PART I

Extent of Use and Pharmacological Considerations

COPYRIGHTED MATERIAL

CHAPTER 1

The Psychodepressants

INTRODUCTION

The first major group of the drugs and substances of abuse that is discussed in this reference text is the psychodepressants. (See Figure 1.1.) These drugs and substances of abuse can be divided into three major subgroups: (1) opiate analgesics, (2) sedative-hypnotics, and (3) volatile solvents and inhalants. (See Table 1.1.) This chapter presents an overview of each major subgroup of the psychodepressants with attention to the prevalence and characteristics of their use among children and adolescents across North America. It also presents an overview of their general pharmacology—their proposed mechanisms of psychodepressant action and common toxicities, including their propensity for physical and psychological dependence and for overdosage.

Before beginning this overview, it is important to note that much of the information presented in this chapter in regard to demographics and use statistics, as well as that presented in Chapter 2, *The Psychostimulants*, and Chapter 3, *The Psychodelics*, is based on government-supported or sponsored national surveys. While generally constructed to be valid and reliable measurement instruments, these surveys suffer from some noted limitations that may affect the generalizability of their related findings and also bias readers toward trends of use that are significantly lower than they actually are. As such, they may detrimentally influence decisions regarding the need for prevention and treatment programs aimed specifically at children and adolescents. These noted limitations include nonrepresentative, nonstratified sampling flaws that rely very heavily—and in some cases exclusively—on: (1) data obtained from convenience samples of children and adolescents who are attending school and ignore other groups of children and adolescents; and (2) methodological flaws, such as sampling and collecting data solely by telephone contact surveys.

Even when the survey methods are inclusive in terms of sampling techniques, they may suffer from other inherent limitations that require explicit identification and discussion. For example, limitations in sampling methods are relatively common as most surveys generally do not include data from children and adolescents who are usually identified as being at particular high risk for using the drugs and substances of abuse. These children and adolescents include

1. Homeless, runaways, or those living on the streets
2. Absent or truant students or school drop-outs who are not in attendance at the school when the survey is administered
3. Those incarcerated in youth correctional facilities
4. Those living in homes that do not have a land-line telephone[1]
5. Those living on American Indian/Canadian Aboriginal reservations and reserves, respectively

[1] The absence of a land-line home telephone is particularly high among low-income households, particularly those below the poverty level and those that are transient, or otherwise mobile—groups that are not mutually exclusive. For example, American Indian and Aboriginal children of the United States and Canada, respectively, who are living on reservations and reserves have a significantly higher incidence of absenteeism and school drop-out rates in comparison to the other children and adolescents usually sampled for national surveys (Sarche & Spicer, 2008).

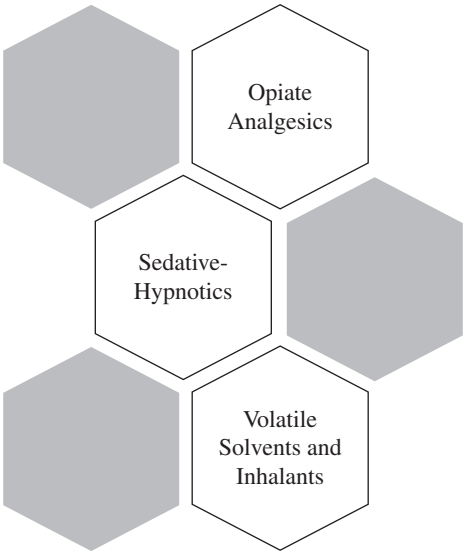

Figure 1.1 The Psychodepressants

Thus, the findings of the national surveys and reports generally tend to underestimate the use of the drugs and substances of abuse by North American children and adolescents. In order to address this limitation of these widely cited national government-supported and sponsored surveys and reports, we have included, whenever possible, the findings of studies and reports that specifically address the generally higher-risk subpopulations of children and adolescents that the large, national surveys often miss or neglect.

OPIATE ANALGESICS

The opiate analgesics comprise a group of natural (e.g., morphine; codeine), semisynthetic (e.g., heroin; hydrocodone [Lortab®]; oxycodone [OxyContin®]), and synthetic (e.g., meperidine [Demerol®]; pentazocine [Talwin®]) derivatives of the opium resin that is obtained from the plant *Papaver somniferum*—the "poppy that causes sleep." One to three weeks after flowering, the opium resin is harvested from the unripe seed pod and dried.[2] Classified as an herb, *Papaver somniferum* is indigenous to southeastern Europe and western Asia where it has been widely cultivated for millennia. It also has been introduced to other countries throughout the world by travelers and immigrants. However, climatic conditions similar to those of southeastern Europe and western Asia are required for its successful cultivation.

Prevalence and Characteristics of Opiate Analgesic Use Among North American Children and Adolescents

During the 1990s, the use of prescription opiate analgesics (e.g., hydrocodone [Hycodan®]) rapidly increased among adolescents. In fact, the use of hydrocodone became epidemic in California, where it also was commonly used by movie stars and other celebrities. Traditionally, youth were thought to be at low risk for opiate analgesic use. However, it was during this time that changes in the availability of opiate analgesics and their methods of use (i.e., intranasal insufflation, or snorting) significantly increased their popularity among high school students, particularly in the United States (Pagliaro & Pagliaro, 2009). Today, hydrocodone actively competes with the other opiate analgesics[3] for first place.

For example, over 10% of U.S. high school seniors who were surveyed between 2002 and 2006 reported nonmedical use of an opiate analgesic. The majority of these

[2] The dried resin of the opium poppy contains opium and the isoquinoline alkaloids codeine, morphine, noscapine, papaverine, and thebaine. Semisynthetic opiate analgesics are derived from natural products (e.g., heroin is chemically derived from morphine, and hydrocodone [Lortab®] and oxycodone [OxyContin®] are derived from codeine and thebaine). Other opiate analgesics, such as meperidine (Demerol®) and pentazocine (Talwin®), are totally chemically synthesized.

[3] Other prescription opiate analgesics that also are commonly used by children and adolescents, listed in descending order of use, are oxycodone (OxyContin®), methadone (Dolophine®), and fentanyl (Duragesic®) (C. P. O'Brien, 2008; Pagliaro & Pagliaro, 2009).

TABLE 1.1 The Psychodepressants

Subclassification, Category, and Generic Name	Brand/Trade Names®[a]	Common Street Names[b]
Opiate Analgesics: Used for dreams (pipe dreams); euphoria; pain relief; prevention/self-management of the opiate analgesic withdrawal syndrome; warm rush; and a sleepy state (on the nod)		
Pure Agonists, Natural		
Opium		Poppy
Codeine[c]	Codeine Contin®, Ratio-Codeine®	Codies, cough syrup, school boy, T3
Morphine	M.O.S.®, MS Contin®	Drug store, good ole M, hospital heroin, morph, MS
Pure Agonists, Synthetic/Semisynthetic		
Fentanyl	Actiq®, Duragesic®	Fen, murder 8, perc-O-pop
Heroin		Black tar, brown, capital H, charley, horse, junk, shit
Hydrocodone[d]	Dicodid®, Hycodan®	Hyke, tuss, vikes
Hydromorphone	Dilaudid®	Delaud, dillies, hillbilly heroin
Levorphanol	Levo-Dromoran®	
Meperidine	Demerol®	Dems, mep
Methadone	Dolophine®	Adolph, dollies, done, wafer
Oxycodone	OxyContin®	Cotton, oxycotton, poor man's heroin, percs
Oxymorphone	Numorphan®	
Propoxyphene[e]	Darvon®	Footballs, yellows
Mixed Agonist/Antagonists, Synthetis		
Buprenorphine	Buprenex®	Tems
Butorphanol	Stadol®	
Nalbuphine	Nubain®	Nubian
Pentazocine	Talwin®	Big T, Ts
Sedative-Hypnotics: Used for an alcohol-like disinhibitory euphoria or high; anxiety/stress reduction; prevention/self-management of the related alcohol, barbiturate, benzodiazepine, or miscellaneous sedative-hypnotic withdrawal syndromes; relaxation; tranquility. Also, particularly some of the benzodiazepines and miscellaneous sedative-hypnotics, are purposely administered to others without their knowledge in the context of perpetration of a drug facilitated crime (e.g., robbery; sexual assault, including date-rape)		
Barbiturates		
Amobarbital	Amytal®	
Butalbital[f]		
Butabarbital	Butisol®	
Pentobarbital	Nembutal®	Abbots, nembs, yellows
Phenobarbital	Luminal®	Pheno, sleepers
Secobarbital	Seconal®	Lillys, pinks, reds
Thiopental	Pentothal®	
Benzodiazepines		
Alprazolam	Xanax®	Coffins, footballs, xannies
Bromazepam	Lectopam®	
Chlordiazepoxide	Librium®	Libs, libbies
Clonazepam	Clonopin®, Rivotril®	Clo, klonnies
Clorazepate	Tranxene®	
Diazepam	Valium®	Blues, mother's little helper, Vs

(*Continued*)

TABLE 1.1 The Psychodepressants (Continued)

Subclassification, Category and Generic Name	Brand/Trade Names®[a]	Common Street Names[b]
Estazolam	ProSom®	
Flunitrazepam[g]	Rohypnol®	Forget-me pill, La Roche, Mexican Valium, papas, roofies
Flurazepam	Dalmane®	
Lorazepam	Ativan®	Zzz
Midazolam	Versed®	
Nitrazepam	Mogadon®	Dons, moggies
Oxazepam	Serax®	
Temazepam	Restoril®	Green devils, temmies
Triazolam	Halcion®	Halcyon, halcyon daze
Z-Drugs		
Eszopiclone	Lunesta®	
Zaleplon	Starnoc®, Sonata®	
Zopiclone	Imovane®	
Zopidem	Ambien®, Lunata®	Nappien, tic-tacs
Miscellaneous Sedative-Hypnotics		
Alcohol[h]	Beers, wines, and distilled spirits are available by various brand names	Booze, drink, brew, liquid courage, moonshine, suds, vino
Chloral Hydrate	Noctec®[i]	Chlorals, green frogs, mickeys
Gamma-hydroxybutyrate	Xyrem®	Easy lay, Georgia home boy, GHB, grievous bodily harm
Paraldehyde	Paral®[i]	
Volatile Solvents and Inhalants[j]: Used for alcohol-like disinhibitory euphoria or high		
Volatile Solvents		
Acetone		Sniff
Benzene		
Butane		Gas
Gasoline		Gas, petro, petrol
Glue		Gluey
Methanol		
Toluene		
Trichloroethane		
Trichloroethylene		
Inhalants		
Chloroform		
Ether		
Nitrous Oxide		Hippie crack, laughing gas, nitrous, whippets
Propane		

[a]Examples of common brand/trade names are provided, when available.
[b]Partial list. Examples of three to five of the most common street names are provided, when available. See Pagliaro and Pagliaro (2009) for a comprehensive listing of the drugs and substances of abuse and their common street names.
[c]Usually available as one of the ingredients in a multi-ingredient product (e.g., Empirin® #4; Tylenol® #4).
[d]Usually available as one of the ingredients in a multi-ingredient product (e.g., Lortab®, Vicodin®).
[e]In December 2010, the FDA removed propoxyphene from licit production and use within the United States. This action followed a similar move in Europe and was in response to related risk for developing potentially serious, or even fatal, cardiac dysrhythmias associated with propoxyphene use (Gandey, 2010).
[f]Butalbital is available only in combination products (e.g., Fiorinal®).
[g]Although not legally produced in North America, flunitrazepam is widely available worldwide under the brand/trade name Rohypnol® It is commonly known and used as a date-rape drug.
[h]Available as beers, wines, and distilled spirits.
[i]Usually available by generic name.
[j]Partial list.

students reported using opiate analgesics to: (1) "feel good and get high," (2) "see what it's like," and (3) "have a good time with friends" (Anderson, 2009). A series of national studies surveyed adolescent use of the drugs and substances of abuse in the United States from 2002 through 2010. These studies found a similar incidence of approximately 13% for reported use of opiate analgesics "other than heroin" (e.g., hydrocodone [e.g., Vicodin®, a combination product] and oxycodone [OxyContin®]) (Johnston, O'Malley, Bachman et al., 2008, 2010b).[4] In regard to these same prescription opiate analgesics, the national study of U.S. adolescents conducted by the Partnership for a Drug-Free America (2006) found that: (1) a majority of adolescents (i.e., 62%) reported that opiate analgesics are easily obtained from parents' medicine cabinets; (2) almost a third of adolescents (32%) reported that opiate analgesics are readily available and easily purchased over the Internet; and (3) a significant percentage of adolescents (i.e., 37%) reported having friends who used opiate analgesics.

The largest group of opiate analgesic users among children and adolescents is street users—children and adolescents who are homeless, or runaways, and living on the street. Heroin is the primary drug of choice. Currently, approximately 40% of the heroin that reaches North America comes from the opium grown in Afghanistan, Burma, Iran, and Pakistan. Most of the opium is processed into heroin in these countries, with the remainder being processed in Italy, primarily in Sicily. Since the early 1990s, the bulk of the remaining heroin that reaches the streets of the United States (about 40%) comes from opium that is grown in the western hemisphere, primarily from the countries of Colombia and Mexico. Mexico alone supplies a significant and increasing proportion of heroin (about 30%) to the United States, primarily in the form of black tar heroin.

In their survey, Johnston, O'Malley, Bachman, et al. (2008) found that 1% of high school students reported having used heroin within the previous 12 months. The incidence of heroin use varies with fluctuations in availability and with continental descent or ethnicity. In this study and most others, North American adolescents of Hispanic descent report a significantly higher incidence of heroin use than do adolescents of other continental descents or ethnicities. For example, over 5% of high school students who were sampled in Arizona and New Mexico in 2007 reported having used heroin (M. P. O'Brien, 2008).[5] Approximately 1.5% of Americans 18 years of age or older reported having used heroin at least once in their lifetime (Heroin Use USA, 2010).[6] It is interesting to note that most adults who are regular, long-term heroin users report that they began their heroin use during late adolescence (i.e., around 16 years of age) (Pagliaro, Pagliaro, Thauberger, et al., 1993; Pagliaro & Pagliaro, *Clinical Patient Data Files*). In comparison, the Partnership for a Drug-Free America (2006), in its nationwide survey of over 7,000 adolescents, found that 5% of their sample reported having tried heroin and 16% reported having a close friend who had used heroin. An apparently related finding is that, since 1999, fewer

[4] In addition, approximately one-third of sampled high school students reported that it was either fairly easy or very easy to obtain these opiate analgesics.

[5] The reasons for the apparent significantly higher incidence of heroin use among North American adolescents of Hispanic descent, when compared to other adolescents, appears to be primarily related to the availability of, and preference for, black tar heroin from Mexico and multigenerational membership in Hispanic criminal youth gangs that are heavily involved in drug trafficking and related activities (Pagliaro & Pagliaro, 2009; Pagliaro & Pagliaro, *Clinical Patient Data Files*).

[6] This percentage is significantly higher (i.e., approximately 2.5%) for high school students (M. P. O'Brien, 2008). Similarly, M. P. O'Brien (2008), in an analysis of data from the Community Epidemiology Work Group of the National Institute of Drug Abuse, found that 2.3% of U.S. high school students reported lifetime heroin use. Johnston, O'Malley, Bachman, et al. (2010b) report similar percentages. However, their reported data are a little more difficult to quantify precisely because, although they present the reported lifetime prevalence of heroin use among 8th-, 10th-, and 12th-grade students, they present it as two sets of data—with a needle and without a needle; the composite statistic is 1.6%, 1.7%, and 2.5%, respectively. However, they do not report how many students may have used both methods of heroin use.

and fewer adolescents report that they view heroin as a dangerously addictive drug.

Currently, opium and heroin production is at an all-time high. Transshipped from Asian and Colombian sources to North America for distribution at specified geographical locations, heroin is readily available in both higher concentrations and higher purity than it was during the last 4 decades.[7] Its distribution and commerce in the United States and Canada is largely controlled by ethnically defined criminal gangs.[8] Much of the actual distribution and street-level sale of this heroin is accomplished by criminal youth gangs, whose members are both more desperate and desirous of the money to be made and less likely, if arrested, to serve any significant jail time because of their ages (Pagliaro & Pagliaro, *Clinical Patient Data Files*). The ready availability of this high-grade heroin, at relatively low prices, has contributed significantly to an increase in intranasal use (i.e., snorting), particularly among adolescents living in suburban areas.[9]

While the norm for the 1950s, 1960s, 1970s, and 1980s was the intravenous injection of heroin, only approximately 40% of heroin users in North America, men and women alike, now intravenously inject heroin (Pagliaro & Pagliaro, 2009). A re-emerging trend from the 1970s is the more casual, nonintravenous, nondaily, social use of heroin. In the 1970s, this pattern of use was often referred to as chipping (Hanson, 1985). Chipping is a technique in which heroin, rather than being intravenously injected, or mainlined, is subcutaneously injected. However, these more casual heroin users now generally completely avoid needles and syringes by either chasing the dragon (i.e., orally inhaling heroin vapor through a glass tube, or rolled currency, that is held in the mouth) or snorting (i.e., intranasally insufflating the heroin in its powder form). They also may use intranasal instillation, or instill what is known on the street as heroin nose drops[10] into the nostrils in much the same way as they would common nose drops.

Most adolescent heroin users who do not initially inject heroin intravenously but continue to use it usually begin intravenous injection by the time they are young adults. This change in method of use is generally related to both the desired actions associated with heroin use and economics. For example, while desired psychodepressant actions can be achieved with intranasal use, this requires the use of heroin that is higher in purity and concentration and, consequently, more expensive than heroin that can be intravenously injected. Both the desired psychodepressant actions of heroin and a very pleasant rush[11] can be achieved with the intravenous injection of lower-quality, and less expensive, heroin.

---

[7] The average concentration of injectable forms of heroin, at street level, is approximately 27% in comparison to approximately 7% during the 1980s. The purity of street-level Colombian heroin typically ranges from 25% to 80% pure, while Mexican black tar heroin typically ranges from 14% to 60% pure with the highest purity found in cities along the U.S.–Mexican border (e.g., El Paso, Texas) (Pagliaro & Pagliaro, 2009).

[8] For example, the importation and distribution of heroin in Vancouver, Canada, is controlled mostly by Chinese gangs; a significant amount of the retail-level heroin distribution and sales along the northeastern coast is controlled by Dominican gangs, based primarily in New York City; most of the importation and distribution of heroin from Mexico into the southwestern United States is controlled by Mexican gangs (e.g., Sinaloan Cowboys); much of the smuggling of heroin into the United States from southeastern Asia is by Nigerian gangs, based primarily in Chicago; and much of the distribution of Asian heroin that is transshipped through the Port of Los Angeles is controlled by Thai gangs (*Drug trafficking in*, n.d.; National Drug Intelligence Center, 2001; Pagliaro & Pagliaro, 2009).

[9] However, given the observed cyclic trends reported in regard to the use of the drugs and substances of abuse over the past decades, the primary method of use among inner-city adolescents, particularly those living in the northeastern United States, is beginning to shift from snorting (i.e., intranasally insufflating) to mainlining (i.e., intravenously injecting).

[10] Some heroin users dissolve their high-purity, white powdered heroin, usually from Asian or Colombian sources, to make an aqueous solution of heroin nose drops for intranasal instillation.

[11] The rush associated with the intravenous injection of heroin is actually related to a rapid release of histamine in the body that is not directly related to heroin's psychotropic actions. An overwhelming majority of heroin users report that the rush is a very pleasant and highly anticipated experience (Pagliaro & Pagliaro, *Clinical Patient Data Files*).

General Pharmacology

This section discusses the general pharmacology of the opiate analgesics—their apparent mechanisms of psychodepressant action; common toxicities, including their propensity for physical and psychological dependence; and overdosage.

Proposed Mechanism of Psychodepressant Action

The various opiate analgesics primarily achieve their unique and desired psychodepressant actions by acting at specific receptor sites in the brain and the spinal cord. Five major groups of opiate, or endorphin, receptors have been identified: delta, epsilon, kappa, mu, and sigma. Pure opiate analgesic agonists (see Table 1.1) act at the delta, mu, and kappa receptors. These receptors are found in the highest concentrations in the brain stem; cortex; limbic system, including the hypothalamus; midbrain; spinal cord; and thalamus (see Figure 1.2). Acting at the delta receptors, they primarily mediate spinal analgesia. Acting at the mu receptors, specifically the mu 1 and mu 2 receptors, they primarily mediate, respectively, analgesia and various physiologic functions, including: slowing gastrointestinal (GI) motility; causing pupil constriction, or miosis; and depressing respiratory function. The mu 2 receptors also mediate feelings of euphoria and dysphoria and the development of physical dependence (i.e., the development of tolerance to the opiate analgesic agonists and the characteristic opiate analgesic withdrawal syndrome that occurs when they are abruptly discontinued). Kappa receptors mediate analgesia, other than that mediated by the mu 1 receptors; dysphoria; miosis; and respiratory depression. Mixed opiate analgesic agonists/antagonists (e.g., butorphanol [Stadol®], nalbuphine [Nubain®], pentazocine [Talwin®]) appear to act primarily at the kappa receptors. The nausea and vomiting associated with the opiate analgesics are related primarily to their stimulation of the chemoreceptor trigger zone in the medulla oblongata of the brain stem.

Common Toxicities

Several significant toxicities, or adverse effects, have been associated with the use of the opiate analgesics—directly related to their pharmacologic actions and indirectly related to their methods of use. *Direct* toxicities, which can be acute or chronic, affect most body systems, including the cardiovascular, central nervous, GI, and respiratory systems. (See Table 1.2.) *Indirect* toxicities have been associated particularly with both the intranasal and intravenous use of the opiate analgesics.

Intranasal Use Intranasal use of the opiate analgesics, which became increasingly prevalent during the 1990s, has been associated with several adverse effects, including: (1) erosion of the lateral nasal walls, nasopharynx, and soft palate; (2) fungal invasion of the nasal surfaces and rhinosinusitis; (3) infections involving the nasal surfaces with associated mucopurulent exudates; and (4) nasal septal perforation. In addition, severe, life-threatening asthma attacks have been associated with intranasal sniffing (snorting) of heroin by people who have preexisting asthma.[12]

Intravenous Use The adverse effects associated with the intravenous use of the opiate analgesics are often serious, including:

- Human immunodeficiency virus (HIV) infection and acquired immune deficiency syndrome (AIDS)
- Abscesses and infections at injection sites
- Cardiovascular abnormalities, including scarred and collapsed veins
- Respiratory abnormalities, including talc granulomas
- Hepatitis
- Tetanus

[12] For several decades, virtually identical toxicities have been commonly associated with the intranasal use of cocaine. (See Chapter 2, *The Psychostimulants*, for additional related discussion.)

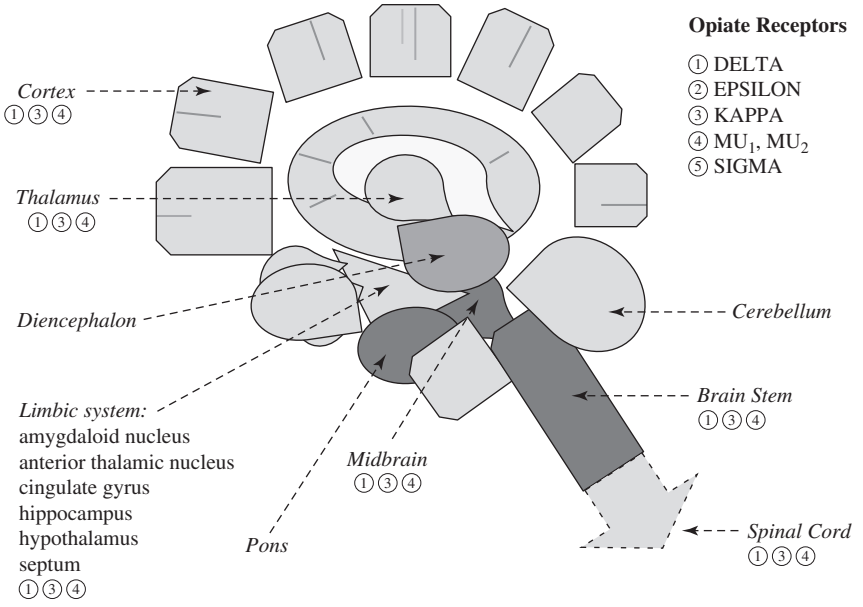

Figure 1.2 Opiate Analgesic Receptors and Sites

(See Table 1.3). These adverse effects and their associated complications are not caused by the opiate analgesics themselves; rather, they are caused by the adulterants used to cut the opiate analgesics for illicit use, nonsterile or shared needles and syringes, and improper injection techniques. It is important to note that if opiate analgesics were ingested, or even smoked or snorted, most of these adverse effects and more serious complications, including those that are life-threatening, would not occur.

Physical and Psychological Dependence

The development of both physical and psychological dependence has been associated with the long-term, regular use of the opiate analgesics. Thus, the abrupt discontinuation of this pattern of use will result in the opiate analgesic withdrawal syndrome. This syndrome also may occur among regular, long-term users of opiate analgesic agonists (e.g., those users who are physically dependent on heroin or morphine) when an opiate analgesic antagonist (e.g., naloxone [Narcan®]) or a mixed opiate analgesic agonist/antagonist (e.g., pentazocine [Talwin®]) is used. The signs and symptoms of the acute opiate analgesic withdrawal syndrome are listed in Table 1.4. Although this withdrawal syndrome is not usually fatal, generally it should be medically managed with appropriate pharmacotherapy and monitoring, particularly when children and adolescents are involved. For children and adolescents who are undergoing detoxification for physical dependence on opiate analgesics, the gradual discontinuation of the opiate analgesic will help to prevent, or minimize, these signs and symptoms. Unfortunately, following detoxification and treatment, relapse commonly occurs.

Overdosage

Opiate analgesic overdosage requires emergency medical support, particularly for the management of the respiratory depression that is characteristically associated with overdosages involving this subclass of the psychodepressants. Attention also must be given to increasing opiate analgesic elimination. Naloxone (Narcan®), a pure opiate analgesic

TABLE 1.2 Signs and Symptoms of Acute and Chronic Opiate Analgesic Toxicity

	Signs and Symptoms	
Body System	**Acute**	**Chronic**
Central nervous	Cognitive impairment; fainting (syncope); headache	Physical dependence and psychological dependence
Cardiovascular	Bradycardia; cardiac arrest; circulatory depression; dilation of superficial blood vessels with resultant warming of the skin (flushing); orthostatic, or postural, hypotension; sedation; shock; with intravenous injection, local pain or phlebitis at injection site (also see Table 1.3)	Anemia
Cutaneous	Diaphoresis, or excessive perspiration; pruritus; with subcutaneous injection, pain at injection site	
Gastrointestinal	Constipation; nausea; vomiting	Constipation
Genitourinary	Impotence (boys); reduced sexual desire; urinary retention	Menstrual irregularities (girls); reduced sexual desire
Muscular-skeletal	With intramuscular injection, pain at injection site	
Ophthalmic	Miosis; urticaria	
Respiratory	Laryngospasm; respiratory arrest; respiratory depression	

antagonist, is the specific antidote for the respiratory depression associated with overdosages involving opiate analgesic agonists and mixed opiate analgesic agonist/antagonists. However, it must be administered cautiously to children and adolescents who may be physically dependent on opiate analgesics because the usual dosage of the antagonist may precipitate the opiate analgesic withdrawal syndrome.[13] Common signs and symptoms of opiate analgesic overdosage are listed in Table 1.5.

It is important to note that many cases of opiate analgesic overdosage also involve other drugs and substances of abuse. For example, psychostimulants (see Chapter 2, *The Psychostimulants*), such as cocaine and methamphetamine, are concomitantly used, particularly with heroin (i.e., speedball). However, more common, and deadly, is the concomitant use of other psychodepressants, such as alcohol and the benzodiazepines (see "Sedative-Hypnotics" section for additional related discussion). These psychodepressants potentiate the respiratory depression associated with opiate analgesic overdosage and, consequently, significantly increase the risk for fatal overdosage (Pagliaro & Pagliaro, 2009; Sporer, 1999). Note, too, that the respiratory depression associated with the concomitant use of the nonopiate psychodepressants is not reversible by the administration of naloxone [Narcan®]).

SEDATIVE-HYPNOTICS

The second major subgroup of the psychodepressants, the sedative-hypnotics, is comprised of drugs and substances of abuse from four general pharmacological classes: (1) barbiturates; (2) benzodiazepines; (3) Z-drugs; and (4) miscellaneous sedative-hypnotics, including alcohol. (See Table 1.1.) Of these four pharmacologic classes, children and adolescents are most likely to use, or be exposed to, alcohol, followed by the

[13] The severity of the withdrawal syndrome depends on the severity of physical dependence (i.e., the characteristics of regular, long-term use in regard to the amount of the opiate analgesic used and the frequency of its use) and the dose of the antagonist administered. If the opiate analgesic antagonist is required for the medical management of serious respiratory depression for children or adolescents who are physically dependent on opiate analgesics, lower dosages and cautious dosage titration, together with careful monitoring, are recommended.

TABLE 1.3 Indirect Toxicities Associated With the Intravenous Injection of the Drugs and Substances of Abuse

Indirect Toxicity
Abscess
Aerobic gram-positive *cocci* infection
Anerobic infection
Aneurysm
Bacteremia
Cellulitis
CNS Infection
Cutaneous venous ulcer[a]
Endocarditis
Gangrene[b]
Hepatitis B
Hepatitis C[c]
HIV infection
Hyperpigmentation and scarring of skin tissue at injection site(s) (i.e., *needle tracks*, *railroad tracks*)
Myonecrosis
Myositis
Necrotizing fasciitis
Phlebitis
Polymicrobial infection
Pyomyositis
Sepsis
Skin and other soft-tissue infection
Tetanus
Thrombophlebitis
Thrombosis
Venous insufficiency, chronic
Venous sclerosis
Wound botulism

[a] Often is a long-term, chronic condition. When affecting the lower extremities, it can be debilitating.

[b] Often requires removal of the infected body tissue or, depending on the extent of the infection, amputation of the fingers, hand, toes, or foot.

[c] Often a precursor to cirrhosis of the liver or cancer of the liver (i.e., hepatocellular carcinoma), either of which may be fatal or require liver transplantation. The most common cause of hepatitis C in North America is the sharing of contaminated needles and syringes.

Notes: These toxicities are identified as indirect toxicities because they are not directly associated with the specific pharmacological actions of the specific psychodepressant drug or substance of abuse itself but rather with the general method of administration: intravenous injection.

Commonly used anatomic sites for intravenous injection of the various drugs and substances of abuse, in decreasing order of use, include the antecubital fossa, forearm, hand, foot, leg, breast, groin, and neck (Pagliaro & Pagliaro, *Clinical Patient Data Files*).

TABLE 1.3 (Continued)

Adulterants (e.g., quinine) and small, unfiltered particles (e.g., powder, talc, and other components of the drug or substance of abuse being injected) significantly contribute to these harmful effects. In addition, unsterile injection equipment, poor methods of injection, and poor hygiene contribute as well.

M. P. O'Brien (2008), reporting for the Community Epidemiology Work Group of the NIDA, found that 2% of U.S. high school students reported lifetime use of illegal injection drugs. As a cross-check of this finding, we note that Johnston, O'Malley, Bachman, et al. (2010b), in their in-school 2010 survey of adolescent use of the drugs and substances of abuse, found that approximately 1% of 8th-grade students, 10th-grade students, and 12th-grade students reported a lifetime prevalence of using a needle to self-administer heroin.

benzodiazepines. The barbiturates, Z-drugs, and the other miscellaneous sedative-hypnotics are least likely to be used by children and adolescents.[14] Thus, they are not specifically discussed in this chapter. However, one miscellaneous sedative-hypnotic, gamma-hydroxybutyrate (GHB), is used primarily by adolescents and young adults and thus is included in this section. We begin with an overview of the use of alcohol by children and adolescents and then turn our attention to the benzodiazepines and, finally, to GHB.

Alcohol

Alcohol is one of the most widely used drugs and substances of abuse. It is used throughout the world for its dose-dependent disinhibition euphoria, or high, and to decrease social and sexual inhibitions (i.e., to achieve a sense of well-being; to relax; and to relieve anxiety, tension, and stress). It also is used by regular, long-term alcohol users to prevent or manage the alcohol withdrawal syndrome, and it is administered to victims for the perpetration of such drug-facilitated crimes as robbery and sexual assault, including date rape.

[14] Children and adolescents occasionally encounter these sedative-hypnotics when "pharming"—gathering any prescription drugs available in the family medicine cabinet or on a parent's dresser or bedside table and taking them to a friend's house, where, along with everyone else who is participating, they dump them in a bowl, spread them on a table, or pile them on the floor, for general selection and use by all.

TABLE 1.4 Opiate Analgesic Withdrawal Syndrome: Common Signs and Symptoms

Body System	Signs and Symptoms
Central nervous	Anxiety, dysphoria, insomnia, irritability, restlessness, sensitivity to pain, yawning
Cardiovascular	Hypertension, tachycardia
Cutaneous	Chills and shivering, piloerection (goose flesh), sweating (excessive)
Gastrointestinal	Abdominal cramps and pain, anorexia, diarrhea, nausea
Musculoskeletal	Backache and other body aches, tremors, weakness
Respiratory	Hyperventilation, rhinitis, rhinorrhea, sneezing
Thermoregulatory	Fever, unexplained

In spite of its desirable psychotropic actions (as noted earlier) and certain other qualities (e.g., pleasant taste; quenching of thirst) the general use of alcohol has been associated with more harm than all of the other drugs and substances of abuse combined (Pagliaro & Pagliaro, 2009).[15] Alcohol-related harm includes: (1) direct physical harm (e.g., fetal alcohol syndrome/fetal alcohol spectrum disorder—see Chapter 5, *Exposure to the Drugs and Substances of Abuse From Conception Through Childhood*); (2) mental harm (e.g., depression; suicide [see also related discussion in Chapter 8, *Dual Diagnosis Among Adolescents*]); and (3) social harm (e.g., increased incidence of child abuse; decreased academic achievement; domestic violence; motor vehicle crashes; and violent crime, including homicide) (e.g., Involvement by young, 2002; Levy, Miller, & Cox, 1999; Miller, Levy, Spicer, et al., 2006; Pagliaro & Pagliaro, 2002, 2009; Sheppard, Snowden, Baker, et al., 2008; Sindelar, Barnett, & Spirito, 2004; Spirito, Rasile, Vinnick, et al., 1997).

Prevalence and Characteristics of Alcohol Use Among North American Children and Adolescents

The personal use of alcohol (and other drugs and substances of abuse) by children and adolescents, as well as adults, is characterized by nine well-defined patterns, or levels, of use from nonuse to resumed nonuse and relapsed use. (See Figure 1.3.) The initial use of alcohol during childhood may occur in association with religious ceremonies (i.e., Holy Communion) or as a result of curiosity (e.g., when a child wants to "see what it's like to taste a sip of beer"—often provided by a parent). The most common form of personal use is social use, which involves the use of alcohol in a wide range of social situations. In North America and other parts of the world, alcohol is socially ingested in the form of beers, wines, and distilled spirits (i.e., whiskey, vodka, liqueurs). Alcohol use is highly variable among individuals and societies and is significantly affected by a variety of factors, including age, race (i.e., genetic predisposition to tolerance or lack thereof [i.e., sensitivity, Asian flush]), cultural and religious customs, personal preferences, and availability and cost.

Trends Alcohol use, other than a sip or a taste, increases with age throughout late childhood (i.e., from around 8 years of age) and adolescence (i.e., to around 20 years of age) (Pagliaro & Pagliaro, 2009). As noted by Donovan (2007) in a review of children's alcohol use in the United States, more than 6% of 9-year-old children reported having consumed more than a few sips of alcohol. This observation also is supported by Eaton, Kann, Kinchen, et al. (2010), who found, in their analysis of data from the Youth Risk Behavior Surveillance System for 2009, that, nationwide, 21.1% of U.S. students in grades 9 through

[15] In the United States, alcohol consumption has been cited as the third leading cause of preventable death (Centers for Disease Control and Prevention, 2004b; McGinnis & Foege, 1993). See related discussion throughout this text for specific examples and reference citations.

TABLE 1.5 Opiate Analgesic Overdosage: Common Signs and Symptoms

Body System	Signs and Symptoms
Central nervous	Diminished or absent reflexes; stupor or coma; however, convulsions may occur with meperidine (Demerol®) or propoxyphene (Darvon®)
Cardiovascular	Hypertension; shock
Cutaneous	Chills and shivering; piloerection (goose flesh); sweating (excessive)
Gastrointestinal	Constipation
Musculoskeletal	Backache and other body aches, tremors, weakness
Ophthalmic	Miosis; however, mydriasis may occur with extreme hypoxia or with meperidine (Demerol®) overdosage
Respiratory	Decreased or absent respirations with cyanosis; pulmonary edema
Thermoregulatory	Subnormal body temperature

12 reported having drunk alcohol (other than a few sips) for the first time before they were 13 years of age (range 11.5% to 29.4 % across state surveys)—an age range reported by most adults as the time they first consumed their non-sip alcoholic drink (*Alcohol Use USA*, 2010).

The Partnership for a Drug-Free America and the Metlife Foundation (2010), in their 2009 study of over 3,000 adolescents in grades 9 through 12, found that 39% of their adolescent participants reported having drunk alcohol during the past month. Another study, the National Institute on Drug Abuse (NIDA)–sponsored Monitoring the Future survey for 2009, found that 14.9% of 8th-grade students, 30.4% of 10th-grade students, and 43.5% of 12th-grade students reported past month use of alcohol (Adolescent cigarette smoking, 2010). These data have been relatively constant over the past several years in regard to alcohol use with a very slight downward trend. However, in comparison to data for the early 1990s, each grade level currently sampled reports an approximately 10% overall decrease in alcohol use during the previous month (Johnston, O'Malley, Bachman, et al., 2010b).

In Canada, average reported age of initial use of alcohol is 16 years of age (Health Canada, 2010b)—an initial age of use noted to be significantly higher than that reported for the United States. Although the legal age for drinking in Canada varies from province to province (i.e., from 18 years of age to 21 years of age), the minimal legal drinking age across the entire United States (i.e., in all 50 states) is 21 years of age. As such, all alcohol use by children and adolescents in the United States (i.e., all underage drinking) is illicit (Substance Abuse and Mental Health Services Administration, 2010). Once alcohol consumption begins, it generally continues throughout a user's lifetime—except for users who discontinue alcohol use, primarily for religious or health reasons.

Currently, most studies indicate that approximately 80% of North Americans regularly consume alcoholic beverages.[16] For example, M. P. O'Brien (2008), in an analysis of data from the Community Epidemiology Work Group of the NIDA, found that 75% of U.S. high school students reported lifetime use of alcohol—the highest reported lifetime use rate for any of the drugs or substances of abuse selected for analysis. Similarly, Eaton, Kann, Kinchen, et al. (2010), in their analysis of data from the Youth Risk Behavior Surveillance System for 2009, found that more than 72% of U.S. students in grades 9 through 12 reported alcohol use with a range of approximately 40% to 80% across state surveys. Over 25% of these students reported having consumed alcohol on more than 100 days during the past

[16] Of the 20% of North Americans who do not consume alcohol, approximately half do not consume alcohol for religious reasons (e.g., Church of Jesus Christ of Latter-day Saints [Mormons], Muslims, Seventh-day Adventists), and the remaining half do not consume alcohol for medical reasons. Included in the latter group are people who are recovering from alcoholism and who subscribe to the principles of Alcoholics Anonymous or other similar 12-step programs (e.g., see Chapter 9, *Preventing and Treating Child and Adolescent Use of the Drugs and Substances of Abuse*).

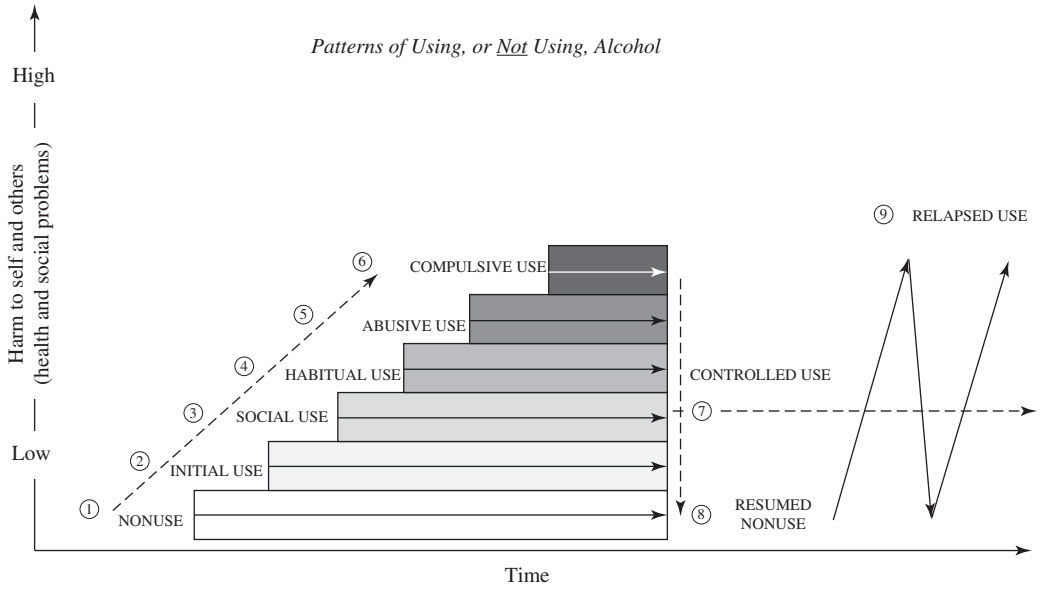

Figure 1.3 Patterns of Alcohol Use and Increasing Harm

year (*Alcohol Use USA*, 2010). Interestingly, Eaton, Kann, Kinchen, et al. (2010) also found that 4.5% of U.S. students nationwide in grades 9 through 12 had drunk at least one alcoholic beverage while on school property during the previous 30 days (range, 2.7% to 8.0% across state surveys).[17] In addition, Johnston, O'Malley, Bachman, et al. (2010b), in their 2010 in-school survey, *Monitoring the Future*, found that 16.3% of 8th-grade students, 36.9% of 10th-grade students, and 54.1% of 12th-grade students reported a lifetime prevalence of having been drunk.

Binge Drinking Binge drinking (i.e., traditionally defined for adolescent boys and young men as consuming five or more alcoholic drinks on a single occasion and for adolescent girls and young women as consuming four or more alcoholic drinks on a single occasion) is highly correlated with acute impairment and significant adverse health consequences (Pagliaro & Pagliaro, 2009; Wechsler, Davenport, Dowdall, et al., 1994).[18] However, more recently, Donovan (2009), using a modified version of the Widmark equation to calculate blood alcohol concentrations (BACs) for boys and girls, suggested a significant revision to the binge-drinking criteria.

Specifically based on his calculated estimates of differences between children and adults in total body water and alcohol elimination rates, Donovan (2009) recommends that binge drinking be defined as:

- Three or more drinks per drinking occasion for children and adolescents 9 to 13 years of age
- Three or more drinks for adolescent girls 14 to 17 years of age
- Four or more drinks for adolescent boys 14 and 15 years of age
- Five or more drinks for adolescent boys 16 and 17 years of age

While we would agree that the number of drinks needed to define binge drinking should be lowered for children and adolescents, we

[17] The incidence was reportedly highest (i.e., 7.9%) for boys of Hispanic descent.

[18] The defined pattern of alcohol consumption for binge drinking is generally equivalent for both adolescent boys and girls to the amount of alcohol consumption necessary to achieve a blood alcohol concentration (BAC) of 0.08 gram% (i.e., 80 mg%)—the legal level of alcohol intoxication in the United States (National Institute on Alcohol Abuse and Alcoholism, 2004).

would caution that there are, as yet, no empirical data to support Donovan's recommendations, and genetic differences in body weight and alcohol metabolism and elimination may vary significantly among North American children and adolescents.

For example, alcohol is predominantly water soluble. As such, doses of alcohol based on body weight will yield a significantly higher BAC among obese children and adolescents when compared to children and adolescents who are of normal body weight for their height and age. In addition, for postpubescent adolescents, on average, girls have significantly more body fat than do boys. Thus, we would expect a significant amount of variance in regard to binge-drinking definitions and criteria for children and adolescents.

Johnston, O'Malley, Bachman, et al. (2008), in their national study of adolescent drug use in the United States during 2007, found that approximately 20% of 10th- and 12th-grade students surveyed reported binge drinking (i.e., consuming five or more drinks in a row) during the 2 weeks prior to the survey. In addition, more than 41% of 10th-grade students and more than 55% of 12th-grade students, reported a lifetime prevalence of having been drunk. Even though they are underage drinkers, 90% of 12th-grade students reported that alcohol was either fairly easy or very easy to obtain.

Grucza, Norberg, and Bierut (2009) analyzed available data from the National Survey on Drug Use and Health (i.e., a pooled sample of more than 500,000 adolescent and young adult subjects) in regard to binge drinking among adolescents and young adults in the United States. Overall, from 1979 to 2006, they found that the incidence of binge drinking decreased significantly for boys (i.e., by approximately 15%) but increased significantly for girls (i.e., by approximately 50%). Their findings for adolescents for 2006, classified according to gender and age cohorts, are displayed in Table 1.6. As noted in the table, the incidence of binge drinking among adolescents: (1) increases with increasing age; (2) is significantly higher among boys, although girls are gaining parity; and (3) there appears to be an interaction effect between age and gender in regard to the incidence of binge drinking (i.e., for adolescents 12 to 14 years of age, girls have a significantly higher incidence of binge drinking than do boys; for adolescents 15 to 17 years of age, the incidence of binge drinking is essentially the same; and for adolescents 18 to 20 years of age, boys have a significantly higher incidence of binge drinking). Similarly, Miller, Naimi, Brewer, et al. (2007), in a study of approximately 14,000 high school students, found that 27.5% of boys and 23.5% of girls had engaged in binge drinking during the 30 days preceding their survey.

TABLE 1.6 Binge Drinking: Incidence for Boys and Girls in the United States, 2006

Gender	Age (years)	Binge Drinkers (%)
Girls	12–14	3.5
	15–17	15.1
	18–20	30.1
Boys	12–14	2.7
	15–17	18.1
	18–20	41.0

Source: Grucza, Norberg, & Bierut, 2009.

Although the results indicate a higher incidence of binge drinking among boys, this finding may be due to the definitional use of five or more drinks in a row on 1 or more of the 30 days preceding the survey to measure binge drinking—instead of the standard measurement of binge drinking for girls as 4 or more drinks (see earlier discussion in this section). Using the same definitional and measurement criteria as Miller, Naimi, Brewer, et al. (2007), Eaton, Kann, Kinchen, et al. (2010), in their analysis of the data from the Youth Risk Surveillance System for 2009, found that 24.2% of U.S. students in grades 9 through 12 reported binge drinking (range across state surveys, 11.5% to 30.7%). Among U.S. high school students, who reported current alcohol use, binge drinking was reported by an alarming 60.9% (Centers for Disease Control and Prevention, 2010d).

Among the adolescents who binge drink, it has been noted that approximately:

- 60% drink with others
- 40% drink to get high
- 30% drink when bored

McKinnon, O'Rourke, Thompson, et al. (2004) examined the rates of binge drinking among high school students in grades 9 through 12 who were sampled from 16 U.S. high schools along the United States–Mexico border. The majority of students who participated in the study were of Hispanic descent. Of these students, 45% reported binge drinking, 19% reported high-risk driving behaviors (e.g., drinking and driving), and 46% reported riding with a driver who had been drinking. These percentages were found to be significantly higher than U.S. national averages and highly correlated with reported alcohol-related problems and lower academic grades. Equally significant and disturbing, the students who participated in the study reported even higher rates of binge drinking (i.e., odds ratio [OR] = 6.44), risky driving (OR = 5.39), and riding with a driver who had been drinking (OR = 5.39) "when visiting Mexico."

Per-capita binge drinking episodes have increased significantly over the past two decades and appear to continue to increase across North America, particularly among young adults (Courtney & Polich, 2009; Grucza, Norberg, & Bierut, 2009; Pagliaro & Pagliaro, 2009).[19] Grucza, Norberg, and Bierut (2009), in their study of binge drinking, found the highest rates among young adults 21 to 23 years of age (i.e., 58.5% for young men and 38.6% for young women). It has long been noted that binge drinking is significantly higher among lesbian and bisexual adolescents and young women than among those who are not lesbian or bisexual (Drabble, Midanik, & Trocki, 2005; Hughes & Wilsnack, 1997; Hyde, Comfort, McManus, et al., 2009). (Also see related discussion in Chapter 8, *Dual Diagnosis Among Adolescents*, in the "Sexual or Gender Identity Disorders" section.)

Alcohol and Caffeinated Energy Drinks

Since the beginning of the new millennium, older adolescents and young adults have been increasingly drinking energy drinks—nonalcoholic drinks that are highly laden with caffeine (see related discussion in Chapter 2, *The Psychostimulants,* "Caffeine" section). These energy drinks, including Red Bull®, RevItUp®, and Rock Star®, often are used by adolescents and young adults in an attempt to enable them to drink more alcohol during a drinking episode without becoming drunk (Kaminer, 2010). For example, Malinauskas, Aeby, Overton, et al. (2007) found that over 50% of U.S. college students reported regularly consuming energy drinks and almost half of these adolescents and young adults reported commonly consuming three or more energy drinks, together with alcohol, while partying.[20] Miller (2008), in a similar study of North American undergraduate college students, found that the association between energy drink consumption and related problem behaviors (e.g., aggression, insomnia) was particularly significant for students of European descent but not for those of African descent. Use statistics and related behaviors for senior high school students are expected to be very similar to the data reported for undergraduate college students (Pagliaro & Pagliaro, *Clinical Patient Data Files*).

As noted, many adolescents and young adults generally assume that the psychostimulant actions of caffeine can ameliorate the psychodepressant actions of alcohol and, consequently, enable them to consume as much alcohol as they like. However, it is important

[19] Among college students of European American descent, the rate of binge drinking has been significantly correlated with the use of volatile solvents and inhalants during adolescence (Bennett, Walters, Miller, et al., 2000).

[20] Interestingly, Oteri, Salvo, Caputi, et al. (2007) reported similar findings for a large sample of medical students in Italy.

to note that the cognitive and psychomotor impairment associated with increasing BACs (see Table 1.7) are not significantly reduced by the caffeine consumed in energy drinks (Ferreira, de Mello, Pompéia, et al., 2006; Ferreira, de Mello, Rossi, et al., 2004)—even though the adolescent's or young adult's self-perception of his or her alcohol intoxication is significantly reduced (Marczinski & Fillmore, 2006). As we have noted previously in other venues, what is achieved is a wide-awake drunk. Instead of falling asleep or passing out with a BAC of 0.25 to 0.30, the adolescent or young adult remains awake and, consequently, is able to engage in hazardous behavior (e.g., drunk driving, physical assault) that may result in increased personal and social harm (see related discussion in "Common Toxicities" section, below; also see Table 1.8). Adolescents and young adults also use energy drinks to help them to stay awake to study (e.g., cram for a final examination; finish a term paper). (Also see related discussion in Chapter 2, *The Psychostimulants.*)

General Pharmacology

This section considers the proposed mechanism of alcohol's psychodepressant action and its common toxicities, including the development of physical and psychological dependence and the occurrence of the alcohol withdrawal syndrome when regular, long-term alcohol use is abruptly discontinued.

Proposed Mechanism of Psychodepressant Action The exact mechanism of action by which alcohol exerts psychodepression has not been determined. It appears to act by modifying the membrane environment of the gamma-aminobutyric acid (GABA) receptor complex (see Figure 1.4). Thus, the affinity for both endogenous GABA and other exogenous sedative-hypnotics, such as the barbiturates and benzodiazepines, is significantly increased (i.e., GABAergic inhibition is enhanced). Acute alcohol consumption significantly decreases overall brain glucose metabolism, which may also result in psychodepressant effects, including those that adversely affect learning and memory among children and adolescents. (See Chapter 6, *Effects of the Drugs and Substances of Abuse on Learning and Memory During Childhood and Adolescence.*) The pharmacologic effects, both physical and psychological, of alcohol use are well correlated with BACs (Pagliaro & Pagliaro, 2009). (See Table 1.7.)

Common Toxicities Among the acute and chronic physical and psychological toxicities associated with alcohol use (see Table 1.8), the use of alcohol among adolescent girls and young adult women of reproductive age has been associated with the leading cause of mental retardation in North America, the fetal alcohol syndrome/fetal alcohol spectrum disorder (FAS/FASD) among their offspring. In addition, approximately 1 in 5 North Americans report significant harm associated with their use of alcohol at least 1 time during their lives (Pagliaro & Pagliaro, 2009), with adolescents and young adults, including college and university students, experiencing significant alcohol-related injuries and sometimes death.[21] Also of concern is the occurrence of physical and psychological dependence and its associated sequelae, including the development of alcoholism and Wernicke-Korsakoff Syndrome, a condition that remains relatively rare among adolescents and young adults but appears to be increasing.

Fetal Alcohol Syndrome/Fetal Alcohol Spectrum Disorder. In North America, FAS/FASD is the third most commonly known cause of mental retardation and is the most common preventable cause of mental deficiency. Although suspected for centuries, FAS/FASD was fully described only during

[21] Alcohol-related injuries result in over 2 million hospitalizations of adolescents in the United States annually and 3,400 deaths (Miller, Levy, Spicer, et al., 2006).

TABLE 1.7 Blood Alcohol Concentration (BAC) and Associated Physical and Psychological Effects

BAC grams %, or grams per 100 ml	*Associated Effects*	
	Physical	**Psychological**
0.01–0.03	Generally normal appearance	Generally normal behavior
0.03–0.06	Mild impairment of coordination and ability to perform fine motor tasks Feeling relaxed Sense of warmth	Mild euphoria with decreased inhibitions and increased sociability and talkativeness Mild decrease in alertness and concentration
0.06–0.08	Increasing loss of coordination with slight loss of balance Slight loss of speaking ability	Mild impairment of reasoning and memory Intensification of emotions Increased disinhibition euphoria with apparent stimulant effect on behavior and extroversion Lowered interest in sex
0.08–0.11	Mild impairment of hearing, speech, and vision	Mild impairment of both judgment and self-control with an increased probability or incidence of accidents
0.10–0.15	Continued loss of coordination Marked impairment of balance Slowed reaction time Slightly slurred speech	Increased emotional instability Euphoria is increasingly replaced with dysphoria Significant impairment of judgment and ability to make good decisions Probability or incidence of accidents is increased 10-fold
0.15–0.20	Significant drowsiness Slurred speech Significantly prolonged reaction times Significant visual impairment with blurred vision, reduced glare recovery, and decreased peripheral vision	Significant impairment of perception Further deterioration of judgment Gross intoxication Probability or incidence of accidents is increased by up to 30-fold
0.20–0.30	Severe motor and speech impairment with an appearance of a sloppy drunk May require assistance to stand upright or to walk Impaired gag reflex with risk of choking on food or own vomit Risk of serious injury related to falls, walking into traffic, being attacked or robbed (i.e., being rolled)	Significant mental confusion—may be dazed or disoriented Loss of normal understanding Significant pain tolerance (feeling no pain) Memory loss and alcoholic blackouts May become stuporous, or achieve a state of near-unconsciousness
0.30–0.35	Total loss of motor control Reflexes are significantly depressed or absent Incontinence, or loss of voluntary bladder control Heart rate is significantly slowed Respiratory rate is significantly slowed	Level of consciousness diminishes to a state of stupor, a complete lack of mental alertness or a condition of significantly impaired ability to respond to external environmental stimuli Level of consciousness diminishes to coma, or an extremely deep stupor—a condition in which the person cannot be aroused by external environmental stimuli (e.g., talking to the person, calling the person by name, or gently shaking the person in an effort to arouse him or her) Total lack of response to painful stimuli, such as pinching the skin or pricking the skin with a pin or needle (i.e., level of surgical anesthesia)
0.35–0.40+	Impaired circulation of the blood throughout the body Death, usually due to respiratory arrest	Severe CNS depression Unconsciousness

(*Continued*)

TABLE 1.7 Blood Alcohol Concentration (BAC) and Associated Physical and Psychological Effects (Continued)

Notes: The BACs listed and their associated effects are meant to provide a general guideline. Variability from one drinker to another does occur and can be significant, particularly in the context of acquired tolerance.

Because of a paucity of relevant available data for children and adolescents, this table was constructed from adult data. Given the known pharmacokinetics of alcohol, the extrapolation of these data to adolescents is expected to be quite valid and reliable. However, the data in this table should *not* be applied directly to children.

0.1 grams % = 100 mg %

the late 1970s. The condition is caused by the consumption of alcohol by adolescent girls and women during pregnancy. Although the ingestion of up to 2 drinks per day by pregnant adolescent girls and women generally has been considered to be safe to the fetus, the safe amount of alcohol ingested during pregnancy has not been well documented and may be highly variable. Controversy regarding the incidence of FAS continues. However, because of the serious nature and irreversibility of the related sequelae, we recommend that adolescent girls and women of reproductive age completely avoid the consumption of alcohol during pregnancy (Pagliaro & Pagliaro, 2000, 2002, 2009).

Since 1977, published data have accumulated implicating high maternal alcohol consumption during pregnancy with FAS. Alcohol ingestion during the first trimester is most likely to cause fetal malformations resulting in physical birth defects. Alcohol ingestion later during pregnancy is most likely to adversely affect fetal nutrition with resultant decrements in head circumference, body length, and body weight. However, maternal alcohol use throughout gestation can adversely affect central nervous system (CNS) development and related neurocognitive processes (i.e., result in mental birth defects) among offspring.

Current available data suggest that neuronal apoptosis,[22] induced by maternal alcohol consumption during pregnancy, may be the underlying pathophysiologic basis for the development of the FAS/FASD and its associated neurobehavioral impairments (Olney, Wozniak, Jevtovic-Todorovic, et al., 2002). In this case, the third trimester of pregnancy, which correlates with the beginning of the brain growth spurt period (i.e., period of high synaptogenesis that commences in the sixth month of fetal development), would appear to be the time of maximal vulnerability for the development of the FAS/FASD-related neurobehavioral disorders (Ikonomidou, Bittigau, Koch, et al., 2001). The incidence of FAS/FASD in North America remains at a significantly high level and, unfortunately, actually is increasing among some subpopulations, such as Native Americans (Eustace, Kang, & Coombs, 2003; Pagliaro & Pagliaro, 2009). (Also see related discussion in Chapter 5, *Exposure to the Drugs and Substances of Abuse From Conception Through Childhood*.)

Alcohol-Related Injury and Death: College Drinking Annually, across college campuses in North America, it is estimated that there are 1,400 student deaths, 500,000 unintentional injuries, and 600,000 physical assaults (including rape) directly related to alcohol consumption (Hingson, Heeren, Winter, et al., 2005; Hingson, Heeren, Zakocs, et al., 2002; Hingson, Zha, & Weitzman, 2009).[23] In addition, over 30% of four-year college students sampled in the United States report problems specifically related to their alcohol use (e.g., alcohol-related academic problems;

[22] Neuronal apoptosis is the process in which brain cells disintegrate into particles that are consumed (i.e., phagocytosed) by other cells (e.g., leukocytes, macrophages). Thus, brain growth and development is prevented, inhibited, or slowed.

[23] College students are more likely to engage in problematic drinking behaviors than are same-age cohorts who do not attend college (O'Malley & Johnston, 2002).

TABLE 1.8 Alcohol Use Among Children and Adolescents: *Acute (A)* and *Chronic (C)* Toxicities

Absenteeism from school or work (*A*) (*C*)
Accidents, general (e.g., drowning, falls) (*A*) (*C*)
Abusive and aggressive behavior, physical and psychological (*A*) (*C*)
Alcoholic blackouts (*A*) (*C*)
Alcoholic ketoacidosis *(A)* (*C*)
Alcoholism (*C*)
Alcohol withdrawal syndrome (*C*)
Amnesia (*A*) (*C*)
Anemia (*C*)
Boyfriend or girlfriend abuse, physical and psychological (*A*) (*C*)
Cardiac dysrhythmias (*C*)
Cardiovascular heart disease (*C*)
Child abuse, physical and psychological (*A*) (*C*)
Cognitive dysfunction (*A*) (*C*)
Coma *(A) (C)*
Criminal behavior *(A) (C)*
Date-rape (facilitation of perpetration) *(A)*
Decreased immune response *(C)*
Decreased social inhibitions *(A)*
Diabetes mellitus *(C)*
Dual diagnosis *(C)*
Dysfunctional parenting *(A) (C)*
Dysmenorrhea, or severe pain associated with menstruation (C)
Eye movements, diminished (*A*)
Fetal alcohol syndrome/fetal alcohol spectrum disorder among offspring of adolescents and young women of reproductive age who drink during pregnancy (*A*) (*C*)
Gastritis (*A*) (*C*)
Guilt (*A*) (*C*)
Hallucinations (*A*)
Hangover (*A*)
Homicide, increased involvement—both as perpetrator or victim (*A*)
Hypertension (*C*)
Hypertriglyceridemia (*C*)
Hypoglycemia (*A*) (*C*)
Hypokalemia *(A)*
Hypothermia, or a decrease in body temperature *(A)*
Korsakoff's psychosis (C)[a]
Malnutrition (e.g., thiamine deficiency) (*C*)
Memory dysfunction (*A*) (*C*)
Mental depression (*A*) (*C*)
Motor vehicle crashes, increased (*A*)
Neuropathy *(C)*
Neurotoxicity (*A*) (*C*)
Peripheral neuropathy (*C*)
Peripheral vasodilation (flush) (*A*)
Physical dependence (*C*)
Psychological dependence (*C*)
Psychomotor impairment (*A*)
Psychosis (*A*)
Respiratory depression (*A*)
Risk taking, increased (A)
Schoolwork/academic performance, decreased (*A*) (*C*)
Self-neglect (*A*) (*C*)
Sexual abuse/assault (facilitation of perpetration by decreasing social inhibitions) (*A*)
Sexual activity, increased (*A*)
Sexual dysfunction (males) (*A*)
Sexual inhibitions, decreased (*A*)
Sexually transmitted diseases, increased (*A*)

(*Continued*)

TABLE 1.8 Alcohol Use Among Children and Adolescents: *Acute (A)* and *Chronic (C)* Toxicities (Continued)

Short-term memory, impaired (*A*)
Sick days, increased (*C*)
Slurred speech (*A*)
Social problems (e.g., absence from school or work; arguments with family members; delinquency) (*A*) (*C*)
Strained or impaired relationship with parent(s)/primary care giver(s) (*A*) (*C*)
Suicide, increased (attempted or completed suicide) (*A*) (*C*)
Victimization (e.g., physical assault, sexual assault) (*A*) (*C*)
Violent behavior, including homicide, physical assault, and rape (*A*)
Vomiting *(A)*
Wernicke's encephalopathy *(C)*[b]
Work productivity, decreased (*A*) (*C*)

[a] Korsakoff's psychosis is an extremely rare occurrence among adolescents and young adults. However, some few cases have been identified among older adolescents who are homeless and have a long history (i.e., several years) of heavy drinking (Pagliaro & Pagliaro, *Clinical Patient Data Files*).

[b] Wernicke's encephalopathy is an extremely rare occurrence among adolescents and young adults. However, some few cases have been identified among older adolescents who are living on the streets and have long histories (i.e., several years) of heavy drinking and associated malnourishment (Pagliaro & Pagliaro, *Clinical Patient Data Files*).

drinking in hazardous situations, such as drinking and driving)[24] (Knight, Wechsler, Kuo, et al., 2002). (See Figure 1.5.) Student risk for excessive alcohol use is highest at U.S. colleges and universities (1) at which fraternities and sororities play a dominant social role, (2) where athletic events and campus sports are held in particularly high esteem, and (3) that are located in the Northeast (Presley, Meilman, & Leichliter, 2002).[25] The toxicities associated with alcohol use are specifically related to its pattern of use. (See Figure 1.3.)

Physical and Psychological Dependence

Alcohol has a high abuse potential for both physical and psychological dependence. The former is characterized by the development of tolerance, which is commonly identified among chronic alcoholics, and a classic alcohol withdrawal syndrome that occurs when regular, long-term alcohol use is abruptly discontinued. Tolerance—the need to drink more and more alcohol to achieve desired psychodepressant actions (i.e., a disinhibition euphoria, relief of tension)—and the desire to avoid the alcohol withdrawal syndrome work in unison along with the development of psychological dependence—a craving for alcohol characterized by continued use despite harmful effects to self and others with the recognition by alcoholic adolescents or young adults that they "just can't help" themselves. The extent to which physical and psychological dependence develop, and their associated physical, psychological, and social consequences occur, is directly related to the specific patterns in which alcohol is consumed. (See Figure 1.3.)

Although infrequent use in small amounts (e.g., 1 or 2 drinks on holidays and special occasions) generally has been associated with little or no harmful effects among children and adolescents, both physical dependence and psychological dependence, in the form of increasingly serious forms of alcoholism, have been noted when moderate to large

[24] Even at lower BACs, drinking and driving have been demonstrated to be particularly hazardous for inexperienced drivers, including adolescents, 16 to 18 years of age (*Alcohol implicated*, 2010; Car crashes, 2007) (see Figure 1.5). Drinking and driving, particularly by inexperienced drivers, contributes significantly to automobile crashes, which is the leading cause of death for North American adolescents and young adults (Centers for Disease Control and Prevention, 2010c; Female auto crash, 2007; Pagliaro & Pagliaro, 2009). This statistic may not be too surprising given that, annually, over 30 million Americans admit to driving while drunk, and the highest percentage is in the 16- to 25-year-old age group (Hendrick, 2010).

[25] The correlates of underage drinking on college campuses by students who are younger than 21 years of age include, in decreasing order: (1) drinking beer; (2) residing in a fraternity or sorority; (3) having easy access to alcohol; and (4) being able to obtain alcohol at lower prices (Wechsler, Kuo, Lee, et al., 2000).

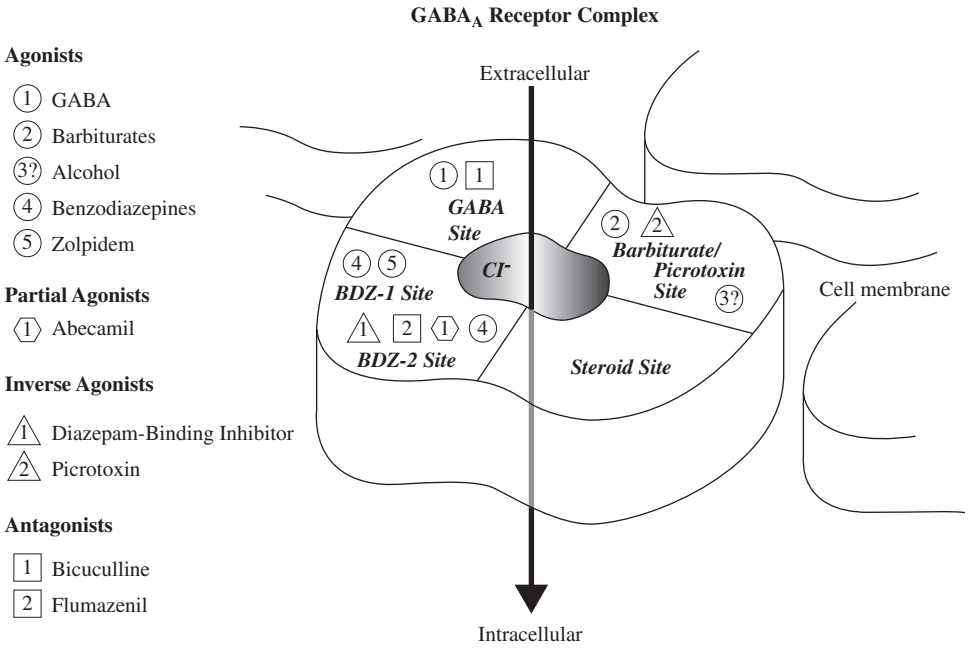

Figure 1.4 Stylized Model of the GABA$_A$ Receptor Complex
Reproduced with permission from: L. A. Pagliaro & A. M. Pagliaro (1998), Chapter 2, The Psychotropics (p. 51). In L. A. Pagliaro & A. M. Pagliaro, *The pharmacologic basis of psychotherapeutics: An Introduction for psychologists*. Washington, DC: Brunner/Mazel.

amount of alcohol are regularly ingested over prolonged periods of time (i.e., months). As noted by the American Academy of Pediatrics (2001):

> Addiction to alcohol is underdiagnosed in adolescents. . . . Alcoholism should be suspected in young people who are often intoxicated or experience withdrawal symptoms from chronic or recurrent alcohol use; those who tolerate large quantities of alcohol; those who attempt unsuccessfully to cut down or stop alcohol use; those who experience blackouts attributable to drinking; or those who continue drinking despite adverse social, educational, occupational, physical, or psychological consequences or alcohol-related injuries. (p. 186)

Alcoholism The term "alcoholism" may be defined as the use of alcohol that results in increasing harm to the user as measured by related changes in physical and mental health, school/work productivity, family relationships, and social life. The development of alcoholism has several specific characteristics, including notions that it is: (1) progressive, in that it becomes more serious with time; (2) chronic, in that it is continuous; and (3) insidious, in that there is a general inability on the user's part to recognize, without outside assistance, that her or his use of alcohol is resulting in significant personal and social harm. As mentioned, the incidence of alcoholism is approximately 15% of the entire North American adult population (Pagliaro & Pagliaro, 2009).

Although complex in nature and more specifically identified as consisting of several alcoholisms, or like FAS/FASD as a spectrum disorder, the clinical entity of alcoholism has been characterized by various specific behaviors, including:

- Drinking alone
- Sneaking drinks
- Gulping down drinks
- Developing increased tolerance to alcohol
- Experiencing personality changes
- Inability to account for specific periods of time (i.e., alcoholic blackouts)

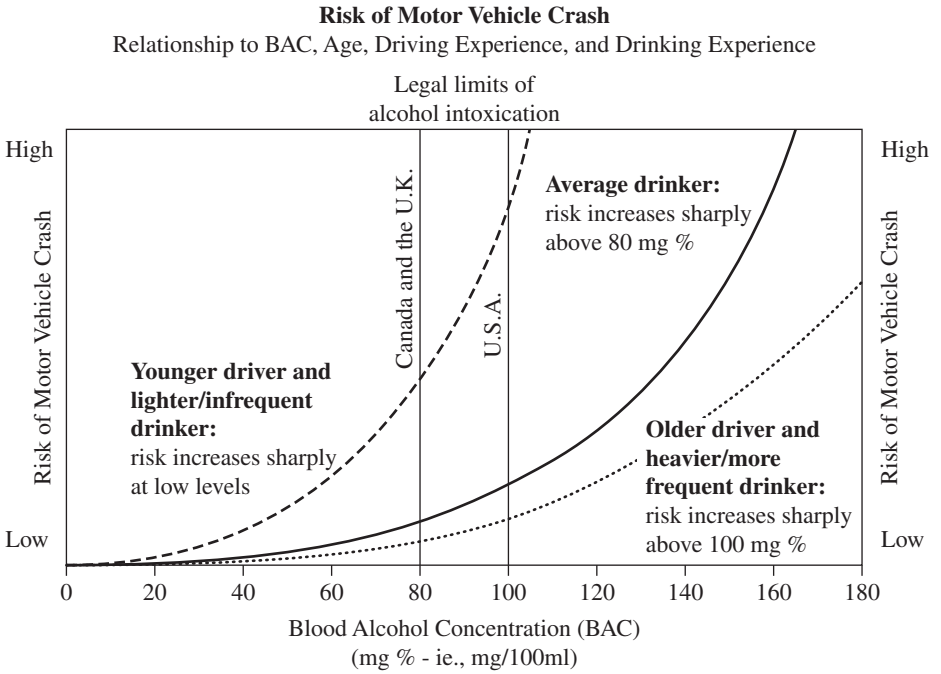

Figure 1.5 Age and Alcohol-Related Risk for Motor Vehicle Crashes
Reproduced with permission from: A. M. Pagliaro & L. A. Pagliaro (1996), Chapter 8, Substance-related accidents and violence: Children and adolescents as victims (p. 187). In, *Substance use among children and adolescents: Its nature, extent, and effects from conception to adulthood.* New York, NY: John Wiley & Sons.

Among North Americans 18 years of age or older, approximately one-third will develop an alcohol use disorder (AUD) sometime during their lifetime (Hasin, Stinson, Ogburn, et al., 2007).[26] Although adequate and reliable data regarding the incidence of alcoholism or AUD among North American adolescents is not currently available, case reports, clinical experience, and drug and substance abuse treatment center records provide evidence that it is a serious and growing problem (Pagliaro & Pagliaro, *Clinical Patient Data Files*).

Alcohol Withdrawal Syndrome As tolerance develops for many of the physiological and psychological effects of alcohol, regular, long-term drinkers will increasingly use larger and larger amounts of alcohol in an effort to achieve these desired effects. They also may drink more frequently or throughout the day in an effort to prevent the occurrence of the signs and symptoms of the alcohol withdrawal syndrome. This withdrawal syndrome, which commences upon the abrupt discontinuation of heavy, prolonged alcohol consumption, is characterized by anxiety, craving for alcohol, hallucinations, insomnia, irritability, psychomotor agitation, restlessness, tremulousness, and a variety of other associated physiological effects (e.g., diaphoresis, fever, mydriasis) (Bayard, McIntyre, Hill, et al., 2004).

When particularly acute or severe, this group of signs and symptoms has been generally identified as the syndrome of delirium tremens (DTs), historically referred to as alcoholic delirium and colloquially as rum fits. This form of the alcohol withdrawal syndrome is characterized by various classic signs and symptoms, including: agitation (severe), confusion, delirium, diarrhea, disorientation, fever, grand mal seizures, hallucinations

[26] For adolescent boys and adults of American Indian descent, the reported incidence is significantly higher (i.e., approximately 42%).

(often bizarre and extremely frightening), hypertension, hyperthermia, mydriasis, nausea, sweating (profuse), and tachycardia. The signs and symptoms appear to be moderated, at least in part, by a decrease in GABA-ergic inhibitory function and an increase in glutamatergic excitatory function (Malcolm, 2003).[27] Cardiovascular collapse may occur if DTs is left untreated, and may be fatal. Medical management of DTs generally involves hospitalization in order to provide cautious administration of long-acting benzodiazepines,[28] careful monitoring of body systems, and appropriate supportive care.

Wernicke-Korsakoff Syndrome Wernicke-Korsakoff syndrome is a major syndrome associated with the regular, long-term heavy drinking of alcohol. This syndrome, comprised of Wernicke's encephalopathy and Korsakoff's psychosis, is not directly caused by alcohol itself but by a vitamin B1, or thiamine, deficiency. This vitamin deficiency occurs as a result of inadequate nutrition—a condition that commonly occurs among people who have severe alcoholism. Severe alcoholism can be displayed by people of all socioeconomic and cultural backgrounds. However, it is particularly prevalent among people who live on the street or in hostels that are provided by social agencies and charities, such as the Salvation Army. This nutritional deficiency results in acute Wernicke's encephalopathy and, if treatment is delayed, the chronic syndrome of Korsakoff's psychosis.

Korsakoff's psychosis is characterized by increasing memory impairment as severe brain damage occurs. Because the syndrome is characterized by confusion, defective muscular coordination, disorientation, double vision, hallucinations, hypotension, memory failure, and muscular spasticity (i.e., many of the common signs and symptoms associated with acute alcohol intoxication), it is often confused with acute alcohol intoxication—particularly by law enforcement officers. The treatment for this condition involves thiamine replacement, the establishment of proper nutrition, and supportive care. However, even with appropriate treatment, the prognosis for this condition is poor. Unfortunately, only 20% of people diagnosed as having Korsakoff's psychosis are cured, 30% have little to moderate improvement, and 50% demonstrate no improvement.

Benzodiazepines

The benzodiazepine molecule was synthesized in the late 1950s. Over the following 50 years, more than 2,000 different benzodiazepine derivatives were developed. Touted as being the safest sedative-hypnotics available for clinical use because of their high therapeutic index, the benzodiazepines became the most widely prescribed, and abused, sedative-hypnotics in the world, including North America. Although the benzodiazepines continue to be widely used by adults for their desired anxiolytic and hypnotic actions, their therapeutic use has now been increasingly replaced in North America with the more recently developed sedative-hypnotics, the Z-drugs. (See Table 1.1, "Sedative-Hypnotics" section.)

Prevalence and Characteristics of Benzodiazepine Use Among North American Children and Adolescents

Children and adolescents generally use the benzodiazepines to: (1) achieve an alcohol-like disinhibitory euphoria, or high; (2) reduce anxiety and stress (e.g., family, school, or job-related stress); or (3) sleep better (i.e., cope with the anxiety or insomnia related to their everyday problems, including parental expectations and household rules, schoolwork demands,

[27] This explanation is consistent with the observed clinical efficacy of the benzodiazepines (e.g., chlordiazepoxide [Librium®], diazepam [Valium®]) in managing the signs and symptoms of the alcohol withdrawal syndrome.

[28] The benzodiazepines (e.g., chlordiazepoxide [Librium®]) are the drugs of choice for the medical management of DTs as well as for milder forms of alcohol withdrawal (Pagliaro & Pagliaro, 2000, 2009).

job requirements, financial needs, and dating and sexual issues).[29] Children and adolescents also may use benzodiazepines in an effort to prevent, or self-manage, the benzodiazepine withdrawal syndrome. Increasingly, some children and adolescents use benzodiazepines (e.g., flunitrazepam [Rohypnol®, roofies]) to facilitate robberies and sexual assaults (i.e., date-rape).[30]

Children and adolescents generally obtain benzodiazepines by: (1) pharming—stealing prescription benzodiazepines from their parent(s) or other family members and then sharing them with other children or adolescents or trading them for more desired drugs and substances of abuse (See earlier discussion); (2) buying them from illicit dealers, including older siblings and schoolmates; and (3) obtaining them by purchase over the Internet. As noted by Johnston, O'Malley, Bachman, et al. (2008) in their national study of adolescent drug use in the United States for 2007, 20% of the high school students surveyed reported that the benzodiazepines were either fairly easy or very easy to obtain.

Although the overall use of the benzodiazepines by children and adolescents has decreased significantly from the highs of the 1970s and 1980s, it is still significant, as indicated by reports of drug-related admissions from both addiction treatment centers and hospital emergency departments across the United States (Forrester, 2006a; M. P. O'Brien, 2008). The benzodiazepines, particularly alprazolam (Xanax®), clonazepam (Rivotril®), diazepam (Valium®), and lorazepam (Ativan®), account for the majority of these reports. In addition, a significant number of children and adolescents who seek assistance from addiction counselors for cocaine or opiate analgesic dependence (actually, up to one-third) also have issues with benzodiazepine dependence (Pagliaro & Pagliaro, *Clinical Patient Data Files*.

The most popular benzodiazepines used by U.S. high school students are alprazolam (Xanax®) and diazepam (Valium®). Johnston, O'Malley, Bachman, et al. (2008) found that approximately 6% of U.S. high school students reported personal benzodiazepine use within the previous 12 months. In comparison, available Canadian data for benzodiazepine use for 2009 indicated that 4% of youth 15 to 24 years of age used them during the previous year (Health Canada, 2010b).

General Pharmacology

This section considers the proposed mechanism of action of the benzodiazepines and their common toxicities, including their potential for physical and psychological dependence and overdosage.

Proposed Mechanism of Psychodepressant Action The benzodiazepines cause dose-related CNS depression ranging from mild impairment of cognitive and psychomotor functions to hypnosis. They appear to act at

[29] See, for example, Chapter 8, *Dual Diagnosis Among Adolescents*, for related discussion of alcohol and other sedative-hypnotic use by adolescents in the context of the combination of substance use disorders and other mental disorders.

[30] Flunitrazepam (Rohypnol®, forget-me drug, La Roche, roofies) is a widely used date-rape drug. (See Table 1.1.) Although not legally available in North America, it is available by prescription in over 70 countries in Europe and Latin America, where it is used to treat anxiety and insomnia and as a preoperative adjunct to anesthesia (Anglin, Spears, & Hutson, 1997; Pagliaro & Pagliaro, 2009). The majority of this pharmaceutically produced drug is smuggled into the United States from Mexico.

In their national in-school survey of adolescent use of the drugs and substances of abuse, Johnston, O'Malley, Bachman, et al. (2010b) found that 0.9% of 8th-grade students and 1.4% of 10th-grade students reported lifetime prevalence of flunitrazepam use. The highest incidence of use, often in combination with beer and cannabis, is found among adolescent boys and young men of European or Hispanic descent. Among this latter group, use primarily occurs in bars, nightclubs, and raves. Of concern is the increasing use of flunitrazepam by sexually active adolescent girls and young women, who use it in combination with alcohol and other drugs and substances of abuse, particularly psychodelics (e.g., 3,4-methylenedioxymethamphetamine [MDMA]), in order to decrease inhibitions and enhance sexual experiences (Pagliaro & Pagliaro, 2009). A significant number of these adolescent girls and young women have reportedly been physically or sexually assaulted while under the influence of flunitrazepam.

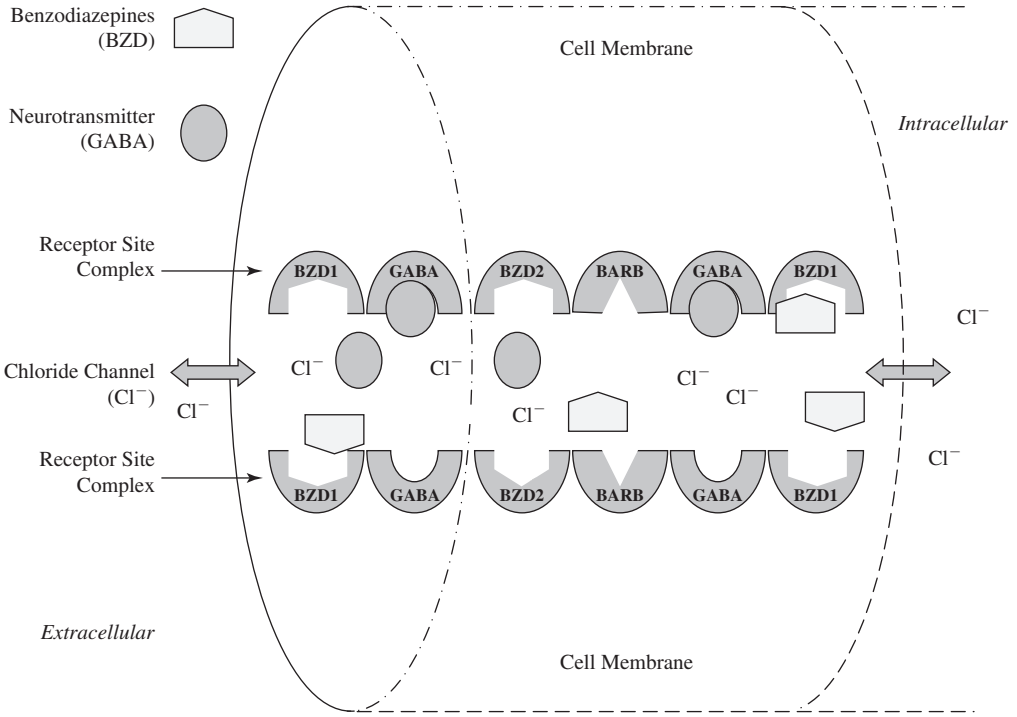

Figure 1.6 Benzodiazepines: Mechanism of Action
Reproduced with permission from: L. A. Pagliaro & A. M. Pagliaro (2009), *Pagliaros' Comprehensive Guide to Drugs and Substances of Abuse* (2nd ed.) (p. 40). Washington DC: American Pharmacists Association.

the benzodiazepine receptors (types 1 and 2). These receptors are found at several sites in the CNS, particularly in the cerebral cortex and the limbic system. The benzodiazepine receptors are found primarily in conjunction with the $GABA_A$ receptor. Thus, it appears that the benzodiazepines elicit their pharmacologic actions by potentiating the actions of GABA, a major inhibitory neurotransmitter, within the CNS. A simplified, stylized representation of the principal sites and mechanisms of action of the benzodiazepines is shown in Figure 1.6.

Common Toxicities Although relatively safe to use, the benzodiazepines have been associated with various adverse cognitive effects. (See, for example, the discussion of their adverse effects on memory in Chapter 6, *Effects of the Drugs and Substances of Abuse on Learning and Memory During Childhood and Adolescence*.) Their potential for physical and psychological dependence, including the development of tolerance and a benzodiazepine withdrawal syndrome upon the abrupt discontinuation of regular, long-term use, have now been well documented. The benzodiazepines also have been associated with overdosage fatalities, particularly when used with alcohol (Pagliaro & Pagliaro, 2009).

Physical and Psychological Dependence In regard to abuse potential, the benzodiazepines have a low to moderate potential for physical dependence and a moderate to high potential for psychological dependence. It has been long recognized that psychological dependence could develop with the regular, long-term use of benzodiazepines—at both lower and higher dosages. Available data now indicate that the regular, long-term use of benzodiazepines, even within therapeutic dosage ranges, can lead to true physical dependence in a significant minority of users (Pagliaro & Pagliaro, 2009).

In addition, benzodiazepine users, including children and adolescents, who have a past personal or family history of alcoholism appear to be at increased risk for developing physical dependence, including the development of tolerance and a withdrawal syndrome that occurs with the discontinuation of use.

Tolerance Tolerance to the actions of the benzodiazepines develops within 4 months of initial, daily use regardless of the dosage range (i.e., low or high) or if medically prescribed or not. However, the rate of tolerance development varies from person to person and from benzodiazepine to benzodiazepine. Generally, tolerance develops more quickly to the hypnotic effects of the benzodiazepines than to their anxiolytic effects.

Some general indicators of benzodiazepine dependence include: (1) regular use of a benzodiazepine extending over 30 days; (2) expressed craving or a desire for the benzodiazepine; (3) a need to increase the dosage of the benzodiazepine in order to achieve, or maintain, the desired effect(s); and (4) the appearance of the characteristic signs and symptoms of the benzodiazepine withdrawal syndrome when the use of the benzodiazepine is abruptly discontinued for any reason (e.g., inability to renew a prescription; lack of funds to buy more of the drug; inability to obtain the drug from others by begging, stealing, or trading). (Also see the "Benzodiazepine Withdrawal Syndrome" section for additional related discussion.)

Benzodiazepine Withdrawal Syndrome The characteristic signs and symptoms of what is now identified as the benzodiazepine withdrawal syndrome have been widely documented in regard to the abrupt discontinuation of regular, long-term benzodiazepine use (e.g., Bateson, 2002).[31] Usually mild to moderate in intensity, these signs and symptoms include anxiety (rebound), convulsions, dysphoria (generally mild), insomnia, irritability, muscle cramps, nervousness, shaking, sweating, tension, and tremors. These characteristic signs and symptoms, which are essentially the opposite of the desired effects of the benzodiazepines, are more likely to occur with: (1) short-acting benzodiazepines (e.g., alprazolam [Xanax®], lorazepam [Ativan®], triazolam [Halcion®]); (2) higher dosages of the benzodiazepine; (3) regular, daily use of the benzodiazepine for 4 months or longer; and (4) the abrupt discontinuation of the benzodiazepine after regular, daily use.[32]

Signs and symptoms of the benzodiazepine withdrawal syndrome have included life-threatening seizures at dosages within the recommended range for some benzodiazepines (e.g., alprazolam [Xanax®]). Children and adolescents who have a history of epilepsy or other seizure disorders are at particular risk for seizures related to benzodiazepine withdrawal. The severity and duration of the withdrawal syndrome appear to be related primarily to the dosage and duration of benzodiazepine pharmacotherapy or regular personal use.

Generally, the benzodiazepine withdrawal syndrome can be avoided, or at least minimized, by gradually decreasing the dosage. It is often handled cold turkey (without medical care or prescribed pharmacotherapy) but can be managed with the substitution of an equivalent dose of a long-acting benzodiazepine (e.g., diazepam [Valium®]) that is gradually reduced over a period of 2 to 3 weeks.

---

[31] Interestingly, the signs and symptoms of the benzodiazepine withdrawal syndrome also have been noted with the discontinuation of concurrent pharmacotherapy that inhibits the cytochrome P450 isoenzymes responsible for the metabolism of the benzodiazepines (Ninan, 2001) (e.g., the antifungals itraconazole [Sporanox®] and ketoconazole [Nizoral®]; the antisecretory proton pump inhibitor omeprazole [Losec®, Prilosec®]) (Pagliaro & Pagliaro, 1998).

[32] Short-acting benzodiazepines are more likely to produce insomnia when abruptly discontinued than are long-acting benzodiazepines and may contribute to their continued use. Long-acting benzodiazepines are less likely to produce insomnia when they are discontinued, probably because of their longer half-lives of elimination, which may provide an automatic tapering-off effect when use is abruptly discontinued.

Overdosage Signs and symptoms of benzodiazepine overdosage include coma, confusion, diminished reflexes, incoordination, and somnolence. Respiratory arrest is more common with short-acting benzodiazepines (e.g., alprazolam [Xanax®], midazolam [Versed®], and triazolam [Halcion®]). Benzodiazepine overdosage is usually not fatal, because the benzodiazepines possess a high LD_{50} (i.e., the median lethal dose, or the dose that would be expected to cause death in 50% of an exposed population). However, fatalities commonly occur when overdosages involve the use of benzodiazepines in combination with alcohol or opiate analgesics. Benzodiazepine overdosage requires emergency medical support of body systems, with attention to increasing benzodiazepine elimination. The benzodiazepine receptor antagonist flumazenil (Anexate®, Romazicon®) may be required.

Gamma-Hydroxybutyrate

Gamma-hydroxybutryrate (GHB) occurs naturally in the human body as both a precursor and a metabolite of GABA. It was first chemically synthesized in 1960 in France as an anesthetic. However, the use of GHB was associated with insufficient analgesia and seizure activity, particularly tonic-clonic movements of the face or limbs (Vickers, 1969). During the 1980s, GHB gained popularity as a nutritional supplement (i.e., a growth hormone stimulator) among body builders, and its availability and sales greatly increased in health food stores and over the Internet. During this time, GHB also became widely known as a date-rape drug (see later discussion in this section).

In 2000, the use of GHB was made illegal across the United States with the passage of the federal Hillory J. Farias and Samantha Reid Date-Rape Drug Prohibition Act (H.R. 2130). However, its chemical precursor, gamma-butyrolactone (GBL; blue nitro, gamma G), which can be easily converted to GHB, continued to be widely available over the Internet.[33] In late 2002, the use of GBL decreased when the United States Drug Enforcement Agency arrested over 100 dealers in 84 cities in the United States and Canada. Despite these efforts, GHB use remains high, and is expected to increase, with diversions of the recently approved prescription product from its legitimate clinical use as adjunctive pharmacotherapy for the symptomatic management of narcolepsy. When legally used in this context, GHB generally is referred to by its generic name, sodium oxybate, or brand/trade name, Xyrem®.

GHB is often illicitly used in combination with other drugs and substances of abuse (see "Overdosage" section) to enhance their actions or diminish their associated toxicities. For example, GHB may be used with 3,4-methyl enedioxymethamphetamine (MDMA, ecstasy) because it reportedly attenuates the unpleasant effects (e.g., anxiety, tachycardia) associated with MDMA use.

Prevalence and Characteristics of GHB Use Among North American Adolescents

The primary users of GHB are adolescents and young adults who use the drug to relieve anxiety or to achieve alcohol-like disinhibitory euphoria, or high, without the hangover associated with alcohol use. Other major desired actions or reasons for use include: (1) arousal of sexual desire and increased sociability, along with decreased sexual inhibitions, particularly among bisexual and gay adolescent boys and young men; (2) as a nutritional supplement for body builders; and (3) the prevention or self-management of the alcohol and opiate analgesic withdrawal syndromes. In addition,

[33] Simple-to-follow recipes for the conversion of GBL to GHB are widely available over the Internet. In fact, some sites even offer kits complete with instructions and the requisite chemicals. Also illicit and available over the Internet is 1,4-butanediol (BD, thunder nectar, weight belt cleaner), which is converted (metabolized) in the body by the enzymes alcohol dehydrogenase and aldehyde dehydrogenase to GHB.

GHB continues to be administered to others without their knowledge in the context of perpetrating drug-facilitated crimes (e.g., robbery and sexual assault, including date-rape) (Lee & Levounis, 2008; Pagliaro & Pagliaro, 2009).

GHB is available as an oral solution by its generic name. Illicit powders and oral solutions also are produced in, imported into, and distributed across North America. Prior to ingestion, these illicit powders and solutions may be added to a container of bottled water at a rave or mixed into an alcoholic beverage at a circuit party (i.e., a gay dance/sex event party) or dance club. They also may be secretly mixed into another person's drink at a bar or mixed into a punch bowl at a social gathering (e.g., frat house party, postgame celebration).[34]

The typical user is a young man in his early 20s of European descent. Use predominantly occurs in the social context of all-night parties, dance clubs, music festivals, and raves. Increasingly, sexually active adolescent boys and girls and young adult men and women deliberately use GHB to enhance their sexual experiences. In this context, GHB is often used in combination with alcohol and other drugs and substances of abuse, particularly the psychodelics. (See Chapter 3, *The Psychodelics.*) Another population group that is associated with extremely high GHB use is bisexual and gay adolescent boys and men, regardless of continental descent. In fact, GHB is one of the five main club drugs (i.e., cocaine, GHB, ketamine, methamphetamine, and MDMA [ecstasy]) commonly used socially by this population group at circuit parties.

In their national survey of more than 7,000 students in the 7th through 12th grades, the Partnership for a Drug-Free America (2006) found that 4% of their participants reported use of GHB. Hopfer, Mendelson, Van Leeuwen, et al. (2006), in their study of youth in treatment for substance abuse, found that 7% reported GHB use.

General Pharmacology

GHB is a naturally occurring, or endogenous, precursor and metabolite of the major inhibitory neurotransmitter gamma-hydroxybutyric acid (GABA). It is found in several body tissues but has been studied most intensively in the CNS. Consequently, it has been used therapeutically as an adjunct to general anesthesia, for the treatment of alcohol and opiate analgesic dependence (in Europe) (Caputo & Bernardi, 2010; Leone, Vigna-Taglianti, Avanzi, et al., 2010), and to treat cataplexy associated with narcolepsy (Fuller, Hornfeldt, Kelloway, et al., 2004; Galloway, Frederick, Staggers, et al., 1997). In order to prevent the diversion of medical GHB to illicit markets for distribution and sale, several precautions were undertaken by the Food and Drug Administration, including the use of a different generic and brand/trade name (i.e., sodium oxybate [Xyrem®]) and the development of a restricted drug distribution system (i.e., the Xyrem® Success Program).

The use of GHB as a date-rape drug became increasingly common in North America during the 1980s and 1990s, when it was found to facilitate sexual assault while reducing the likelihood that a perpetrator would be charged, arrested, and convicted of aggravated sexual assault as a direct result of the drug's pharmacologic characteristics and actions. In this regard, GHB was the perfect drug—it is odorless, colorless, and easily dissolved in alcohol (Pagliaro & Pagliaro, 2009; Stillwell, 2002). It also is capable of causing muscle relaxation, profound sedation, social disinhibition (with associated increased sexual desire), and anterograde amnesia. Thus, along with public concern about the frequency and seriousness of GHB-facilitated date-rapes, another major concern was the difficulty associated with achieving successful prosecutions of perpetrators because of: (1) its relatively short half-life of elimination (i.e., approximately 30 minutes);

[34] GHB is available as a powder or as a liquid solution. The solution has a distinctly salty or soapy taste that is masked most often by chilling it in the refrigerator or mixing it in an alcoholic beverage.

(2) the lack of readily available specific assays for detecting GHB in victims; (3) the difficulty of differentiating levels of endogenous GHB from exogenous, or illicitly administered, GHB; and (4) its pharmacologic actions, including anterograde amnesia (Borgen, Okerholm, Lai, et al., 2004; Carter, Koek, & France, 2009; Ferrara, Zotti, Tedeschi, et al., 1992; Scharf, Lai, Branigan, et al., 1998; Slaughter, 2000).

Proposed Mechanism of Sedative-Hypnotic Action The exact mechanism of GHB's psychodepressant action has not been determined. However, four contributory mechanisms have been empirically confirmed:

1. GHB binds to its own endogenous receptors in the CNS that are found predominantly in the basal ganglia and hippocampus.
2. GHB appears to enhance the inhibitory actions that are modulated by the $GABA_B$ receptors.
3. GHB acts both presynaptically and postsynaptically to modulate the activity of other neurotransmitters in the CNS (e.g., the firing of dopaminergic neurons).
4. GHB presynaptically inhibits the release of dopamine into the synaptic cleft, resulting in an accumulation of dopamine in the presynaptic neuron (Pagliaro & Pagliaro, 2009).

Thus, it has been demonstrated that GHB is both a weak agonist of the $GABA_B$ receptor and a potent agonist of the excitatory GHB receptor with a biphasic effect on dopamine (i.e., initially dopamine release is inhibited, but at higher GHB concentrations, it is stimulated). Exogenously administered GHB also elicits its effects indirectly by means of its conversion to GABA (Carter, Koek, & France, 2009; Sewell & Petrakis, 2011).

Common Toxicities The use of GHB has been associated with several acute and chronic toxicities. Acute toxicities include: amnesia (anterograde); apnea; ataxia; bradycardia; cognitive impairment; coma (i.e., deep sleep, usually of short duration, from which the child or adolescent is difficult to arouse); confusion; diarrhea; dizziness; drowsiness; enuresis; headache; heartburn; hypersalivation; hypotension (particularly orthostatic); hypotonia; loss of consciousness; myoclonic seizures; nausea; psychomotor impairment; respiratory depression (with higher dosages); sleep (deep); slurred speech; sweating; vomiting; and weakness. Chronic toxicities include menstrual irregularities, physical and psychological dependence, somnambulism, and tinnitus (Garrison & Mueller; 1998; O'Connell, Kaye, & Plosay, 2000; Pagliaro & Pagliaro, 2009).

Physical and Psychological Dependence: GHB Withdrawal Syndrome A specific GHB withdrawal syndrome has been identified and described. Characteristic signs and symptoms include: agitation (severe), anxiety, autonomic excitation or instability, delirium (prolonged), diaphoresis, dizziness, dysphagia, hallucinations (auditory and visual), hypertension, insomnia, muscle aches, nystagmus, psychosis, rhabdomyolysis, seizures, tachycardia, and tremor (Rosenberg, Deerfield, & Baruch, 2003; Stijnenbosch, Zuketto, Beijaert, et al., 2010; van Noorden, Kamal, de Jong, et al., 2010; Wojtowicz, Yarema, & Wax, 2008; Zepf, Holtmann, Duketis, et al., 2009). As with other drugs and substances of abuse, the signs and symptoms of the GHB withdrawal syndrome vary in expression and intensity, according to the level of regular, long-term use prior to abrupt discontinuation.

The most severe forms of the GHB withdrawal syndrome occur among regular, long-term users who use GHB every 1 to 3 hours around the clock. Among these users, the GHB withdrawal syndrome may begin within 1 hour of the last use of GHB and last up to 15 days (Dyer, Roth, & Hyma, 2001; Perez, Chu, & Bania, 2006). This withdrawal syndrome may be potentially life threatening. It also is often quite resistant to pharmacotherapeutic management with the benzodiazepines, such as

diazepam (Valium®) or lorazepam (Ativan®), and significantly higher than usual dosages are often required (Rosenberg, Deerfield, & Baruch, 2003; Stijnenbosch, Zuketto, Beijaert, et al., 2010; Tarabar & Nelson, 2004; van Noorden, van Dongen, Zitman, et al., 2009). The cases of GHB withdrawal that are refractory to benzodiazepine pharmacotherapy may respond to other sedative-hypnotic pharmacotherapy, such as barbiturate (e.g., phenobarbital [Luminal®]) or chloral hydrate (Noctec®) pharmacotherapy (McDonough, Kennedy, Glasper, et al., 2004). Along with medical support and monitoring, physical restraint may be required (Dyer, Roth, & Hyma, 2001).

Overdosage GHB overdosage may be fatal. However, fatalities are relatively rare (i.e., less than 200 fatalities have been reported to date) and are usually associated with polyuse of the drugs and substances of abuse, particularly other psychodepressants, including alcohol and other sedative hypnotics and the opiate analgesics (Knudsen, Jonsson, & Abrahamsson, 2010).[35] Alcohol, heroin, and MDMA (ecstasy) are the other drugs and substances of abuse that are most often involved in GHB overdosage. GHB users who overdose usually present to the emergency department in an unconscious state, often in a coma. Other presenting signs and symptoms of overdosage may include agitation, apnea, blurred vision, bradycardia, confusion, delirium, headache, hypothermia, loss of bladder and bowel control, muscle weakness, myoclonic seizures, nausea, psychomotor impairment, respiratory impairment, sweating, and vomiting. Generally, with proper recognition and care—in particular, with attention to cardiac and respiratory support, including aspiration precautions—complete recovery, without sequelae, can be expected within 6 to 8 hours. There is no known antidote (Carter, Pardi, Gorsline, et al., 2009; Mason & Kerns, 2002; Pagliaro & Pagliaro, 2009).

VOLATILE SOLVENTS AND INHALANTS

The volatile solvents are a diverse group of chemical compounds that are liquid at room temperature and readily evaporate when exposed to air. Virtually any marketed product that contains a volatile organic solvent is capable of being used for its major psychodepressant action that produces a desirable, alcohol-like disinhibitory euphoria, or high. The volatile inhalants are primarily anesthetic gases (e.g., nitrous oxide or laughing gas) but also include propane and other gases, all of which are inhaled in much the same way as volatile solvents. These psychodepressants (see Table 1.1) are generally easy to use, and the large surface area of the lungs assures both their rapid absorption into the circulatory system and rapid onset of action.

The major volatile solvents include:

- Acetone, found in nail polish remover, model (e.g., airplane, car) glue, permanent markers, and rubber cements
- Benzene, found in cleaning fluids, gasoline, rubber cements, and tire tube repair kits
- Butane, found in cigarette lighters, cooking fuel gas, hair spray, spray paint, and some air fresheners and deodorants
- Chlorinated hydrocarbons (e.g., toluene), found in airplane glues, correction fluids, degreasers, gasoline, lacquer thinners, nail polish, plastic cements, shoe polish, and spray paints)
- Fluorinated hydrocarbons (e.g., freons), found in aerosols, air conditioning units, refrigerants, and propellants #11 and #12
- Gasoline
- Paint thinner
- Trichloroethylene and trichloroethane, which are also chlorinated hydrocarbons,

[35] This incidence is notably higher among adults in some other countries, such as Sweden, and is expected to increase initially among adults primarily as the prescription form of GHB (i.e., sodium oxybate, Xyrem®) increasingly is diverted for personal use (Zvosec, Smith, & Hall, 2009).

found in degreasers, dry cleaner formulations, Liquid Paper® or other correction fluid, refrigerants, spot removers, and PVC cement.
- Xylene, used in chemical production and manufacturing[36]

The volatile gases include several gases that are used for their psychodepressants actions, including nitrous oxide and propane.[37] Nitrous oxide, once commonly used as an anesthetic in dentistry, is still used as a short-acting anesthetic for some dental procedures. Propane is commonly used as a motor vehicle and cooking fuel. It also is used for home heating.

Prevalence and Characteristics of Volatile Solvent and Inhalant Use Among North American Children and Adolescents

Over 25 million North Americans have abused volatile solvents or inhalants at least once in their lives (Pagliaro & Pagliaro, 2009; Volkow, 2009). Currently, largely due to easy accessibility and relatively low cost, the number of new volatile solvent and inhalant users in the United States appears to be increasing (Brouette & Anton, 2001; Pagliaro & Pagliaro, 2009; Pagliaro & Pagliaro, *Clinical Patient Data Files*) with over 1 million new users being recorded annually from across all of North America (Spiller, 2004).[38] Among adolescents, these psychodepressants are now the fifth most commonly used drugs and substances of abuse after alcohol, caffeine, cannabis (marijuana), and nicotine (tobacco) (Pagliaro & Pagliaro, 2009).

Trends

The reported lifetime prevalence of volatile solvent and inhalant use peaked at approximately 20% in the mid-1990s among North American adolescents 10 to 20 years of age (U.S. Department of Health and Human Services, 2001). Since that time, use has remained relatively constant at approximately 15% (Anderson & Loomis, 2003; Crocetti, 2008; Intelligence brief, 2001; Lorenc, 2003; Muilenburg & Johnson, 2006; J. F. Williams & Storck, 2007). For example, in its national survey of over 7,000 adolescents, the Partnership for a Drug-Free America (2006) found, in regard to inhalant use, that 20% of respondents reported lifetime use, 12% reported past-year use, and 7% reported past-month use (i.e., use during the previous 30 days).

Johnston, O'Malley, Bachman, et al. (2008), in their national study of adolescent drug use, found in 2007 that the use of inhalants within the previous year was reported by 8.3% of 8th-grade students, 6.6% of 10th-grade students, and 5% of 12th-grade students. More recently, in an analysis of the data for the Community Epidemiology Work Group of the NIDA, M. P. O'Brien (2008) found that 13.3% of U.S. high school students reported lifetime inhalant use. In their 2010 in-school survey of adolescent use of the drugs and substances of abuse, Johnston, O'Malley, Bachman, et al. (2010b) found that 14.5% of 8th-grade students, 12% of 10th-grade students, and 9% of 12th-grade students reported a lifetime prevalence of inhalant use. These reported percentages of inhalant use across grade levels are interesting because they decrease with increasing grade level—a pattern of use that is exactly the opposite of what is observed for virtually all of the other drugs and substances of

[36] This is only a partial list of commonly used volatile solvents. Literally hundreds of other volatile solvents can be, and have been, used for their psychodepressant actions. Between 1993 and 2008, U.S. poison control centers dealt with exposures to over 3,400 different volatile solvent and inhalant products (Marsolek, White, & Litovitz, 2010).

[37] Propane is used in some products (e.g., certain hair sprays and spray paints) as an aerosol propellant.

[38] Widespread use of the volatile solvents and inhalants among children and adolescents also is increasing worldwide, in both developed and developing countries, particularly among girls (e.g., Basu, Jhirwal, Singh, et al., 2004; Medina-Mora & Real, 2008).

abuse, which conversely increase with increasing grade level, at least through adolescence.

Attraction to Use

Children and adolescents primarily use the volatile solvents and inhalants to get high. Although some adults,[39] including those who are homeless or have mental disorders (e.g., schizophrenia), sometimes use volatile solvents as their major drug of choice, children and adolescents currently comprise the largest group of users (Marsolek, White, & Litovitz, 2010; Pagliaro & Pagliaro, 2009; Spiller, 2004).

Virtually all of these children and adolescents are introduced to the volatile solvents and inhalants by their siblings, classmates, or friends. Among these children and adolescents, volatile solvent and inhalant use typically is a shared group experience. As such, peer pressure plays a significant role in regard to which volatile solvents and inhalants are used, where they are used, and their frequency of use. In their state-wide interviews of adolescents who were in youth services residential care, Perron and Howard (2008) found that those who had friends or siblings who used volatile solvents and inhalants were significantly more likely to associate little or no risk with volatile solvent and inhalant use and indicate intentions for future volatile solvent and inhalant use.

Although volatile solvent use has been reported for both boys and girls[40] as young as 4 or 5 years of age, young adolescent boys[41] are the major users. These boys usually are from low socioeconomic backgrounds and are often members of families that are experiencing severe financial problems, parental alcoholism, and other significant family discord.[42] Reports of lifetime use of the volatile solvents and inhalants also are extremely high among samples of youth involved with the juvenile justice system (Barclay, 2009; Howard, Balster, Cottler, et al., 2008; Howard & Perron, 2009).

The overwhelming majority of youth who have used the volatile solvents and inhalants can be categorized as experimental users. Few become regular, long-term users. Of the wide variety of volatile solvents and inhalants currently available in North America, the most abused products are correction fluid, gasoline, glue, lighter fluid, nitrous oxide, paint thinner, shoe polish, and spray paint (Pagliaro & Pagliaro, 2009; Wu, 2005). Some of the common signs and symptoms associated with the use of volatile solvents and inhalants for the achievement of their psychodepressant effects are presented in Table 1.9.

Common Methods of Use

The volatile solvents are not deliberately ingested orally in order to get high.[43] Generally they are poured onto a rag, or into a balloon or plastic bag, that is then held up to the face, where the fumes are inhaled through the mouth or sniffed through the nostrils. Other common

---

[39] For example, volatile solvents and inhalants may be used by refrigeration and air conditioning repair technicians, who selectively use freon, and anesthetists, who selectively use nitrous oxide.

[40] Over the 1990s, published studies (e.g., McGarvey, Clavet, Mason, et al., 1999; Neumark, Delva, & Anthony, 1998) increasingly found no differences between boys and girls in regard to the use of the volatile solvents.

[41] Excluding North American adolescents of African or Asian descent, among whom volatile solvent and inhalant use has always been low.

[42] For example, use traditionally has been very high among preadolescents and adolescents of Aboriginal descent, including First Nations peoples and Inuits in Canada and American Indians and Alaskan Natives in the United States (Pagliaro & Pagliaro, 2009). Although the United States observed a significant decline in volatile solvent use among American Indian youth during the 1990s (Beauvais, Wayman, Jumper-Thurman, et al., 2002), Saylor, Fair, Deike-Sims, et al. (2007) found, in their study of preadolescent students, that 11.5% of 5th-, 6th, and 7th-grade students of Alaskan Native descent reported lifetime use of inhalants. In addition, since 2000, several Indian reserves in Canada reported volatile solvent use affecting over 50% of their youth (Dell, 2005; D. O'Brien, 2005; Pagliaro & Pagliaro, *Clinical Patient Data Files*).

[43] Volatile solvents may be accidentally ingested in poisoning cases, which may be fatal, particularly for young children. (See related discussion of unintentional childhood poisoning with the drugs and substances of abuse in Chapter 5, *Exposure to the Drugs and Substances of Abuse From Conception Through Childhood.*)

TABLE 1.9 Volatile Solvents and Inhalants: Common Signs and Symptoms of Use

Anxiety	Inattentiveness
Anorexia	Incoordination
Apathy	Insomnia
Appearance of drunkenness	Irritability
Ataxia	Light-headedness
Belligerence	Memory impairment or loss
Burns	Muscle weakness
Cache (i.e., "stash") of solvents or inhalants in unusual location (e.g., bedroom, school locker)	Nausea
	Nystagmus
Chest pain	Paint stains on clothes or face
Chemical odor on breath or clothes	Perioral pyodermas
Cognitive impairment	Pneumonitis
Contact dermatitis, or inflammation of the skin by direct contact with the solvent or inhalant that may result in a rash or blistering of the skin and redness, swelling, and itching	Poor grooming and hygiene
	Rapid mood change
	Rash around the mouth or nose
Coughing	Red-colored nose
Dazed appearance	Rhinitis
Depression	Rhinorrhea
Diplopia	Runny or watery eyes
Disorientation	Slurred speech
Dizziness	Sneezing
Drowsiness	Sores around the mouth or nose
Drunken appearance	Spray paint speckles around the mouth or nose
Dypsnea	Strong chemical odor on the breath
Empty solvent or spray paint containers in unusual location (e.g., bedroom, school locker)	Strong chemical odor from clothing
	Sudden decrease in academic performance
Epistaxis, unexplained	Sudden decrease in school attendance
Encephalopathy (i.e., any brain dysfunction)	Thirst, unusual or persistent
Euphoria	Tinnitus
Excitability	Tremor
Falling asleep in class (often after recess)	Volatile solvent-soaked clothes or rags (e.g., in closet or school locker)
Fatigue	
Forgetfulness	Vomiting
Headache	Weight loss
Impaired judgment	Wheezing

Note: These signs and symptoms, when uncharacteristic or cannot be explained by other causes for a child or adolescent, may be indicative of volatile solvent or inhalant use. However, they are not exclusive to their use and are thus not pathognomonic. However, the more signs and symptoms that a child or adolescent has, the more likely he or she is to be using volatile solvents or inhalants. Note also that, in addition to the individual differences that may be observed among children and adolescents in regard to these signs and symptoms, significant variability also occurs in relation to the specific volatile solvent or inhalant used and the dosage or amount used.

methods of use include spraying an aerosol product directly into the mouth or nose, placing a solvent-soaked rag in the mouth and inhaling the fumes as the rag is held in the mouth, and removing the lid of a solvent container and directly inhaling the fumes from the container. The use of volatile solvents and inhalants for their psychodepressant actions is variously referred to by users as airblasting, bagging, gasing, glading, huffing, oiling, painting, penny cleaning, sacking, sniffing, spraying, or Texas shoe-shining. Users, alone or in small groups, also simply may go into a small enclosed space (e.g., bathroom, car, or closet), spray several cans of computer duster spray, cooking spray, hair spray, or spray deodorant into the air, and then breathe in the fumes. They often warm the container by holding it in their hands or over an external heat source, such as the stove or radiator of a car. Warming the container significantly increases the volatility and amount of the solvent inhaled, which intensifies the resultant high (Pagliaro & Pagliaro, 2009).

Association with Mental Disorders

Volatile solvent and inhalant use by children and adolescents often has been identified as presaging problematic behavior and the diagnosis of several mental disorders among older adolescents and young adults. For example, heroin use in young adulthood (Storr, Westergaard, & Anthony, 2005; Wu & Howard, 2007), problematic patterns of alcohol use in college students (Bennett, Walters, Miller, et al., 2000), and injection drug use among adolescents (Wu & Howard, 2007) have all been noted to follow significant histories of childhood or early-adolescent volatile solvent and inhalant use.

In regard to the nature of the relationships between volatile solvent and inhalant use and the problematic use of other drugs and substances of abuse among children and adolescents, we tend to agree with the observation made by Wu, Pilowsky, and Schlenger (2004) that, "Adolescents with an inhalant use disorder may represent a subgroup of highly troubled youths with multiple vulnerabilities" (p. 1206).

Other clinicians and researchers (e.g., Perron & Howard, 2009; Sakai, Hall, Mikulich-Gilbertson, et al., 2004) have shared similar observations. Thus, the use of volatile solvents and inhalants may precede the development of other substance use disorders and other mental disorders (OMDs). However, it does not appear to cause them. Some intervening variables(s), or cofactor(s), that may be genetically or environmentally controlled appear to be instrumental in this regard. For example, FAS/FASD or severe childhood physical or sexual abuse may, in some cases, be the factor primarily responsible for both the use of volatile solvents and inhalants and the related OMDs that are later diagnosed. (See related discussion in Chapter 8, *Dual Diagnosis Among Adolescents.*)

This view appears to account largely for the commonly observed related behavior of children and adolescents who live on reservations and reserves in the United States and Canada. As previously noted, Aboriginal peoples of North America (i.e., Alaska Natives, First Nations Peoples, American Indians, Inuits)—particularly children and adolescents—have the highest combined rate of volatile solvent and inhalant use of all groups in North America (Pagliaro & Pagliaro, 2009; Pagliaro & Pagliaro, *Clinical Patient Data Files*; Siqueira & Crandall, 2006). These children and adolescents also have extremely high rates of FAS/FASD (see Chapter 5, *Exposure to the Drugs and Substances of Abuse From Conception Through Childhood*), and the highest rates of: physical abuse (7%) (D. K. Bohn, 2003; Libby, Orton, Novins, et al., 2004); sexual abuse (4% to 5% overall, and much higher for girls than boys) (Duran, Malcoe, Skipper, et al., 2004; Koss, Yuan, Dightman, et al., 2003; Libby, Orton, Novins, et al., 2004); and extreme poverty, including food insecurity (Brenneman, Rhoades, & Chilton, 2006; Sarche & Spicer, 2008; Singleton, Holve, Groom, et al., 2009; Willows, Veugelers, Raine, et al., 2009). Consequently, they also suffer more than their fair share of "pains, disappointments, and impossible tasks" (Freud, 1930/1989). As identified in a study of adolescent volatile solvent and inhalant users, they used these drugs and substances of abuse as a means of mental escape (Siegel, Alvaro, Patel, et al., 2009, p. 597).

Novins and colleagues (e.g., Novins, Beals, & Mitchell, 2001; O'Connell, Novins, Beals, et al., 2007) have characterized the use of other drugs and substances of abuse as progressing from the use of volatile solvents or inhalants (i.e., serving as gateway drugs) by American Indians as consonant with stage theory. While we agree, it is probably worthwhile to state the obvious: that is, the reasons that children begin using volatile solvents and inhalants, as opposed to other drugs and substances of abuse, include that they are readily available at home or in school and are easy to use, as illustrated by the example of a 5-year-old sniffing glue rather than snorting cocaine.

General Pharmacology

The various volatile solvents are used to rapidly achieve a short-lived disinhibition euphoria that is similar to that achieved with acute alcohol intoxication. Volatile solvents have no generally approved medical use and, thus, little is known about their actual human pharmacology because they were never intended for personal use by humans.[44] From what is known, they appear to demonstrate similar pharmacologic actions and desired and undesired effects and toxicities. These actions are generally associated with their concentration, method of use, and frequency of use. Once inhaled into the lungs, the volatile solvents and inhalants are readily absorbed into the bloodstream and rapidly reach their psychotropic site of action—the brain. The effects of the volatile solvents and inhalants occur within minutes of inhalation and, depending on the solvent or inhalant used, its concentration, and its method of use, last from 10 to 60 minutes—the perfect time frame for a child to get high at school during lunch or recess and return to class without his or her use of the volatile solvent or inhalant being readily detected by the teacher.

Proposed Mechanism of Psychodepressant Action

The volatile solvents and inhalants depress the CNS through a variety of mechanisms that have not been fully elucidated. The result of use is a rapid and short-lived disinhibition euphoria that is very similar to acute alcohol intoxication. As previously noted, the volatile solvents have no generally approved medical use, and little is known about their actual human pharmacology because they were never intended for human personal use involving inhalation. However, most of the inhalant gases were developed for use during surgical procedures as anesthetics. Thus, there is more information about their therapeutic use and toxicities in humans.

Common Toxicities

The human data that are available are predominantly based on case studies and reports of either accidental or deliberate overdosage. Still, even in these cases, it is extremely difficult to identify the exact cause or mechanism associated with the observed toxicity for three reasons:

1. Products (e.g., cleaning products; glues) are often reformulated as new or improved products, which increases the likelihood of changes being made to their ingredients and concentrations.
2. The nature of the case reports, which are based largely on interviews of children and adolescents, including, in many cases, friends of the deceased who have been engaged in the same activity.
3. The nature of the volatile solvent or inhalant, as noted above in regard to its proposed mechanism of psychodepressant action.

For example, in relation to the third reason listed, a pregnant adolescent girl may huff gasoline and subsequently give birth to a baby with FAS/FASD-characteristic physical features. Consequently, because these features also have been associated with toluene, which is found in gasoline, they may be identified as being the result of toluene embryopathy. (See Chapter 5, *Exposure to the Drugs and Substances of Abuse From Conception Through Childhood.*) However, gasoline typically contains more than 150 different chemicals, including benzene, ethyl benzene, MTBE, toluene, and other chemicals that may vary with the source of the crude petroleum base, the manufacturer,

[44] No controlled studies on the use of volatile solvents by humans have been conducted, and none is expected to be conducted in the future. The major reason for the lack of research in this area is the difficulty in designing ethical research studies that do not pose a high risk to subjects. The data that are available include: published retrospective studies obtained from emergency room medical histories and progress notes; published medical case histories that report observed toxicities, related sequelae, and treatment; reports and statistics on overdose deaths; and published qualitative studies and anecdotal reports obtained from volatile solvent and inhalant users who may also share this information over various Internet sites.

the production process, and even the time of year. Therefore, while ascribing the noted effects to toluene may be correct, it is at best only speculative. In addition, it is highly likely that the pregnant adolescent also consumed alcohol during her pregnancy.

Marsolek, White, and Litoritz (2010) analyzed data from the National Poison Data System of 35,453 cases involving volatile solvents and inhalants reported to U.S. poison control centers from 1993 to 2008. Gasoline, paint, and propellants were the volatile solvents and inhalants most frequently involved, but air fresheners, butane, and propane had the highest associated fatality rates. In terms of lethality, Spiller (2004), using national data from the Toxic Exposure Surveillance System, found that air fresheners, butane, gasoline, and propane were responsible for the majority of deaths. Although the use of volatile solvents and inhalants for their psychodepressant actions is generally reported as occurring roughly equally among boys and girls, 75% of the poison system cases involved boys. This finding suggests, as noted by Marsolek, White, and Litoritz (2010), "that boys may pursue riskier usage behaviors" (p. 906).

The toxicity of the solvents and inhalants are difficult to categorize because of their diverse nature. However, in general, they typically are directly irritating to the respiratory system upon inhalation, the GI system when orally ingested (e.g., in the context of accidental poisoning or deliberate suicide attempts), and the cutaneous system when, for example, they are inadvertently spilled or splashed on the face, or in the eyes, or otherwise come into contact with the hands, legs, or other parts of the body. In addition, as noted by their classification as psychodepressants, they can directly cause varying degrees of CNS depression, ranging from drowsiness or mild sedation to profound sedation. They also can cause dose-dependent respiratory depression that can, in the worst-case scenario, be fatal (Pagliaro & Pagliaro, 2009).

Acute Toxicities The signs and symptoms of acute toxicity that have been associated with the use of the volatile solvents include anorexia; fatigue; slowed, unclear thinking; and thirst. The volatile solvents primarily adversely affect the central and peripheral nervous systems. Most volatile solvents seem to cause a rapid depression of the CNS resulting in an alcohol-like disinhibition euphoria. Concomitantly, there is drowsiness and gross motor and fine motor incoordination that result in impaired ambulation and slurred speech. Amnesia also can occur, and hallucinations occasionally have been reported. The extent of these toxic effects depends on the volatile solvent or inhalant used, the amount used, and the acute duration of use. If the user is otherwise healthy, the toxicities associated with the acute use of volatile solvents are generally temporary and reversible. However, acute toxicity can be fatal, as described in the following sections.

Fatalities Fatalities associated with child and adolescent use of the volatile solvents and inhalants for the purpose of getting high was first reported in 1970 (Bass, 1970). Two fatalities attributed to butane and propane abuse serve to emphasize the potential for death. As shared by Siegel and Wason (1990):

> An 11-year-old boy collapsed in a movie theater bathroom. A butane cigarette lighter fuel container and a plastic bag were found next to him. He also had several bottles of typewriter correction fluid in his pocket. Cardiopulmonary resuscitation was instituted; efforts proved unsuccessful and he was pronounced dead shortly thereafter. Post mortem examination showed no evidence of organic disease or anatomic cause of death. Toxicologic analysis confirmed the presence of butane in the patient's blood and lung tissue.
>
> A 15-year-old boy was found unconscious in a backyard. Three companions related that the four teenagers had taken a 20-gallon propane tank from the family gas grill, placed some of the gas in a plastic bag and were inhaling it in order to get high. They also engaged in "torch breathing" whereby they purposefully exhaled the propane gas and ignited it. The subject collapsed soon after inhaling the gas; fumes,

> ignited by a match, resulted in a flash fire. The patient did not sustain any burns. He could not be resuscitated and died en route to the hospital. Post mortem examination in this case, too, failed to reveal an organic cause of death. Propane was detected in the blood and lung tissues. (p. 1638)

In North America, approximately 200 deaths occur annually in relation to the use of the volatile solvents and inhalants. Related deaths have been reported among children as young as 8 years of age (Maxwell, 2001). These volatile solvent and inhalant-related deaths have been attributed to severe damage to internal body organs, as well as accidental injury, asphyxiation or suffocation, and sudden sniffing death (see the following sections for further discussion).

Accidental Injury Death by accidental injury typically results from falls and other events that may be associated with the poor judgment and impulsive behavior that occurs during intoxication with a volatile solvent or inhalant. Death by accidental injury also may be due to fires associated with the use of these flammable substances or to head injuries sustained when losing consciousness or passing out. (Also see the next section, "Asphyxiation.")

Asphyxiation Asphyxiation, or suffocation, has been associated directly with the method of volatile solvent and inhalant use as well as the pharmacology of volatile solvents and inhalants as psychodepressants. Quite often, a plastic bag is placed over the nose and mouth or the entire head to contain the fumes of the volatile solvent and, thus, increase the amount inhaled. This method of use creates the risk of death as a result of fainting, or losing consciousness, and suffocating as a result of the plastic bag being left in place over the nose and mouth. Death in these cases also is associated with the amount of the volatile solvent or inhalant used. For example, any of the volatile solvents, when used in sufficient quantities, can depress the CNS and cause respiratory arrest. In addition, the inhalation of butane may induce severe laryngeal edema and laryngospasm resulting in death. The inhalation of propane and other volatile inhalants directly displaces oxygen from the surrounding atmosphere that can induce asphyxia and resultant death. In some cases, death has been a deliberate outcome of a suicide attempt (Gross & Klys, 2002). However, in other cases, it has been the undesired consequence of deliberately using propane to induce hypoxia in order to obtain associated autoerotic stimulation (Jackowski, Römhild, Aebi, et al., 2005; Musshoff, Padosch, Kroener, et al., 2006; Sauvageau & Racette, 2006).

Sudden Sniffing Death Sudden sniffing death may occur among children and adolescents who use the volatile solvents and inhalants as a result of heart failure or severe respiratory depression. For example, the use of halogenated (e.g., fluorinated) hydrocarbons (e.g., freon), in particular, has been associated with fatal cardiac dysrhythmias.[45] As well, any volatile solvent or inhalant can cause paralysis of the respiratory centers if a large enough dose is absorbed into the bloodstream. In most cases, however, sudden sniffing death occurs when a child or adolescent has been engaged in some type of strenuous activity (e.g., running) or has experienced sudden unexpected stress (e.g., being unexpectedly discovered by a parent or teacher) immediately after heavy use of the solvent or inhalant. Both strenuous activity and unexpected stress cause the sudden release of epinephrine in the body. It is believed that volatile solvents and inhalants increase the

[45] The use of nonhalogenated hydrocarbons, including butane, isobutane, and propane, also has been associated with fatal cardiac dysrhythmias (Edwards & Wenstone, 2000; Girard, Le Tacon, Maria, et al., 2008; Sugie, Sasaki, Hashimoto, et al., 2004; Williams & Cole, 1998). Some researchers (e.g., El Menyar, 2006; El-Menyar, El-Tawil, & Al Suwaidi, 2005) have suggested that these heart attacks may be a result of volatile solvent or inhalant-induced coronary artery spasm.

heart's sensitivity to the stimulant actions of epinephrine and thus contribute to the heart attack (i.e., myocardial infarction) experienced by the child or adolescent (Pagliaro & Pagliaro, 2009).[46]

Chronic Toxicities Regular, long-term use of the volatile solvents (e.g., gasoline) and inhalants can result in gradual and progressive polyneuropathy, including optic neuropathy and peripheral neuropathy. In addition, cerebellar ataxia, encephalopathy, and Parkinsonism may occur, depending on the solvent or inhalant used (Burns, Shneker, & Juel, 2001; Williams & Storck, 2007).[47]

Toluene (methylbenzene) is one of the most common compounds found in volatile solvents, particularly glues, and its use causes a central neuropathy characterized by encephalopathy with ataxia, behavioral changes (e.g., self-mutilation), convulsions, and hallucinations. Regular, long-term use of toluene has been associated with the deterioration of the CNS characterized by neuropsychiatric disorders (e.g., dementia), persistent cerebellar ataxia, and peripheral neurotoxicity (Filley, Halliday, & Kleinschmidt-DeMasters, 2004). Although reflexes are normal, profound muscle weakness and rhabdomyolysis have been reported. The profound weakness may be related to electrolyte imbalance, particularly hypokalemia (Baskerville, Tichenor, & Rosen, 2001). Renal toxicity with severe electrolyte imbalances has been reported among adults, as have renal calculi. These toxicities are thought to be due to increased renal excretion of hippurate, a metabolite of toluene. Other effects have been reported, such as abdominal pain, nausea, and vomiting, including hematemesis.

Although many of the volatile solvents and inhalants are associated with significant morbidity and mortality, currently they are used widely by North American children and adolescents, primarily because of their: 1) desired actions; 2) universal availability; and 3) low cost.

Physical and Psychological Dependence

The use of toluene as a means to achieve desired psychodepressant actions has been associated with both physical and psychological dependence. However, the abuse potential for the majority of the other volatile solvents and inhalants has not been well characterized and is still not completely understood. It now appears that tolerance to the desired actions of the volatile solvents generally occurs with regular, long-term use. In addition, several signs and symptoms, including anxiety, depression, dizziness, insomnia, irritability, and tremors, are commonly observed among users when regular, long-term volatile solvent use is abruptly discontinued. However, it has not been established whether these signs and symptoms are

[46] The majority of reported cases of sudden sniffing death over the past two decades, which involved children and adolescents deliberately abusing the volatile solvents and inhalants (primarily, butane), have originated primarily in Europe and the Middle East.

[47] As previously noted, volatile solvents are usually available to the public not as pure single chemicals but as mixtures containing two or more ingredients in a commercial product. A variety of additives are added to improve performance, stability, or production of these products. Often a second minor ingredient that does not cause the high is more dangerous to the health of the user than the major high-producing ingredient. In addition, the various ingredients sometimes can work together, causing serious toxicity or death, even though, when used individually, toxicity would not result.

Manufacturers frequently change the ingredients of their volatile solvent products or their concentrations (e.g., labels that read *new*, *improved*, *reformulated*, *extra strength*) so that a product that was safe and nontoxic previously may subsequently, due to a change in formulation or concentration, cause serious toxicity or death. For example, during the early 1970s, seven young men used a popular lacquer thinner that they had safely used many times previously. However, the product was reformulated to decrease production costs during an oil embargo. The result was death for one of the men as a result of respiratory failure; permanent respiratory paralysis for two of the men; and severe muscle and nerve damage for four of the men, who subsequently required the use of wheelchairs. From this tragic example, it is apparent that the potential for serious toxicity accompanies the use of all volatile solvents—even those that have been used previously and were believed to be safe.

physical or psychological in origin (Pagliaro & Pagliaro, 2009).

Overdosage

Relatively few overdosages have been associated with the use of the volatile solvents and inhalants other than those occurring as a result of accidental poisonings among infants and toddlers. (See related discussion in the earlier "Acute Toxicities" section under "Fatalities" and "Accidental Injury.")

CHAPTER SUMMARY

This chapter presented an overview of the prevalence and characteristics of North American child and adolescent use of the psychodepressants—the opiate analgesics, particularly heroin and oxycodone (OxyContin®); the sedative-hypnotics, particularly alcohol, the benzodiazepines, and GHB; and the volatile solvents and inhalants, particularly air fresheners, butane, gasoline, and propane, which have been associated with the highest rates of death among North American children and adolescents. The general pharmacology of these drugs and substances of abuse also was presented with attention to their proposed mechanisms of action and related common acute and chronic toxicities, including physical and psychological dependence, and overdosage.

Changing trends in the use of these drugs and substances of abuse, including their methods of use, also were presented. For example, the intravenous use of opiate analgesics generally has been replaced with intranasal insufflation (i.e., snorting) and pulmonary inhalation (i.e., smoking). Other trends include the "pharming" of prescription sedative-hypnotics and the troubling illicit use of GHB in the perpetration of date-rape and other serious crimes. Binge drinking among adolescents and young adults, particularly college students, has increased significantly along with the more recent trend of drinking large amounts of alcohol with the concomitant drinking of caffeinated energy drinks in an attempt to prevent or slow the occurrence of drunkenness. Also troubling is the increased use of alcohol by adolescent girls and young adult women while pregnant, regardless of the potential risk of FAS/FASD. While volatile solvents and inhalants are generally used experimentally by children and adolescent boys, they continue to be related to several fatalities each year related to internal body organ damage, accidental injury, asphyxiation, and sudden sniffing death. Aboriginal peoples of North America, particularly children and adolescents, continue to have the highest combined rate of volatile solvent and inhalant use.

This chapter also identified the potential limitations of government-supported and sponsored national surveys and other studies that may be biased and restricted in the generalizability of their findings and subsequent reporting of lower levels of child and adolescent use of the drugs and substances of abuse. These limitations may occur because of methodological and sampling flaws, such as the neglect of groups of children and adolescents at particularly high risk—including those without land-line phones, those who are school drop-outs, and those who are homeless runaways, living on the streets. Regardless, the various psychodepressants continue to be readily available, and, often mediated by peer influences and other related factors, children and adolescents continue to commonly use these drugs and substances of abuse for their psychodepressant actions and effects.