effects may be increased. The effects of the drug are reported to be similar to those of ketamine, LSD, and marijuana.

## OTHER DRUGS OF ABUSE

A number of other pharmacologically diverse drugs of abuse are often referred to as "club drugs" because these are frequently used in bars, at concerts, and at rave parties. Commonly abused club drugs include flunitrazepam, GHB, and ketamine and are described below. Methamphetamine, MDMA, and LSD are also considered club drugs and were described earlier in this chapter. Abuse of club drugs at high doses, especially in combination with alcohol, can be lethal and should be treated as a medical emergency. GHB and ketamine can be identified in blood, and flunitrazepam can be identified in urine and hair samples. Flunitrazepam and GHB toxicity can be treated with antagonists at benzodiazepine and γ-aminobutyric acid B ($GABA_B$) receptors, respectively.

*Flunitrazepam* (Rohypnol) is a benzodiazepine derivative primarily used to treat insomnia, but it has significant abuse potential because of its strong hypnotic, anxiolytic, and amnesia-producing effects. It is a club drug commonly referred to as a "date-rape drug" or "roofies." The drug enhances $GABA_A$ receptor activity, and overdose can be treated with flumazenil, a benzodiazepine receptor antagonist. Flunitrazepam is typically used orally but can be snorted or injected. Concomitant use of alcohol or opioids is common, and this enhances the sedative and hypnotic effects of flunitrazepam and also the risk of motor vehicle accidents. Overdose can produce life-threatening respiratory depression and coma. Abrupt cessation after chronic use may result in a benzodiazepine withdrawal syndrome consisting of anxiety, insomnia, disordered thinking, and seizures.

*GHB* (Xyrem) is a sedative drug that is approved by the FDA for the treatment of narcolepsy. It is classified as a club drug, is sometimes used in combination with alcohol or other drugs of abuse, and has been implicated in cases of date rape. It is also used by body builders as a growth hormone stimulant. GHB is usually available as a liquid, is taken orally, and has no distinctive color or odor. Its stimulant properties are attributed to agonist activity at the GHB receptor, but it also has sedative effects at high doses that reflect its activity at $GABA_B$ receptors. $GABA_B$ antagonists can reverse GHB's sedative effects, and opioid antagonists (naloxone, naltrexone) can attenuate GHB effects on dopamine release. Low doses of GHB may produce euphoria and disinhibition, whereas high doses result in nausea, agitation, convulsions, and sedation that can lead to unconsciousness and death from respiratory depression. In 2011, more than 2400 emergency ward admissions involved GHB.

*Ketamine* (Ketaset, Ketalar) is a dissociative anesthetic, similar to PCP. In veterinary medicine, it is used for brief immobilization. In clinical medicine, it is used for sedation, analgesia, and to supplement anesthesia. Ketamine increases heart rate and blood pressure, with less respiratory depression than other anesthetics. Ketamine's popularity as a club drug appears to reflect its ability to induce a dissociative state and feelings of depersonalization, accompanied by intense hallucinations and subsequent amnesia. It can be administered orally, by smoking (usually in combination with tobacco and/or marijuana), or by IV or IM injection. Like PCP, it binds to NMDA receptors and acts as a noncompetitive NMDA antagonist. In 2011, ketamine accounted for 1550 emergency ward admissions. Ketamine has a complex profile of action and appears to be useful as an antidepressant in treatment-resistant patients and as an analgesic in patients with chronic pain. The extent to which chronic recreational use leads to memory impairment remains controversial.

## POLYDRUG ABUSE

Although some drug abusers may prefer a particular drug, the concurrent use of multiple drugs is common. Polydrug abuse often involves substances that may have different pharmacologic effects from the preferred drug. For example, concurrent use of such dissimilar compounds as stimulants and opioids or stimulants and alcohol is common. The diversity of reported drug use combinations suggests that achieving a change in subjective state, rather than any particular direction of change (stimulation or sedation), may be the primary reinforcer in polydrug abuse. There is also evidence that intoxication with alcohol, opiates, and cocaine is associated with increased tobacco smoking. Nicotine and cocaine enhance each other's effects in clinical laboratory studies, and this drug combination maintains significantly higher levels of self-administration than either drug alone in preclinical models of addiction. There are relatively few controlled studies of multiple drug interactions. However, the combined use of cocaine, heroin, and alcohol increases the risk for toxic effects and adverse medical consequences. Similarly, some hallucinogens (MDMA, LSD) and club drugs (GHB, ketamine, flunitrazepam) are used in various combinations with an associated increase in toxic consequences.

One determinant of polydrug use patterns is the relative availability and cost of the drugs. For example, alcohol abuse, with its attendant medical complications, is one of the most serious problems encountered in former heroin addicts participating in methadone maintenance programs. Cocaine abuse often increases during methadone maintenance.

The physician must recognize that perpetuation of polydrug abuse and drug dependence is not necessarily a symptom of an underlying emotional disorder. Neither alleviation of anxiety nor reduction of depression accounts for initiation and perpetuation of polydrug abuse. Severe depression and anxiety are the consequences of polydrug abuse as frequently as they are the antecedents. Interestingly, some adverse consequences of drug use may be reinforcing and contribute to the continuation of polydrug abuse.

Adequate treatment of polydrug abuse, as well as other forms of drug abuse, requires innovative intervention programs. The first step in successful treatment is detoxification, a process that may be difficult when several drugs with different pharmacologic actions (e.g., alcohol, opiates, and cocaine) have been abused. Because patients may not recall or may deny simultaneous multiple drug use, diagnostic evaluation should always include urinalysis for qualitative detection of psychoactive substances and their metabolites. Treatment of polydrug abuse often requires hospitalization or inpatient residential care during detoxification and the initial phase of drug abstinence. When possible, specialized facilities for the care and treatment of drug-dependent persons should be used. Outpatient detoxification of polydrug abuse patients is unlikely to be effective and may increase risk for dangerous medical consequences.

Drug abuse disorders often respond to effective treatment, but periods of relapse may occur unpredictably. The physician should continue to assist patients during episodes of relapse with compassion and understanding. The physician and the patient must recognize that occasional recurrent drug use is not unusual in this complex behavioral disorder.