturates than with benzodiazepines. They are diagnosed in DSM-5 as sedative, hypnotic, or anxiolytic withdrawal with perceptual disturbances when reality testing is intact (the individual is aware the drug is causing the psychotic symptoms). If reality testing is not intact (the individual believes the hallucinations are real), a diagnosis of substance/medication-induced psychotic disorder is more appropriate. Clinicians can further specify whether delusions or hallucinations are the predominant symptoms,

including the type (e.g. auditory, visual, or tactile). Other Disorders. Sedative and hypnotic use has also been associated with mood disorders, anxiety disorders, sleep disorders, and sexual dysfunctions. Unspecified Sedative-, Hypnotic-, or Anxiolytic-Related Disorder. When none of the previously discussed diagnostic categories is appropriate for a person with sedative-, hypnotic-, or anxiolytic-related disorder, and he or she does not meet the diagnostic criteria for any general substance-related disorder (see page 621), the appropriate diagnosis is unspecified sedative-, hypnotic-, or anxiolytic-related disorder. CLINICAL FEATURES Patterns of Abuse Oral Use. Sedatives and hypnotics can all be taken orally, either occasionally to achieve a time-limited specific effect or regularly to obtain a constant, usually mild, intoxication state. The occasional use pattern is associated with young persons who take the substance to achieve specific effects—relaxation for an evening, intensification of sexual activities, and a short-lived period of mild euphoria. The user's personality and expectations about the substance's effects and the setting in which the substance is taken also affect the substance-induced experience. The regular use pattern is associated with middle-aged, middle-class persons who usually obtain the substance from a family physician as a prescription for insomnia or anxiety. Abusers of this type may have prescriptions from several physicians, and the pattern of abuse may go undetected until

obvious signs of abuse or dependence are noticed by the person's family, coworkers, or physicians. Intravenous Use. A severe form of abuse involves the intravenous use of this class of substances. The users are mainly young adults who are intimately involved with illegal substances. Intravenous barbiturate use is associated with a pleasant, warm, drowsy feeling, and users may be inclined to use barbiturates more than opioids because barbiturates are less costly. The physical dangers of injection include transmission of the human immunodeficiency virus (HIV), cellulitis, vascular complications from accidental injection into an artery, infections, and allergic reactions to contaminants. Intravenous use is associated with rapid and profound tolerance and dependence and a severe withdrawal syndrome. Overdose Benzodiazepines. In contrast to the barbiturates and the barbiturate-like substances, the benzodiazepines have a large margin of safety when taken in overdoses, a feature that has contributed significantly to their rapid acceptance. The ratio of lethal dose to effective dose is about 200 to 1 or higher, because of the minimal degree of respiratory depression associated with the benzodiazepines. A list of equivalent therapeutic doses of benzodiazepines is given in Table 20.8-2. Even when grossly excessive amounts (more than 2 g) are taken in suicide attempts, the symptoms include only drowsiness, lethargy, ataxia, some confusion, and mild depression of the user's vital signs. A much more serious condition prevails when benzodiazepines are taken in overdose in combination with other sedative-hypnotic substances, such as alcohol. In such cases, small doses of benzodiazepines can cause death. The availability of flumazenil (Romazicon), a specific benzodiazepine antagonist, has reduced the lethality of the benzodiazepines. Flumazenil can be used in emergency rooms to reverse the effects of the benzodiazepines. Table 20.8-2 Approximate Therapeutic Equivalent Doses of Benzodiazepines

Barbiturates. Barbiturates are lethal when taken in overdose because they induce respiratory depression. In addition to intentional suicide attempts, accidental or unintentional overdoses are common. Barbiturates in home medicine cabinets are a common cause of fatal drug overdoses in children. As with benzodiazepines, the lethal effects of the barbiturates are additive to those of other sedatives or hypnotics, including alcohol and benzodiazepines. Barbiturate overdose is characterized by the induction of coma, respiratory arrest, cardiovascular failure, and death. The

lethal dose varies with the route of administration and the degree of tolerance for the substance after a history of long-term abuse. For the most commonly abused barbiturates, the ratio of lethal dose to effective dose ranges between 3:1 and 30:1. Dependent users often take an average daily dose of 1.5 g of a short-acting barbiturate, and some have been reported to take as much as 2.5 g a day for months. The lethal dose is not much greater for the long-term abuser than for the neophyte. Tolerance develops quickly, to the point at which withdrawal in a hospital becomes necessary to prevent accidental death from overdose. Barbiturate-like Substances. The barbiturate-like substances vary in their lethality and are usually intermediate between the relative safety of the benzodiazepines and the high lethality of the barbiturates. An overdose of methaqualone, for example, can result in restlessness, delirium, hypertonia, muscle spasms, convulsions, and, in very high doses, death. Unlike barbiturates, methaqualone rarely causes severe cardiovascular or respiratory depression, and most fatalities result from combining methaqualone with alcohol.

TREATMENT AND REHABILITATION

Withdrawal Benzodiazepines. Because some benzodiazepines are eliminated from the body slowly, symptoms of withdrawal can continue to develop for several weeks. To prevent seizures and other withdrawal symptoms, clinicians should gradually reduce the dosage. Several reports indicate that carbamazepine (Tegretol) may be useful in the treatment of benzodiazepine withdrawal. Table 20.8-3 lists guidelines for treating benzodiazepine withdrawal.

Table 20.8-3 Guidelines for Treatment of Benzodiazepine Withdrawal

Barbiturates. To avoid sudden death during barbiturate withdrawal, clinicians must follow conservative clinical guidelines. Clinicians should not give barbiturates to a comatose or grossly intoxicated patient. A clinician should attempt to determine a patient's usual daily dose of barbiturates and then verify the dosage clinically. For example, a clinician can give a test dose of 200 mg of pentobarbital every hour until a mild intoxication occurs but withdrawal symptoms are absent (Table 20.8-4). The clinician can then taper the total daily dose at a rate of about 10 percent of the total daily dose. Once the correct dosage is determined, a long-acting barbiturate can be used for the detoxification period. During this process, the patient may begin to experience withdrawal symptoms, in which case the clinician should halve the daily decrement. Table 20.8-4

Pentobarbital Test Dose Procedure for Barbiturate Withdrawal

In the withdrawal procedure, phenobarbital can be substituted for the more commonly abused short-acting barbiturates. The effects of phenobarbital last longer, and because barbiturate blood levels fluctuate less, phenobarbital does not cause observable toxic signs or a serious overdose. An adequate dose is 30 mg of phenobarbital for every 100 mg of the short-acting substance. The user should be maintained for at least 2 days at that level before the dose is reduced further. The regimen is analogous to the substitution of methadone for heroin. After withdrawal is complete, the patient must overcome the desire to start taking the substance again. Although substitution of nonbarbiturate sedatives or hypnotics for barbiturates has been suggested as a preventive therapeutic measure, this often results in replacing one substance dependence with another. If a user is to remain substance free, follow-up treatment, usually with psychiatric help and community support, is vital. Otherwise, a patient will almost certainly return to barbiturates or a substance with similar hazards.

Overdose The treatment of overdose of this class of substances involves gastric lavage, activated charcoal, and careful monitoring of vital signs and central nervous system (CNS) activity. Patients who overdose and come to medical attention while awake should be kept from slipping into unconsciousness. Vomiting should be induced, and activated charcoal should be administered to delay gastric absorption. If a patient is comatose, the clinician must establish an

intravenous fluid line, monitor the patient's vital signs, insert an endotracheal tube to maintain a patent airway, and provide mechanical ventilation, if necessary. Hospitalization of a comatose patient in an intensive care unit is usually required during the early stages of recovery from such overdoses. EXPERT OPINION The International Study of Expert Judgment on Therapeutic Use of Benzodiazepines and Other Psychotherapeutic Medications was designed to gather systematic data on the opinions of leading clinicians concerning the benefits and risks of benzodiazepines and alternative treatments of anxiety. This survey study addressed the relative risks of

benzodiazepines compared with other agents and comparative risks within the class. The expert panel assessed risk based on a drug's potential to produce tolerance, rebound symptoms, a withdrawal syndrome, and ease of discontinuation. Two thirds of the expert panel reported that long-term use of benzodiazepines for the treatment of anxiety disorders does not pose a high risk of dependence and abuse. Although agreement was that the pharmacological properties of the medication may be the most important contributor to development of withdrawal symptoms, no consensus existed on whether benzodiazepines with shorter and longer half-lives have similar dependence potential. A clear consensus was that the differences in withdrawal symptoms are clinically negligible with gradual dose tapering. Because differences in abuse liability among the various benzodiazepines have not been demonstrated in humans, and because the benefits of benzodiazepine treatment clearly outweigh the risks, most physicians on the expert panel opposed increased restrictions on benzodiazepine prescribing. Despite the expert opinion stated earlier, state and federal agencies have attempted to restrict the distribution of benzodiazepines by requiring special reporting forms. For example, in New York State, through the use of a newly enacted prescription monitoring program (PMP) called I-STOP, effective since August 27, 2013, doctors cannot write a prescription for a benzodiazepine unless they first search a computerized database that contains the names of all persons in the state who were ever prescribed benzodiazepines and other controlled substances. Governments have taken these and other such measures in an attempt to stem the tide of abuse. However most abuse results from the illicit manufacture, sale, and diversion of substances, particularly to cocaine and opioid addicts, not from physicians' prescriptions or legitimate pharmaceutical companies. These programs do not stem the tide of illegal use of valuable medications and interfere in the practice of medicine and in the confidential relationship between doctor and patient. REFERENCES Auta J, Kadriu B, Giusti P, Costa E, Guidotti A. Anticonvulsant, anxiolytic, and non-sedating actions of imidazenil and other imidazo-benzodiazepine carboxamide derivatives. *Pharmacol Biochem Behav.* 2010;95(4):383. Barceloux DG. Barbiturates (Amobarbital, Butalbital, Pentobarbital, Secobarbital). In: *Medical Toxicology of Drugs Abuse: Synthesized Chemicals and Psychoactive Plants*. Hoboken, NJ: John Wiley & Sons, Inc.; 2012:467. Barnett SR, Riddle MA. Anxiolytics and sedative/hypnotics: Benzodiazepines, buspirone, and other. In: Martin A, Scahill L, Kratochvil C, eds. *Pediatric Psychopharmacology: Principles and Practice*. New York: Oxford University Press, Inc.; 2011:338. Ciraulo DA, Sarid-Segal O. Sedative-, hypnotic-, or anxiolytic-related disorders. In: Sadock BJ, Sadock VA, Ruiz P, eds. *Kaplan & Sadock's Comprehensive Textbook of Psychiatry*. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2009:1397. Hall MT, Howard MO, McCabe SE. Subtypes of adolescent sedative/anxiolytic misusers: A latent profile analysis. *Addict Behav.* 2010;35(10):882. Hoque R, Chesson Jr. AL. Zolpidem-induced sleepwalking, sleep related eating disorder, and sleep-driving: Fluorine-18flourodeoxyglucose positron emission tomography analysis, and a literature review of other unexpected clinical effects of zolpidem. *J Clin Sleep Med.* 2009;5(5):471. Houston CM, McGee TP, MacKenzie G, Troyano-Cuturi K, Rodriguez PM, Kutsarova E, Diamanti E, Hosie AM, Frank NP, Brickley SG. Are extrasynaptic GABAA receptors important targets for sedative/hypnotic drugs? *J*

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