Clinical Manual of

Addiction Psychopharmacology

Henry R. Kranzler, M.D.
Domenic A. Ciraulo, M.D.

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Edited by

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Preface

The past two decades have witnessed dramatic advances in neuroscience, including a substantially improved understanding of the neural basis of addictive disorders and their treatment. For example, developments in neurogenetics and neuroimaging have provided new insights into the etiology and pathophysiology of dependence on a variety of substances. Concomitant with this increased knowledge base, there has been renewed interest in the pharmacological treatment of substance use disorders. Initially driven in the United States by support from the National Institutes of Health, more recently the pharmaceutical industry has shown increased interest in developing new medications to treat these disorders, particularly dependence on opioids, nicotine, and alcohol. The high prevalence of these disorders and the limited pharmacological options in their treatment (compared with, e.g., a saturated market in therapies for other psychiatric disorders such as mood, anxiety, and psychotic disorders) have increased awareness within the pharmaceutical industry of the enormous market potential for such medications. Given the extensive resources at the command of the pharmaceutical industry, such interest is likely to be a harbinger of continued progress in the identification of candidate compounds and their evaluation for use in the treatment of addictive disorders.

In addition to their commercial interest, however, these developments are relevant to the care of patients with addictive disorders and of public health significance. If past experience in the treatment of major depressive disorder is an indicator, one important effect of the availability of efficacious treatments for addictive disorders will be that these disorders will become less stigmatized than they are currently. This will result in greater numbers of individuals with such disorders seeking treatment and finding practitioners who are willing to provide such treatment. As has been seen with the diagnosis and treatment of depression, it is likely that the care of addictive disorders will progressively be-

come the province of primary care practitioners rather than being largely restricted to addiction specialists, as is currently the case. Identification and treatment of nicotine dependence is already occurring commonly in primary care settings, driven in part by the availability of a growing number of efficacious medications to treat the disorder, combined with a growing awareness of the serious health consequences of smoking.

As suggested above, however, developments in the pharmacotherapy of addictive disorders have not occurred uniformly across substances. There are multiple medications approved by the U.S. Food and Drug Administration (FDA) to treat nicotine dependence, including a variety of nicotine formulations for replacement therapy that are available for over-the-counter purchase. There are also a growing number of FDA-approved treatments for opioid and alcohol dependence. However, despite a number of promising developments, there are no FDA-approved treatments for dependence on the other substances discussed in this volume, and this underscores the need for additional research aimed at the identification and testing of new agents for such indications. The substantial insights into the pharmacology of the various abused substances, which are discussed in detail in this volume, provide a basis for medications development, as well as an improved understanding of the etiology and pathophysiology of these disorders.

Henry R. Kranzler, M.D.
Domenic A. Ciraulo, M.D.

1

Alcohol

Henry R. Kranzler, M.D.
Domenic A. Ciraulo, M.D.

Ethanol (or alcohol) is a two-carbon molecule that, in contrast to many other drugs of abuse, such as opioids, cocaine, and nicotine, does not bind to specific brain receptors. Nonetheless, alcohol affects a variety of neurotransmitter systems, including virtually all of the major systems that have been associated with psychiatric symptoms (Kranzler 1995). Alcohol affects these neurotransmitter systems indirectly by modifying the composition and functioning of

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neuronal membranes and of the neurotransmitter receptors that are embedded in those membranes. These neurotransmitter effects appear to underlie many of the psychiatric symptoms that occur commonly in association with heavy drinking (Kranzler and Rosenthal 2003). Alcohol also alters the absorption and metabolism of nutrients, and chronic heavy drinking can disturb intermediary metabolism and produce a variety of deficiency states. Finally, because alcohol results in both psychological and physiological dependence, abrupt cessation of drinking can produce withdrawal states. Although the most common effect of abrupt cessation of drinking is an uncomplicated alcohol withdrawal syndrome, severe effects may also result. If these severe effects, which include tonic-clonic seizures, hallucinations, and delirium tremens, occur in the context of a serious medical illness, they can be lethal.

Epidemiology of Drinking, Heavy Drinking, and Alcohol Use Disorders

Alcohol consumption occurs along a continuum, and drinking patterns vary considerably among individuals, with no clear demarcation between "social" or "moderate" drinking and "problem" or "harmful" drinking (Babor et al. 1987). However, as the average amount of drinking and frequency of intoxication increase, it appears that associated medical and psychosocial problems do also (Kranzler et al. 1990). The most visible group of people affected by alcohol problems are those with alcohol dependence. A less prominent, but more numerous, group consists of individuals with alcohol-related problems who do not meet the criteria for alcohol dependence. These individuals are referred to as alcohol abusers, problem drinkers, or harmful drinkers.

The epidemiology of drinking and alcohol use disorders is covered in detail by Babor and associates (2003) and is described briefly here. Data from the 2002 National Survey on Drug Use and Health, which was based on interviews with approximately 68,000 persons age ≥12 years, suggest that a majority (51.0%, or 120 million people) of the U.S. population age 12 years and older consumed alcohol during the month before the interview (Substance Abuse and Mental Health Services Administration 2003). Nearly a quarter of such individuals (22.9%, or 54 million people) engaged in binge drinking (five or more drinks on the same occasion) at least once during this

time. Heavy drinking (five or more drinks on five separate occasions during the month) occurred in 6.7% of the population, or 15.9 million people. The prevalence of current alcohol use increased with age up to age 21 years, where it reached a peak of 70.9%. This is also the age at which the rate of both binge drinking (50.2%) and heavy drinking (20.1%) peaked.

The 2002 National Survey on Drug Use and Health also showed large gender differences in drinking behavior (Substance Abuse and Mental Health Services Administration 2003). Men were more likely than women to drink (57.4% vs. 44.9%), were twice as likely to binge drink (31.2% vs. 15.1%), and were more than three times as likely to be regular heavy drinkers (10.8% vs. 3.0%). There were also racial/ethnic differences in drinking behavior. Fifty-five percent of whites reported drinking during the past month. The next highest rate was for individuals reporting two or more races (49.9%), followed by 44.7% of American Indians/Alaska Natives, 42.8% of Hispanics, 39.9% of blacks, and 37.1% of Asians. Binge drinking was most common among American Indians/Alaska Natives (27.9%), followed by Hispanics (24.8%), whites (23.4%), blacks (21.0%), and Asians (12.4%).

Several large-scale community studies conducted since 1980 have provided estimates of the lifetime and past-year prevalence of alcohol use disorders in the general population. For example, the National Comorbidity Study, a representative household survey of more than 8,000 individuals ages 15–54 years, was conducted to assess lifetime and past-year alcohol disorders using DSM-III-R criteria (American Psychiatric Association 1987). The study estimated the lifetime prevalence of alcohol abuse and alcohol dependence for adults age 18–54 years to be 9.4% and 14.1%, respectively. Together, these data indicate that more than one of five young to middle-aged adults in the United States met the criteria for a lifetime alcohol use disorder (Kessler et al. 1997). The 12-month prevalence rates for alcohol abuse and dependence were 2.5% and 4.4%, respectively (Kessler et al. 1997).

The 1992 National Longitudinal Alcohol Epidemiologic Survey (NLAES), based on interviews with a national probability household sample of nearly 43,000 adults age 18 years and older, showed the 1-year prevalence of DSM-IV alcohol use disorder to be 7.4% (i.e., 3.0% with alcohol abuse and 4.4% with alcohol dependence) (Grant et al. 1994). Findings from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), a community-based survey of nearly 43,000 individuals conducted in 2001–2002 (Grant

et al. 2004a), permit an evaluation of trends in alcohol use disorder prevalence and characteristics, because the NESARC used methods very similar to those of the 1992 NLAES. The NESARC showed a 12-month prevalence of 4.7% for alcohol abuse and 3.8% for alcohol dependence; thus an estimated total of 17.6 million adult Americans had an alcohol use disorder during 2001–2002. The prevalence of alcohol abuse was significantly increased over that seen in the NLAES in 1992, while the prevalence of alcohol dependence decreased significantly over the 10-year period between the two surveys.

Analyses of national prevalence data also show that rates of alcohol use disorders vary by age, gender, race/ethnicity, socioeconomic status, and geographic location. The prevalence of alcohol use disorders has consistently been shown to be higher among men than among women, by at least twofold (Grant et al. 1994, 2004a; Kessler et al. 1997; Substance Abuse and Mental Health Services Administration 2003). The highest prevalences of alcohol abuse and dependence occur among young adults, with rates declining gradually with increasing age. For example, in the NESARC, the prevalence rate for alcohol use disorders was 16.2% among those ages 18–29 years, 9.7% among those ages 30–44 years, 5.4% in the 45–64-year-old group, and only 1.5% among those age 65 years and older (Grant et al. 2004a). With respect to race/ethnicity, the highest rates of both alcohol abuse and dependence were observed among Native Americans, followed by whites, Hispanics/Latinos, blacks, and Asians (Grant et al. 2004a).

Adverse consequences of drinking include a variety of social, legal, medical, and psychiatric problems (Babor et al. 1987, 2003). Alcohol is among the top four causes of mortality; in 1988, 107,800 deaths, or about 5% of all deaths in the United States, were attributed to alcohol-related causes (Stinson and DeBakey 1992). Approximately 17% of alcohol-related deaths were directly attributable to alcohol, 38% resulted from diseases indirectly attributable to alcohol, and 45% were attributable to alcohol-related traumatic injury (U.S. Department of Health and Human Services 1994). Alcohol-related mortality declined during the latter part of the twentieth century. For example, the age-adjusted mortality rate from liver cirrhosis in 1993 (7.9 deaths per 100,000 persons) was just over half the rate in 1970 (14.6 deaths per 100,000) (Saadatmand et al. 1997), and the proportion of automobile fatalities that was related to the use of alcohol fell to a two-decade low of 33.6% in 1993 (Lane et al. 1997).

Pharmacology of Ethanol and Its Relationship to Medications Development

Pharmacokinetics of Alcohol

Absorption and Distribution

Ethanol is absorbed from both the stomach and duodenum. When food is consumed with alcohol, the food dilutes the ethanol concentration in the stomach and delays passage into the duodenum, slowing absorption and decreasing the subjective effects of alcohol. Food delays and lowers peak blood ethanol concentration but also lowers the total amount of ethanol reaching the systemic circulation. Ethanol absorption is fastest when the stomach empties quickly, as in the fasting state, but high-concentration alcoholic beverages such as distilled spirits may cause pylorospasm and delay emptying.

Ethanol distributes rapidly, with concentrations in body water 10 times higher than in body fat. The tissues with the greatest blood supply equilibrate most rapidly with arterial blood circulation. Shortly after alcohol ingestion, the ethanol concentration in the brain is higher than the venous concentration.

Approximately 5%–10% of ethanol is excreted unchanged in the breath and urine. The blood-to-breath ratio of ethanol is 2,000 to 1, an important relationship that permits blood alcohol determination from expired air, providing the basis for the use of breath alcohol measurement for clinical, research, and forensic applications.

Metabolism

The primary route of ethanol metabolism is oxidation to acetaldehyde and acetic acid (Figure 1–1). Three different enzyme systems are capable of oxidizing ethanol: alcohol dehydrogenase (ADH), catalase, and the microsomal ethanol oxidizing system (particularly cytochrome P450 enzyme 2E1 [CYP2E1] in heavy drinkers). Aldehyde dehydrogenase (ALDH) is the enzyme responsible for metabolizing acetaldehyde, the first product in ethanol oxidation. Functional polymorphisms of ADH, ALDH, and CYP2E1 have importance in altering the risk for development of alcohol dependence and ethanol-associated illnesses. Gastric ADH also metabolizes ethanol, and lower levels of this enzyme in women may account for higher blood ethanol concentrations in women than in men given equivalent amounts of alcohol (Frezza et al. 1990), although a study

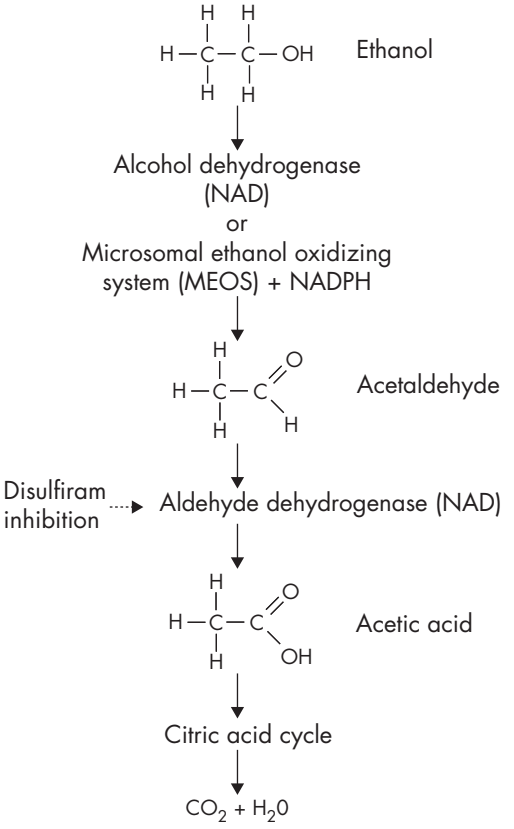

Figure 1–1. Primary route of ethanol metabolism.
Ethanol is oxidized by alcohol dehydrogenase (in the presence of nicotinamide adenine dinucleotide [NAD]) or the microsomal ethanol oxidizing system (MEOS) (in the presence of reduced nicotinamide adenine dinucleotide phosphate [NADPH]). Acetaldehyde, the first product in ethanol oxidation, is metabolized to acetic acid by aldehyde dehydrogenase in the presence of NAD. Acetic acid is broken down through the citric acid cycle to carbon dioxide (CO_2) and water (H_2O). Impairment of the metabolism of acetaldehyde to acetic acid is the major mechanism of action of disulfiram for the treatment of alcoholism.

by Lai et al. (2000) did not replicate the finding. In addition, compared with women, men may have higher hepatic ADH activity (Chrostek et al. 2003). ADH classes I–III are present in the liver and ADH class IV in the stomach; subtypes of each class exist. Different molecular forms of ADH vary considerably in their kinetic properties and, along with ALDH subtypes, have been among the first genetic risk factors to be associated with alcohol dependence. The kinetic properties of the enzymes influence the rate of metabolism. Rapid metabolism of ethanol to acetaldehyde and impaired metabolism of acetaldehyde result in accumulation of that metabolite, leading to unpleasant physiological effects ("the flushing reaction").

Because the prevalence of enzymes with different kinetic properties varies among individuals and racial groups, they act as genetically determined protective factors. For example, more than 90% of Japanese have the *ADH2*2* (*ADH2 Arg47His*) allele, and about 50% have the *ALDH2*2* (*ALDH2 Glu487Lys*) allele, which are rare in individuals of European descent (Sun et al. 2002). Proteins encoded by the *ADH2*2* allele can oxidize ethanol more rapidly to acetaldehyde than those encoded by the *ADH2*1* allele. *ADH2*2* may also differentiate heavy and light drinkers among Israeli Jews (Monteiro et al. 1991). Because proteins encoded by the *ALDH2*2* allele cannot oxidize acetaldehyde rapidly, levels of acetaldehyde accumulate and lead to aversive effects after ethanol consumption. Impairment of the metabolism of acetaldehyde is the major mechanism of action of disulfiram and calcium carbimide for the treatment of alcoholism. Similar effects may be produced by medications used to treat medical conditions, such as some antifungals (e.g., metronidazole), but the severity of the response is highly variable.

One fascinating aspect of the effect of the genetic polymorphisms described earlier is that acculturation can partially overcome the protective factor, and Asian groups born in North America may have only partial protection (Goldman 1993; Tu and Israel 1995). In individuals who consume small amounts of alcohol over time, the aversive effects diminish, an effect similar to that described in clinical reports of patients who developed "a resistance" to the effects of disulfiram.

ADH also has clinical significance in the metabolism of methanol and ethylene glycol, two drugs with toxic metabolites. Methanol is oxidized by ADH to formaldehyde, which damages the retina and can cause blindness. Ethylene glycol is metabolized by ADH to oxalic acid, which has renal tox-

icity. The toxic effects of both methanol and ethylene glycol can be reduced by ethanol administration, which inhibits their metabolism by competing for the oxidizing enzymes and allows elimination of the intact parent compounds.

Catalase is a liver enzyme that uses hydrogen peroxide to oxidize other substances. In vivo, the catalase system does not play a significant role in ethanol metabolism, probably because the quantities of hydrogen peroxide available are insufficient for ethanol metabolism.

The microsomal ethanol oxidizing system is another mechanism of ethanol metabolism. CYP2E1 may be an important enzyme in the metabolism of ethanol in heavy drinkers, who may have a 10-fold increase in activity. Two allelic variants in the gene (*c1* and *c2*) are associated with differing enzymatic activity. Approximately 40% of Japanese have the more active *c2* allele, which is rare in individuals of European heritage (Sun et al. 2002). It is not believed to be a risk or protective factor in the development of alcoholism, although current studies are examining its relationship to a variety of ethanol-related diseases.

Acetaldehyde

Acetaldehyde is the first metabolic product of ethanol. The most important hepatic enzymes involved in its metabolism are a low-K_m mitochondrial ALDH (ALDH2) and cytosolic ALDH1 (Chen et al. 1999), although only variation in the gene encoding ALDH2 appears to be a genetic risk factor for alcoholism. As mentioned previously, there is a functional polymorphism in the *ALDH2*2* gene that is associated with variation in acetaldehyde metabolism. It appears that the inactive allele (*Lys 487*) is dominant, because even heterozygotes experience the flushing reaction to ethanol and the risk for alcoholism is reduced four- to 10-fold in that group (Radel and Goldman 2001; Thomasson et al. 1994).

The role of acetaldehyde in inducing intoxication or in the production of reinforcing effects is controversial (Aragon et al. 1991; Quertemont and Grant 2002). Most evidence suggests that acetaldehyde does not play a role in ethanol intoxication. Supporting this position is the fact that behavioral signs of intoxication parallel ethanol blood levels but not acetaldehyde levels, especially during the ascending limb of the curve for the relationship of ethanol concentration and time. In addition, acetaldehyde levels remain high even during

the period when signs of intoxication are diminishing. Furthermore, pyrazole, which inhibits ADH, thus reducing acetaldehyde formation, does not block or diminish intoxication (which one would predict if acetaldehyde were responsible for reinforcement). On the other hand, there is evidence that acetaldehyde may be reinforcing in animals (Arizzi et al. 2003; Rodd-Henricks et al. 2003), and it increases dopaminergic activity in the ventral tegmental area (VTA) (Foddai et al. 2004), which suggests that central and peripheral acetaldehyde may have different effects (Smith and Amit 1985).

Perhaps even more controversial is the proposition that, together with biogenic amines, acetaldehyde may form condensation products called *tetrahydroisoquinolines* (TIQs). Acetaldehyde can nonenzymatically condense with catecholamines to form TIQs and with indoleamines to form β-carbolines. Salsolinol is the condensation product of dopamine and acetaldehyde. Salsolinol has been detected in the brain tissue of animals after ethanol was administered together with a drug that inhibits TIQ metabolism, and it has also been found in the urine of alcoholic patients on hospital admission. An interesting study reported that salsolinol and tetrahydropapaveroline (THP), when infused in the cerebral ventricles of rats, increase ethanol consumption (Myers and Melchior 1977). Many investigators have been unable to replicate these findings, and some have questioned whether clinically active concentrations are reached. A recent study indicated that pharmacologically relevant concentrations of salsolinol may occur in animals (Rodd-Henricks et al. 2003), and another found that salsolinol may be reinforcing in animal models (Matsuzawa et al. 2000). THP is the condensation product of dopamine and its own aldehyde, 3,4-dihydroxyphenylacetaldehyde (3,4-DHPA), which is formed from dopamine by monoamine oxidase. In an in vitro brain homogenate model, addition of ethanol or acetaldehyde increased the formation of THP from dopamine and 3,4-DHPA. THP has drawn interest because it occurs in the opium poppy, and the μ opioid receptor is involved in the reinforcing effects of ethanol (Collins 2004).

Pharmacodynamics of Alcohol

Early theories of the biological effects of ethanol were based on alterations of lipids in biomembranes (Goldstein et al. 1983; Seeman 1972). Such a nonspecific mechanism provided little guidance for the development of therapeu-

tic agents for alcohol-dependent individuals. More recent research has focused on the action of ethanol on specific neurotransmitter systems and has led to a number of approaches to medications development. Under one model, it is proposed that low doses of ethanol provide positive reinforcement through the dopamine and γ-aminobutyric acid type A ($GABA_A$) receptors, whereas higher doses act as antagonists at *N*-methyl-D-aspartate (NMDA) receptors, which is associated with the negative aspects of intoxication (Heinz et al. 2003). The effects of ethanol on specific neurotransmitter systems and neuromodulators are discussed in later sections; however, the reader should bear in mind that these systems communicate with each other and that the same system may have different functions depending on its location in specific brain regions.

GABA and Ethanol

GABA is the most abundant inhibitory neurotransmitter in the central nervous system (CNS). The development of medications targeting the GABA system is based on the known effects of ethanol on GABA, the effectiveness of GABA agonists (e.g., benzodiazepines) in the treatment of alcohol withdrawal, and the actions of GABA agonists and antagonists in animal models. Acute doses of ethanol increase GABA activity, whereas chronic dosing down-regulates GABA receptor activity. Hyperexcitablity of the GABA system occurs during withdrawal from chronic ethanol administration.

There is evidence to suggest that increases in GABA after acute doses of ethanol are associated with its positive reinforcement. Most animal models have assessed the rewarding effects of ethanol in rats by using self-administration procedures and in mice by using place or taste conditioning paradigms. There are substantial differences in self-administration procedures, including route of administration (oral, intraperitoneal, intravenous/intra-arterial, direct infusion to specific brain areas) and the pattern of administration. Limited access to ethanol is favored (sessions of 30–120 minutes) over continuous administration (24 hours/day) because limited access resembles the pattern of human intake (Chester and Cunningham 2002).

Acute doses of $GABA_A$ antagonists (e.g., picrotoxin and related compounds) generally reduce self-administration of ethanol in animals, an action that can be partially blocked by muscimol (a $GABA_A$ agonist). Some $GABA_A$ antagonists (e.g., isopropylbicyclophosphate, a picrotoxin-type ligand) do not

decrease self-administration acutely but do so only after 7 days of administration. Direct infusion into specific brain regions indicates that the VTA and nucleus accumbens (NAcc) are possible sites of action for GABAergic drugs. A study in which SR 95531, a $GABA_A$ antagonist, was infused into the extended amygdala (defined as the central nucleus of the amygdala, the bed nucleus of the stria terminalis, and the shell of the nucleus accumbens) showed that only injection into the central nucleus of the accumbens decreased ethanol self-administration alone, whereas infusion into other sites decreased both ethanol and water self-administration (Koob et al. 1998). Partial inverse agonists at the benzodiazepine binding site of the $GABA_A$ receptor may also decrease ethanol self-administration, but some of these agents may be effective only transiently.

$GABA_A$ agonists produce complex effects in animal models. In general, most benzodiazepine agonists increase ethanol self-administration or have no effect. In addition, they usually increase other consummatory behaviors. A few studies have shown that ethanol self-administration is decreased after administration of GABA agonists (Chester and Cunningham 2002). Taken together, these studies suggest that $GABA_A$ receptors in the VTA, NAcc, and central nucleus of the amygdala may be important sites of action mediating the rewarding properties of ethanol. The $GABA_A$ type-1 receptor in the ventral pallidum has also been linked to ethanol self-administration and reward (June et al. 2003).

Human studies also indicate that the GABAergic system is important in alcoholism. Brain, cerebrospinal fluid (CSF), and plasma GABA levels are lower in abstinent alcoholic patients, compared with persons without alcoholism (Behar et al. 1999; Davis and Wu 2001; Petty et al. 1997). Reduced benzodiazepine/GABA receptor binding has also been reported in the brains of subjects with chronic alcoholism (Farde et al. 1994; Volkow et al. 1997; Wong et al. 2003). Challenge with benzodiazepine agonists appears to produce smaller electroencephalogram (EEG) responses, less body sway, and decreased saccadic eye movements in high-risk subjects, relative to control subjects (Cowley et al. 1994). Reinforcing effects are inconsistent, with studies using a modified Addiction Research Center Inventory–Morphine Benzedrine Group Scale often showing greater reinforcing effects in high-risk subjects and abstinent alcoholic subjects than in healthy control subjects (Ciraulo et al. 2001; Cowley 1992; Cowley et al. 1994), and studies using other scales not finding

greater mood enhancement (Volkow et al. 1995). One study found that alcoholic subjects treated with lorazepam for alcohol withdrawal were more likely to relapse than those treated with the anticonvulsant carbamazepine, which suggests that positive modulators of the benzodiazepine/GABA receptor may increase alcohol consumption in humans (Malcolm et al. 2002).

Genetic differences may influence an individual's response to alcohol. A Pro385Ser amino acid substitution in the human $GABA_A$ $\alpha 6$ subunit may contribute to altered ethanol sensitivity in children of alcoholic parents (Iwata et al. 1999). Others have found that $GABA_A$ receptors are linked to the beta frequency in EEG (Porjesz et al. 2002). In addition, there is evidence that variations in *GABRA2*, the gene encoding the $GABA_A$ α_2 subunit, are associated with alcohol dependence and beta EEG frequency (Edenberg et al. 2004). The finding of an association of alcohol dependence to allelic variation in *GABRA2* was independently replicated (Covault et al. 2004).

The implications of these findings for pharmacotherapy stem from the use of benzodiazepines, barbiturates, and some anticonvulsants (e.g., valproate) to enhance GABA activity to treat the alcohol abstinence syndrome. Although several $GABA_A$ antagonists have been tested as treatments to block the rewarding effects of ethanol, none has proven successful in humans. One approach in relapse prevention has been to enhance GABA activity with drugs such as gabapentin and topiramate, although these studies are in preliminary stages; furthermore, these drugs have multiple other pharmacological effects that influence the actions of alcohol.

Glutamate and Ethanol

Glutamate is the major excitatory neurotransmitter in the CNS, activating two types of receptors: ligand-gated ion channels and metabotropic receptors linked to G proteins. The ion channel receptors are classified into NMDA and α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA)/kainate subtypes. Channel blockade by magnesium ions (Mg^{2+}) occurs in the resting state but is displaced by depolarization, which follows glutamate and glycine binding and permits the entry of calcium ions (Ca^{2+}). The structure of the receptor is quite complex, with multiple binding sites that modulate its activity. It consists of two subunits, referred to as NR1 and NR2, which in turn have several subtypes that permit a number of different physiologic actions and are

located in specific brain regions (Allgaier 2002; Heinz et al. 2003; Krystal et al. 2003b).

In numerous experimental paradigms, ethanol antagonizes glutamate activity by binding to the NMDA receptor, with the greatest potency at receptors containing NR2A or NR2B subunits (Krystal et al. 2003b; Woodward 2000). Ethanol appears to bind to an extracellular site of the receptor, a phenylalanine residue in the third transmembrane (TM3) domain of the NR1 subunit (Allgaier 2002), a site common to both of the glutamate ligand-gated receptors. This characteristic may explain findings that ethanol also binds to AMPA/kainate receptors (Carlezon and Nestler 2002; Carta et al. 2003; Wirkner et al. 2000).

The clinical implications of the antagonism of NMDA receptors by alcohol have been discussed by Krystal and associates (Krystal et al. 2003a, 2003b), who suggested that the glutamatergic system is closely linked to both the risk of alcoholism and its reinforcing effects. According to their view, vulnerability to alcoholism is related to an altered NMDA response to ethanol that leads to a reduction in the negative effects of heavy drinking. Upregulation of receptors occurs during chronic intake, leading to unopposed increases in glutamate activity after abrupt termination of ethanol. These effects provide theoretical support for glutamate antagonists as potential therapies for both withdrawal and relapse prevention.

Also supporting the glutamate-ethanol link are reports that NMDA antagonists produce ethanol-like effects in humans (Krystal et al. 2003b). The mechanism of the euphoric effect is unknown, but the effect is neither blocked by dopamine D_2 antagonists nor potentiated by amphetamine. It should be recalled that different NMDA antagonists affect receptors in different brain regions and are composed of different subunits. The link between glutamate and other systems complicates interpretation further; some studies suggested that the combination of $GABA_A$ positive modulators and NMDA antagonists substitutes for ethanol more completely than either drug alone (Krystal et al. 2003b).

Other systems also interact with glutamate. Activation of L-type voltage-gated calcium channels (VGCC) occurs with NMDA receptor activation. Lamotrigine blocks several ion channels, including P- and N-type VGCC channels, an action that blocks the euphoric effects of ketamine and reduces dysphoric and cognitive effects (Hundt et al. 1998). Other modulatory sites,

such as the glycine-B site and the polyamine site, also influence NMDA function, with the latter linked by some data to the effects of acamprosate (Littleton 1995; Littleton and Zieglgansberger 2003). Viewing the glutamatergic system as central to the effects of ethanol, Krystal and colleagues (2003b) suggested that a therapeutic approach to the treatment of alcoholism could involve NMDA antagonists that block the rewarding effects or promote the dysphoric effects of ethanol. Agents that may exert their effects through glutamate and that are currently under study include anticonvulsants (topiramate, lamotrigine, and others) and acamprosate.

Serotonin and Alcoholism

Alterations in central nervous system serotonin function have been attributed to both a predisposition to alcoholism and to the consequences of chronic drinking (Pierucci-Lagha et al. 2004). The behavioral effects of ethanol are altered in the presence of serotonin deficiency (e.g., induced by parachlorophenylalanine or 5,6-dihydroxytryptamine), and this deficiency leads to increased alcohol consumption in animal models (Kranzler and Anton 1994). Human studies also suggest that there is a reduction in serotonergic function in alcoholic subjects, as evidenced by low CSF levels of 5-hydroxyindoleacetic acid (5-HIAA), a metabolite of serotonin; however, interpretation of this finding is complicated by the fact that ethanol shifts serotonin metabolism from pathways leading to 5-HIAA to those producing 5-hydroxyindoleacetaldehyde and 5-hydroxytryptophol. Other evidence supporting altered serotonin function in alcoholic subjects includes blunted responses to drugs that are serotonin agonists. Fenfluramine challenge, for example, induced a smaller prolactin response in abstinent alcoholic subjects than in control subjects (Farren et al. 1995). Rapid tryptophan depletion studies, which are used to induce a transient reduction in brain serotonin concentration, have generally produced no effects on ethanol consumption (Petrakis et al. 2001, 2002). On the other hand, a rapid tryptophan depletion study in subjects with co-occurring alcoholism and major depressive disorder demonstrated that depletion of serotonin increased depressive symptoms and the urge to drink (Pierucci-Lagha et al. 2004).

Ethanol acts at 5-HT_{1B}, 5-HT_{2C}, and 5-HT_3 receptors (Krystal et al. 2003b). Animal studies have shown that reduction of ethanol consumption is dependent on the presence of the 5-HT_{3A} receptor (Hodge et al. 2004), a

finding supported by early clinical trials indicating that the 5-HT_3 receptor antagonist ondansetron reduces alcohol consumption in subjects with early-onset alcoholism (Johnson et al. 2000; the results of these trials are described in detail below).

Given the number of studies that have examined the relationship of serotonin and alcoholism, it is not surprising that recent work has examined a genetic predisposition involving genes encoding serotonin reuptake transporters. A functional repeat polymorphism in the promoter region of the serotonin transporter gene (*5-HTTLPR*) alters the expression of serotonin transporters (Heinz et al. 2004). Homozygous carriers of a long allele have greater numbers of serotonin receptors than those with short alleles. Some researchers have argued that high numbers of serotonin transporters in the raphe are associated with a low serotonin turnover rate and reduced response to alcohol (see Heinz et al. 2003). Interactions between the serotonergic, GABAergic, and glutamatergic systems may work to reduce alcohol sensitivity and the risk for the development of alcohol dependence (for a review, see Heinz et al. 2004).

Neuropeptides and Ethanol

Opioid peptides, such as β-endorphin, have been linked both to the rewarding effects of ethanol and to increased risk for alcoholism (Cowen et al. 2004; Gianoulakis et al. 1989, 1996). Alcohol-preferring rats and humans with a family history of alcoholism show greater increases in β-endorphin after an ethanol challenge, compared with control subjects (de Waele et al. 1992, 1994). Enkephalins may also play a role in the reinforcing effects of ethanol (Ryabinin et al. 1997, 2001). As discussed in detail later in this chapter, the efficacy of opioid antagonists (e.g., naltrexone, nalmefene) in the treatment of alcoholism provides further support for the relationship between the rewarding properties of ethanol and the opioid system (Bouza et al. 2004; Mason et al. 1994, 1999).

Findings from animal studies suggest that neuropeptide Y (NPY) may be associated with ethanol consumption. NPY-deficient mice have increased alcohol consumption (Thiele et al. 1998), an effect that is mediated by the Y1 and Y2 receptors (Pandey et al. 2003; Thiele et al. 2000, 2002). It has been suggested that NPY Y1 agonists and Y2 antagonists may have promise in the treatment of alcoholism (Cowen et al. 2004).

Other peptides that have been linked to the actions of ethanol are corticotropin-releasing factor, urocortin, leptin, cholecystokinin, melanocortins, and galanin (for reviews, see Cowen et al. 2004; Egli 2003; Thiele et al. 2003).

Other Actions of Ethanol

Ethanol also reduces the activity of the noradrenergic system in the locus coeruleus, and alterations in norepinephrine activity may account for some aspects of intoxication and the abstinence syndrome. The α_2 antagonist clonidine and the β-receptor antagonist propranolol reduce some symptoms of alcohol withdrawal (Bailly et al. 1992; Carlsson and Fasth 1976; Dobrydnjov et al. 2004; Kahkonen 2003; Petty et al. 1997; Wong et al. 2003).

Chronic administration of ethanol may up-regulate L-type and N-type VGCCs—an effect that may contribute to ethanol withdrawal symptoms (Kahkonen and Bondarenko 2004; McMahon et al. 2000), probably through involvement of NMDA receptors and other neural circuitry (Calton et al. 1999).

Summary

The pharmacodynamic effects of ethanol are complex, and any attempt to link its actions to specific neurotransmitters or isolated brain regions is simplistic. A complicated neural network involved in the actions of ethanol accounts for its reinforcing, intoxicating, and abstinence effects. At the present time, use of medications that target neurotransmitters and neuromodulators affected by ethanol represents a reasonable strategy for the development of pharmacotherapies that reduce the reinforcing effects of alcohol and the craving and withdrawal symptoms that commonly occur in the context of alcohol dependence.

Pharmacotherapy of Heavy Drinking and Alcohol Use Disorders

The two main settings in which medications are used for alcohol treatment are to control the symptoms of alcohol withdrawal (i.e., detoxification) and to reduce or prevent alcohol consumption (i.e., rehabilitation). In the sections that follow, we will first discuss pharmacological approaches to detoxification

from alcohol. We then discuss the two major approaches to the use of pharmacotherapy in alcohol rehabilitation: 1) for the reduction or cessation of drinking, which involves direct efforts to reduce the reinforcing effects of alcohol, and 2) for the treatment of co-occurring psychiatric symptoms, which may be understood as the effort to reduce the mood or anxiety symptoms that commonly occur among alcoholic patients and may impede the recovery process. In discussing all of these applications, we focus on medications that are of current interest to the clinician or that are likely to yield important clinical advances in the near future. Comprehensive reviews of medications to treat alcoholism have been provided previously by Litten et al. (1996), Garbutt et al. (1999), Swift (1999), Kranzler (2000), and Johnson and Ait-Daoud (2000).

Treatment of Alcohol Withdrawal

An important initial intervention for a minority of alcohol-dependent patients is the management of alcohol withdrawal through detoxification. The objectives in treating alcohol withdrawal are relief of discomfort, prevention or treatment of complications, and preparation for rehabilitation. Successful management of the alcohol withdrawal syndrome is generally necessary for subsequent efforts at rehabilitation to be successful; treatment of withdrawal alone is usually not sufficient, because relapse occurs commonly.

The identification of co-occurring medical problems is an important element in detoxification (Naranjo and Sellers 1986). Good supportive care and treatment of concurrent illness, including fluid and electrolyte repletion, are essential (Naranjo and Sellers 1986). Administration of thiamine (50–100 mg/day po or im) and multivitamins is a low-cost, low-risk intervention for the prophylaxis and treatment of alcohol-related neurological disturbances.

Social detoxification, which involves the nonpharmacological treatment of alcohol withdrawal, has been shown to be effective (see Naranjo et al. 1983). It consists of frequent reassurance, reality orientation, monitoring of vital signs, personal attention, and general nursing care (Naranjo and Sellers 1986). Social detoxification is most appropriate for patients in mild-to-moderate withdrawal. The medical problems commonly associated with alcoholism (Sullivan and O'Connor 2004) may substantially complicate therapy, so that care must be taken to refer patients whose condition requires medical management.

Control of early withdrawal symptoms, which prevents their progression to more serious symptoms, is the indication for which medications are most widely prescribed in the treatment of alcohol dependence. The most commonly used agents to treat alcohol withdrawal are the benzodiazepines, a class of drugs that, by virtue of their agonist activity at the $GABA_A$ receptor complex, suppress the hyperexcitability associated with alcohol withdrawal. With widespread use of anticonvulsant medications for bipolar disorder and other disorders associated with behavioral disinhibition and CNS hyperexcitability, anticonvulsants have also been examined for use in the treatment of alcohol withdrawal.

Increasingly, detoxification is being done on an ambulatory basis, which is much less costly than inpatient detoxification (Hayashida et al. 1989). Inpatient detoxification is indicated for patients with serious medical or surgical illness and for those with a past history of adverse withdrawal reactions or with current evidence of more serious withdrawal reactions (e.g., delirium tremens) (Feldman et al. 1975).

A variety of medications have been used for the treatment of alcohol withdrawal. However, because of their favorable side-effect profile, the benzodiazepines have largely supplanted all other medications (Naranjo and Sellers 1986). Although any benzodiazepine will suppress alcohol withdrawal symptoms, diazepam and chlordiazepoxide are often used, because they are metabolized to long-acting compounds, which in effect are self-tapering. Because metabolism of these drugs is hepatic, impaired liver function may complicate their use. Oxazepam and lorazepam are not oxidized to long-acting metabolites and thus carry less risk of accumulation.

Carbamazepine appears to be useful as a primary treatment of alcohol withdrawal (Malcolm et al. 1989, 2002). Although equal to lorazepam in its ability to decrease the symptoms of alcohol withdrawal, carbamazepine was found to be superior to lorazepam in preventing rebound withdrawal symptoms and in reducing posttreatment drinking, especially among patients with a history of multiple episodes of treated withdrawal (Malcolm et al. 2002). Other anticonvulsants have also been examined as adjuncts to standard detoxification treatment. Reoux et al. (2001) compared divalproex at a dosage of 500 mg three times a day for 7 days with matched placebo in patients receiving treatment with oxazepam in a symptom-triggered detoxification protocol. Treatment with divalproex resulted in significantly less use of oxazepam and

a significantly slower progression of withdrawal symptoms. In contrast, in a small trial of gabapentin at a dosage of 400 mg four times a day as an adjunct to clomethiazole, a GABA agonist that is widely used in Europe for treatment of alcohol withdrawal (Bonnet et al. 2003), there was no advantage for the anticonvulsant over placebo. Although both carbamazepine and divalproex appear to be of value in the treatment of alcohol withdrawal, the liver dysfunction that is common in alcoholic patients may affect the metabolism of carbamazepine or increase the risk of hepatotoxicity associated with divalproex, so that careful blood level monitoring of these medications in this context is warranted.

Antipsychotics are not indicated for the treatment of withdrawal, except when hallucinations or severe agitation are present (Naranjo and Sellers 1986), in which case they should be added to a benzodiazepine. In addition to their potential to produce extrapyramidal side effects, antipsychotics lower the threshold for seizures, which is particularly problematic during alcohol withdrawal.

Medications to Reduce or Stop Drinking Behavior

The two major approaches to the use of medications in the secondary prevention or rehabilitation of alcoholism are 1) direct efforts to reduce or stop drinking behavior by producing adverse effects when alcohol is consumed or by modifying the neurotransmitter systems that mediate alcohol reinforcement, and 2) the treatment of persistent psychiatric symptoms, with the aim of reducing the risk of relapse by reducing the motivation to use alcohol to "self-medicate" such symptoms.

Alcohol Sensitizing Agents: Disulfiram

Alcohol sensitizing agents alter the body's response to alcohol, thereby making its ingestion unpleasant or toxic. The only alcohol sensitizing medication that is approved in the United States for treatment of alcoholism is disulfiram (Antabuse), which inhibits the enzyme ALDH. ALDH catalyzes the oxidation of acetaldehyde to acetic acid. Ingestion of alcohol while this enzyme is inhibited results in an elevated blood acetaldehyde concentration, producing the disulfiram-ethanol reaction (DER). The intensity of this reaction varies both with the dose of disulfiram and with the volume of alcohol ingested. The DER includes warmness and flushing of the skin, especially that of the upper chest and face; increased heart rate; palpitations; and decreased blood pres-

sure. It may also include nausea, vomiting, shortness of breath, sweating, dizziness, blurred vision, and confusion. Most DERs last about 30 minutes and are self-limited. Occasionally, the DER may be severe and may include marked tachycardia, hypotension, or bradycardia. Rarely, cardiovascular collapse, congestive failure, and convulsions have occurred as part of the DER.

Pharmacology. Disulfiram is almost completely absorbed after oral administration. Because it binds irreversibly to ALDH, renewed enzyme activity requires the synthesis of new enzyme. This feature creates the potential for the occurrence of a DER for at least 2 weeks after the last ingestion of disulfiram. Consequently, alcohol should be avoided during this period.

Disulfiram produces a variety of adverse effects, which commonly include drowsiness, lethargy, and fatigue (Chick 1999). Other more serious adverse effects, such as optic neuritis, peripheral neuropathy, and hepatotoxicity, are rare. Psychiatric effects of disulfiram are also uncommon. They probably occur only at higher dosages of the drug and may result from the inhibition by disulfiram of a variety of enzymes in addition to ALDH. Included among the enzymes inhibited by disulfiram is dopamine β-hydroxylase, inhibition of which increases dopamine levels, which in turn can exacerbate psychotic symptoms in patients with schizophrenia and occasionally may result in psychotic or depressive symptoms in patients without schizophrenia.

Disulfiram is usually given orally. Because there is an increased risk of side effects and toxic hazards as the dosage is increased, the daily dosage prescribed in the United States has been limited to 250–500 mg/day. However, efforts to titrate the dosage of disulfiram in relation to a challenge dose of ethanol indicated that some patients require in excess of 1 g/day of disulfiram to reach blood levels sufficient to produce a DER (Brewer 1984).

Clinical use. Because the use of disulfiram has intuitive appeal, it has long been employed in the rehabilitation of alcoholic patients (Favazza and Martin 1974), despite a lack of methodologically sound evaluations demonstrating its clinical efficacy. Its approval by the U.S. Food and Drug Administration (FDA) preceded the implementation of the rigorous requirements for efficacy that now must be satisfied for a drug to be marketed in the United States. In the controlled studies that have been conducted, the difference in outcome between subjects receiving disulfiram and those given placebo has generally been minimal.

The largest and most methodologically rigorous study of disulfiram was a multicenter trial conducted by the Veterans Administration Cooperative Studies Group, in which more than 600 male alcoholic patients were randomly assigned to receive either 1 mg/day of disulfiram, 250 mg/day of disulfiram (presumed to be a therapeutic dosage), or an inactive placebo (Fuller et al. 1986). Patients assigned to the two disulfiram groups were told they were being given the drug, but neither the patients nor the staff knew the dosage. The results showed a direct relationship between compliance with the medication regimen (in all three groups) and complete abstinence. Among patients who resumed drinking, those in the group receiving 250 mg/day of disulfiram had significantly fewer drinking days than patients in either of the other two groups. However, there was no significant difference among the three groups on a variety of other outcome measures. On the basis of these findings, it appears that disulfiram may be helpful in reducing the frequency of drinking in men who cannot remain abstinent, although given the large number of statistical analyses, it is possible that this finding arose by chance (Fuller et al. 1986).

In addition, disulfiram may be useful among selected samples of alcoholic patients with whom special efforts are made to ensure compliance. Specific behavioral efforts that may enhance adherence to disulfiram treatment (as well as treament with other medications for alcoholism) include the use of incentives provided to the patient, contracting with the patient and a significant other to work together to ensure adherence, providing regular reminders and other information to the patient, and behavioral training and social support (Allen and Litten 1992). Azrin et al. (1982) found that a trial program of stimulus control training, role playing, communication skills training, and recreational and vocational counseling improved outcome in disulfiram-treated patients, compared with patients who received placebo. There is additional evidence that supervision of patients being treated with disulfiram may be an essential element in ensuring adherence and enhancing the beneficial effects of the medication (Brewer et al. 2000). Chick et al. (1992) randomly assigned patients to receive 200 mg/day of disulfiram or placebo as an adjunct to outpatient alcoholism treatment. The medication was ingested under the supervision of an individual nominated by the patient. In this 6-month study, disulfiram significantly increased the number of days abstinent and decreased total drinks consumed, effects that were confirmed by parallel changes in levels of the hepatic enzyme γ-glutamyltranspeptidase (GGTP).

In deciding whether disulfiram should be used in alcoholism rehabilitation, patients should be made aware of the hazards of the medication, including the need to avoid over-the-counter preparations that include alcohol, the need to avoid drugs that can interact with disulfiram, and the potential for a DER to be precipitated by alcohol used in food preparation. The administration of disulfiram to anyone who does not agree to use it, who does not seek to be abstinent from alcohol, or who has any psychological or medical contraindications is not recommended.

Medications to Reduce the Reinforcing Effects of Alcohol

As reviewed earlier in the section on the pharmacology of ethanol, several neurotransmitter systems appear to influence the reinforcing or discriminative stimulus effects of ethanol. Although these systems appear to function interactively in their influences on drinking behavior, the medications that have been employed to treat alcohol dependence affect neurotransmitter systems relatively selectively. Consequently, these systems will be discussed individually here.

Opioidergic agents. Naltrexone and nalmefene, opioid antagonists with no intrinsic agonist properties, have been studied for the treatment of alcohol dependence. Naltrexone has been studied much more extensively than nalmefene for this indication. In 1984 naltrexone was approved by the FDA for the treatment of opioid dependence, and in 1994 it was approved for the treatment of alcohol dependence. Nalmefene is approved in the United States as a parenteral formulation for the acute reversal of opioid effects (e.g., after opioid overdose or analgesia).

Naltrexone. Approval of naltrexone for alcohol dependence was based on the results of two single-site studies that showed it to be efficacious in the prevention of relapse to heavy drinking (O'Malley et al. 1992; Volpicelli et al. 1992). In a 12-week study, Volpicelli et al. (1992) compared naltrexone with placebo in a sample of alcohol-dependent veterans, initially as an adjunct to an intensive day treatment program. In this study, naltrexone was well tolerated and resulted in significantly less craving for alcohol and fewer drinking days than did placebo. Naltrexone also limited the progression of drinking from initial sampling of alcohol to a relapse to heavy drinking. Study subjects who drank while taking the medication reported less euphoria, suggesting

that naltrexone blocked the endogenous opioid system's contribution to alcohol's "priming effect" (Volpicelli et al. 1995).

O'Malley et al. (1992) replicated and extended the findings of Volpicelli et al. (1992) by comparing the effects of naltrexone in combination with either supportive or cognitive-behavioral therapy (CBT) for ambulatory alcoholic patients. In this 12-week study, naltrexone was well tolerated and was superior to placebo in reducing the number of drinking days and the total number of drinks consumed and in improving scores on a measure of alcohol-related problems. In addition to a main effect of the medication, naltrexone interacted with the psychotherapy, revealing that the medication may be best combined with CBT.

O'Malley and colleagues (1996b) also found that, compared with placebo, naltrexone reduced craving for alcohol, alcohol's reinforcing properties, the experience of intoxication, and the chances of continued drinking following a slip. During a 6-month posttreatment follow-up period, O'Malley et al. (1996a) found that the beneficial effects of naltrexone diminished gradually over time, suggesting that patients may benefit from naltrexone for longer than the 12 weeks of treatment provided in these initial studies.

Many, but not all, subsequent studies of naltrexone provided support for its use in alcohol treatment. The literature on naltrexone treatment of alcohol dependence has been reviewed in detail in four published meta-analyses (Bouza et al. 2004; Kranzler and Van Kirk 2001; Srisurapanont and Jarusuraisin 2002; Streeton and Whelan 2001). These meta-analyses showed an advantage for naltrexone over placebo on a number of drinking outcomes. In a meta-analysis of nine randomized, placebo-controlled naltrexone studies, Kranzler and Van Kirk (2001) found that naltrexone was superior to placebo by an average of 12% with respect to promoting abstinence, 16% for preventing relapse to heavy drinking, and 19% for reducing drinking days. In a meta-analysis of seven trials (Streeton and Whelan 2001), subjects treated with naltrexone experienced significantly fewer episodes of relapse (14% lower risk) and were significantly more likely to remain abstinent (10% greater likelihood), compared with subjects who received placebo. The naltrexone-treated subjects also consumed significantly less alcohol over the study period than the subjects who received placebo, with no significant effect of medication on the risk of having an adverse event or on discontinuing study participation because of an adverse event.

Srisurapanont and Jarusuraisin (2002) identified a total of 14 randomized, placebo-controlled studies of naltrexone and two studies of nalmefene. Naltrexone was superior to placebo in the comparisons of the number of patients who relapsed to drinking (61% in the naltrexone group vs. 69% in the placebo group) (relative risk = 0.88, 95% confidence interval [CI] = 0.80–0.98) and of the percentage or number of drinking days (weighted means difference = –4.52, 95% CI = –5.29 to –3.75). The authors concluded that although naltrexone at a dosage of 50 mg/day is effective for alcohol dependence in short-term treatment, the optimal duration of naltrexone treatment may be longer than 3 months.

The most recent meta-analysis (Bouza et al. 2004) included 19 studies of naltrexone and a total of 3,205 participants with alcohol dependence. The large majority of these studies were of short duration (i.e., ≤12 weeks). Using relapse as an outcome, these studies yielded a highly significant odds ratio (OR) of 0.62 (95% CI = 0.52–0.75), reflecting a 38% lower likelihood of relapse with naltrexone treatment ($P < 0.00001$). The likelihood of total abstinence also favored naltrexone (OR = 1.26, 95% CI = 0.97–1.64), although the result did not reach statistical significance ($P = 0.08$). Outcomes identified as secondary by this meta-analysis, including time to relapse, percentage of drinking days, number of drinks per drinking day, days of abstinence, total alcohol consumption during treatment, and levels of GGTP and aspartate aminotransferase, also showed a significant advantage for the naltrexone-treated group. One 6-month study (Landabaso et al. 1999), which was randomized but open-label, showed an advantage for naltrexone on the rate of both relapse and total abstinence. The study by Krystal et al. (2001) included both 12-week and 52-week treatment durations, neither of which showed an advantage for naltrexone over placebo on any of the outcomes examined. Follow-up studies of patients treated with naltrexone or placebo for 12 weeks (Anton et al. 2000; O'Malley et al. 1996a) showed a gradual increase among naltrexone-treated patients in relapse rate and in the number of drinking days and heavy drinking days. These findings suggest that treatment with naltrexone is warranted for longer than 12 weeks, although the optimal duration of treatment remains to be determined.

A number of studies that extend the findings of earlier studies of naltrexone have implications for the clinical use of the medication. One approach to the use of naltrexone is based on its efficacy in reducing the risk of heavy

drinking in the context of any drinking (i.e., interruption of the "one drink—drunk" phenomenon described by advocates of Alcoholics Anonymous). Following an open-label study of targeted naltrexone for problem drinkers (Kranzler et al. 1997), Kranzler et al. (2003a) compared the effects of 50 mg/day of naltrexone with those of placebo in an 8-week study of problem drinkers. Patients were randomly assigned to receive the study medication on either a daily basis or for use targeted to situations identified by the patients as being high-risk situations for heavy drinking. The number of tablets available for use by patients in the targeted conditions began with enough for daily treatment and declined each week, with no study medication available to them in the last week of the trial. Irrespective of whether they received naltrexone or placebo, the patients in the targeted condition showed a reduced likelihood of any drinking. Overall, there was a 19% reduction in the likelihood of heavy drinking with naltrexone treatment. These results suggest that naltrexone may be useful for reducing heavy drinking, even among patients who may not meet the criteria for alcohol dependence.

A targeted approach to the use of naltrexone was also used by Heinala et al. (2001), who compared 50 mg/day of the drug with placebo, paired with either coping skills therapy or supportive therapy. During the initial 12 weeks of treatment, they found an advantage for naltrexone in preventing relapse to heavy drinking only in combination with coping skills therapy. During a subsequent 20-week period, the subjects were given the same medication they had used daily but were told to use it only when they craved alcohol (i.e., targeted treatment). Differences observed during the intial period of daily treatment with respect to risk of relapse were generally sustained during the period of targeted treatment. Together, these findings suggest that targeted medication administration may be useful both for the initial treatment of problem drinking and for maintenance of the beneficial effects of an initial period of daily naltrexone.

Using a primary-care model of treatment, O'Malley et al. (2003) initially treated alcohol-dependent patients with open-label naltrexone for 10 weeks, in combination with either CBT or primary care management (PCM), a less intensive, supportive approach. They found no effect of psychosocial treatment on response to treatment, although CBT was associated with a lower risk of drinking. Treatment responders from this study were then randomly assigned to one of two placebo-controlled 24-week continuation studies in

which patients received concomitant treatment with either CBT or PCM. Although there was no advantage observed for naltrexone in combination with CBT, among patients receiving PCM, naltrexone treatment was superior to placebo on both response rate and drinking frequency. These findings suggest that the initial treatment effects of naltrexone can be maintained during an extended period through the use of either a more intensive, skills-oriented treatment (i.e., CBT) or a less intensive, supportive treatment when combined with continued naltrexone administration.

Because poor compliance with oral naltrexone may reduce the potential benefits of the medication, there has been considerable interest recently in long-acting injectable formulations of the medication. In a small pilot study, alcoholic patients treated subcutaneously with a depot formulation of naltrexone had detectable plasma concentrations of the drug for more than 30 days after the injection (Kranzler et al. 1998). The active formulation was superior to placebo in reducing the frequency of heavy drinking in these patients. Two long-acting naltrexone formulations developed for intramuscular injection have also been tested for safety and efficacy in alcoholic patients. A depot naltrexone formulation produced by DrugAbuse Sciences, Inc., was evaluated in a 12-week, placebo-controlled trial in 315 patients who also received motivational enhancement therapy (Kranzler et al. 2004). In that study, the active formulation was well tolerated. Although it did not reduce the risk of heavy drinking, it delayed the onset of any drinking, increased the total number of days of abstinence, and doubled the likelihood that subjects would remain abstinent throughout the study period (Kranzler et al. 2004). More recently, a randomized, double-blind, placebo-controlled study was conducted with a different long-acting formulation (Garbutt et al. 2005). More than 600 alcohol-dependent adults were randomly assigned to receive 6 monthly long-acting injections of 380 mg of naltrexone, 190 mg of naltrexone, or matching volumes of placebo. The medication and the injections were well tolerated. Compared with placebo treatment, long-acting naltrexone (380-mg injections) resulted in a 25% reduction in the rate of heavy drinking. There was a strong effect in men (48% reduction) but no advantage over placebo in women. Long-acting naltrexone (190-mg injections) resulted in a 17% reduction in heavy drinking, although this result did not reach statistical significance.

There is also a growing number of studies in which naltrexone has been compared or combined with acamprosate. Kiefer et al. (2003) randomly as-

signed 160 detoxified alcoholic patients to receive naltrexone, acamprosate, naltrexone plus acamprosate, or placebo for 12 weeks under double-blind conditions. They found that naltrexone, acamprosate, and the two medications combined were significantly more efficacious than placebo. In addition, the naltrexone group showed a tendency for a better outcome on time to the first drink and time to relapse than did the acamprosate group. The combined medication group had a significantly lower relapse rate than either the placebo group or the acamprosate group, but the combined medication was not statistically superior to naltrexone. A single-blind study by Rubio et al. (2001) compared 50 mg/day of naltrexone with 1,165–1,998 mg/day of acamprosate over a 12-month treatment period. These investigators found a significant advantage for naltrexone over placebo on the following outcomes: rates of abstinence and relapse, cumulative abstinence, time to relapse, number of drinks per drinking day, severity of craving, and retention rate. The COMBINE Study, a large placebo-controlled study comparing naltrexone, acamprosate, and their combination with either medical management or an intensive psychotherapy, may provide definitive answers to the questions of whether naltrexone is superior to acamprosate and whether combination therapy with naltrexone and acamprosate is superior to naltrexone alone (COMBINE Study Research Group 2003a, 2003b). The COMBINE Study may also help to determine the optimal intensity of psychotherapy to be used in combination with these medications and may provide information on the patient characteristics that moderate the response to these medications.

Nalmefene. Nalmefene has also been evaluated for the treatment of alcohol dependence. A pilot study (Mason et al. 1994) showed that 40 mg/day of nalmefene was superior to either 10 mg/day of the drug or placebo in the prevention of relapse to heavy drinking in a small sample of alcoholic patients. A subsequent study showed no difference between 20 mg/day of nalmefene and 80 mg/day of nalmefene, although the combined group of nalmefene-treated subjects had significantly better outcomes on measures of heavy drinking than did the placebo group (Mason et al. 1999). Recently, a 12-week, multisite dose-ranging study was conducted comparing placebo with 5, 20, or 40 mg of nalmefene in recently abstinent alcoholic outpatients (Anton et al. 2004). Although during the study all subjects showed reductions in self-reported heavy drinking days and on biological measures of drinking, there was no difference between the active medication and placebo groups on these measures.

Summary. There now exists abundant evidence supporting the use of naltrexone for treatment of alcohol dependence. In unselected samples of patients, the medication exerts a modest overall effect. There is growing evidence, however, that naltrexone may be of particular utility in subgroups of patients, so that the ready identification of individuals who are more likely to respond to treatment is of great clinical interest, as is the potential utility of combining naltrexone with other medications and with specific kinds of psychotherapy. The optimal dosage and duration of treatment are two important clinical questions that remain to be adequately addressed. New approaches to the use of naltrexone, including targeted administration and long-acting injectable formulations, promise to enhance the clinical utility of the medication. The literature supporting the use of nalmefene is less well developed.

Acamprosate. Acamprosate (calcium acetylhomotaurinate), an amino acid derivative, affects both GABA and excitatory amino acid (i.e., glutamate) neurotransmission (the latter effect most likely being the one that is important for its therapeutic effects in alcoholism). Initially evaluated in a single-center trial in France, acamprosate was shown to be twice as effective as placebo in reducing the rate at which alcoholic patients returned to drinking (Lhuintre et al. 1985). The safety and efficacy of the medication have been studied most widely in Europe, and three of these studies provided the basis for the recent approval of acamprosate by the FDA for clinical use in the United States. As with naltrexone, there exist a number of meta-analytic studies that provide consistent evidence of the efficacy of the medication in the treatment of alcohol dependence.

Kranzler and Van Kirk (2001) included 11 acamprosate studies in a meta-analysis involving more than 3,000 subjects. The magnitude of the advantage shown by acamprosate over placebo in those studies varied as a function of the outcomes examined, which included the percentage of patients who were abstinent throughout the study, cumulative abstinent days, and the rate of study retention, all of which favored the active medication. Acamprosate yielded outcomes that were, on average, 7%–13% better than those shown by individuals who received placebo.

A recent meta-analysis of total abstinence as an outcome in clinical trials of acamprosate (Mann et al. 2004) included 17 studies and a total of more than 4,000 patients. The authors found a significant advantage for acampro-

sate over placebo in the effect on continuous abstinence rates. The size of the effect, although modest, increased progressively as treatment duration increased from 3 to 6 and then to 12 months.

Chick et al. (2003) conducted a meta-analysis that included data from 15 studies of acamprosate in an effort to determine whether acamprosate reduces the severity of relapse for patients in abstinence-oriented treatment who fail to abstain completely. Among patients who relapsed to drinking, acamprosate was significantly associated with less quantity and frequency of drinking, compared with placebo, at each of four follow-up periods (i.e., at 30, 90, 180, and 360 treatment days). During each of these periods, there were also fewer acamprosate-treated patients who drank an average of five or more drinks per day.

Verheul et al. (2004) pooled data from seven European acamprosate studies in an effort to identify patient-related predictors of response to the medication. Although they examined a number of potential predictors, including patients' level of physiological dependence before treatment, family history of alcoholism, age of onset of alcoholism, baseline anxiety symptom severity, baseline craving, and gender, none was shown to interact with acamprosate treatment. These findings led the authors to conclude that, although the effect size for acamprosate was moderate, the medication can be considered potentially effective for all patients with alcohol dependence.

One study of acamprosate has implications for the use of that medication in combination with disulfiram (Besson et al. 1998). In that study, patients were randomly assigned to receive acamprosate or placebo, with a separate randomization for patients who were taking disulfiram. Acamprosate was shown to be superior to placebo on measures of total abstinence and on the cumulative number of days abstinent. It is interesting to note that the group receiving both acamprosate and disulfiram showed a significantly greater percentage of days abstinent than any of the other three groups, although, because the design was not fully randomized, additional studies of this combination therapy are needed to evaluate the validity of the findings.

In summary, studies involving more than 4,000 patients provided consistent evidence of a beneficial effect of acamprosate in relapse prevention. On the basis of the drug's efficacy (as demonstrated by at least a doubling of the total abstinence rate in three European studies, two of which were of 12 months' duration) and a good safety profile, the FDA approved the medica-

tion for clinical use in the United States. Although a multicenter trial conducted in the United States failed to show an advantage of acamprosate over placebo on an intent-to-treat basis, a beneficial effect of the medication on cumulative days of abstinence was evident in secondary analyses (Mason and Goodman 2000).

Anticonvulsants. The potential utility of anticonvulsants for the treatment of alcohol dependence was demonstrated initially in placebo-controlled studies of carbamazepine (Mueller et al. 1997), divalproex (Brady et al. 2002), and topiramate (Johnson et al. 2003). In a 12-month pilot study, despite limited rates of medication adherence and study completion, Mueller et al. (1997) found an early advantage to carbamazepine in effects on drinks per drinking day, time to first heavy drinking day, and consecutive days of heavy drinking. In a 12-week double-blind, placebo-controlled pilot study of divalproex in alcohol-dependent individuals, Brady et al. (2002) found that a significantly lower percentage of individuals receiving divalproex relapsed to heavy drinking. There was also a significantly greater decrease in irritability in the divalproex-treated group. Johnson et al. (2003) conducted a single-site, 12-week placebo-controlled study of an escalating dosage (to a maximum of 300 mg/day) of topiramate in 150 alcoholic patients. Topiramate-treated patients had large reductions in drinks per day, drinks per drinking day, drinking days, heavy drinking days, and GGTP levels, all of which were significantly greater than those seen among patients receiving placebo treatment. On the basis of this findings, this use of anticonvulsant medications to treat alcohol dependence is a promising area of investigation. A large, multicenter study of topiramate is currently under way to evaluate its safety and efficacy in the treatment of moderate-to-severe alcohol dependence.

Serotonergic agents. A variety of serotonin reuptake inhibitors (SRIs) have been tested in humans to determine their effects on alcohol consumption (Amit et al. 1985; Angelone et al. 1998; Balldin et al. 1994; Gerra et al. 1992; Gorelick and Paredes 1992; Kabel and Petty 1996; Kranzler et al. 1993, 1995; Naranjo et al. 1984, 1987, 1989, 1990, 1992, 1995; Pettinati et al. 2000; Tiihonen et al. 1996). The two most intensively studied medications in this category are fluoxetine and citalopram. Because the design of the published studies varies considerably, to our knowledge, no quantitative meta-analysis of the effects of serotonergic medications has been published.

Naranjo et al. (1990) first reported that fluoxetine reduced alcohol consumption. These investigators found that 60 mg/day of fluoxetine reduced average daily alcohol consumption by approximately 17% from baseline levels and that treatment with 40 mg/day of fluoxetine or placebo had no effect. When alcoholic inpatients were given access to alcohol, fluoxetine pretreatment initially reduced alcohol consumption, but the effect was transient (Gorelick and Paredes 1992). Using a crossover design, Gerra et al. (1992) compared the effects of fluoxetine, acamprosate, and placebo in alcoholic patients with and without a family history of alcoholism. Although they found both active medications to be superior to placebo in reducing the number of drinks consumed, the effect of fluoxetine was significant only in the family-history-positive patients, while acamprosate produced a significant reduction only in the family-history-negative patients. Subsequent studies showed no advantage for fluoxetine over placebo in effects on drinking behavior among subjects with severe alcoholism recruited from an alcoholism treatment program at a Veterans Affairs Medical Center (Kabel and Petty 1996) and no advantage for fluoxetine in combination with coping skills psychotherapy in a 12-week placebo-controlled trial (Kranzler et al. 1995). A further analysis of those data showed a reduction in the beneficial effects of coping skills training among the subgroup of patients with high levels of both premorbid vulnerability and alcohol-related problems (Kranzler et al. 1996).

Naranjo et al. (1987) also found that 40 mg/day of citalopram, but not 20 mg/day, reduced the number of drinks per day and increased the number of days abstinent, relative to baseline drinking, in a sample of nondepressed, early-stage problem drinkers, a finding that these investigators subsequently replicated (Naranjo et al. 1992). However, in a subsequent study, in which 40 mg/day of citalopram was combined with a brief psychosocial intervention in a 12-week treatment trial, the active drug showed an advantage over placebo during only the first week of treatment (Naranjo et al. 1995). Although Balldin et al. (1994) found no overall advantage to citalopram, when the data were reanalyzed on the basis of the pretreatment level of alcohol consumption, subjects in the lighter drinking subgroup had lower daily alcohol intake with citalopram, compared with placebo. Tiihonen et al. (1996) found a significant advantage for citalopram over placebo in effects on study retention and on collateral informants' reports of the patient's condition, with a trend for decreased alcohol consumption and GGTP levels in the active treatment group.

In summary, studies of the effects of SRIs on drinking behavior have been conducted in diverse subject samples, including heavy drinkers who were not seeking to reduce or stop their drinking. Some, but not all, studies examined medication effects in the context of psychotherapeutic treatment. Nonetheless, overall, these studies suggest that SRIs are efficacious only in subgroups of alcoholic patients. Kranzler et al. (1996) found that patients with high-risk/high-severity (i.e., type B) alcoholism (one characteristic of which is an earlier age at alcoholism onset) showed a poorer response to fluoxetine than to placebo. Pettinati et al. (2000) found that subjects with low-risk/low-severity (type A) alcoholism (i.e., those with later age at alcoholism onset) drank on fewer days and were more likely to be abstinent in a 12-week treatment trial when treated with sertraline, compared with placebo. In a 6-month posttreatment follow-up of these patients (Dundon et al. 2004), the type A subgroup treated with sertraline maintained the beneficial effects that were observed during treatment. In contrast, compared with subjects who received placebo, subjects with type B alcoholism who were initially treated with sertraline increased their heavy drinking during the follow-up period.

In a similar vein, ondansetron (a 5-HT_3 antagonist) was shown by Johnson et al. (2000) to selectively reduce drinking behavior among individuals with onset of problem drinking before age 25 years (i.e., people with early-onset alcoholism). Specifically, at a dosage substantially lower than that used for its anti-emetic effects, ondansetron was superior to placebo in its effects on the proportion of days abstinent and on the intensity of alcohol intake. In contrast, among people with late-onset alcoholism, the effects of ondansetron on drinking behavior were in nearly all respects comparable to those of placebo. In an 8-week, open-label study of ondansteron at a dosage of 4 μg/kg twice daily (the dosage shown to be optimal by Johnson et al. [2000]), Kranzler et al. (2003b) found that patients with early-onset alcoholism had a significantly greater decrease in drinks per day, drinks per drinking day, and alcohol-related problems, compared with patients with late-onset alcoholism. Prospective studies with the aim of matching serotonergic treatments with alcoholic subtypes (e.g., based on age at onset) may define a clearer role for such medications in the treatment of heavy drinking or alcohol dependence.

Summary. Currently, the most promising agents that directly reduce alcohol consumption are the opioid antagonists and acamprosate. Further re-

search is required to determine which patient groups, dosage schedules, route and duration of therapy, and concomitant psychosocial treatments are optimal for the use of these medications. Furthermore, trials that compare and/or combine medications that show initial promise for relapse prevention (including SRIs) are needed to determine the best strategies for relapse prevention in alcoholic patients.

Medications to Treat Co-occurring Psychiatric Symptoms or Disorders in Alcoholic Patients

Although many alcoholic patients report substantially fewer mood or anxiety symptoms once they have completed acute withdrawal, for many others anxiety, insomnia, and depressed mood may persist for weeks or months. Even among patients without substantial symptoms of alcohol withdrawal, persistent, low-level symptoms may develop, a condition that has been called "subacute withdrawal." Other symptoms may reflect diagnosable psychiatric disorders. Although medications (e.g., SRIs) are often used during the post-withdrawal period to relieve these symptoms, it remains to be clearly demonstrated that the treatment of persistent or subacute withdrawal symptoms that do not meet diagnostic criteria for a co-occurring psychiatric disorder results in a generally better outcome in alcoholic patients.

Many of the early studies of the efficacy of medications for treatment of mood disturbances targeted symptoms of depression and anxiety in unselected groups of detoxified alcoholic patients. These circumstances, combined with other methodological limitations of these studies, led to a failure to demonstrate an advantage over control conditions with respect to reductions in either psychiatric symptoms or drinking behavior (Ciraulo and Jaffe 1981).

There is renewed interest in the incidence and prevalence of co-occurring psychiatric disturbances among individuals with alcohol abuse/dependence. Co-occurring psychiatric disorders are discussed in detail by Kranzler and Tinsley (2004). Community studies have shown high rates of co-occurrence of drug dependence and psychiatric disorders in alcohol-dependent individuals in the community (Grant and Harford 1995; Grant et al. 2004b; Kessler et al. 1994, 1997; Regier et al. 1990). It is also evident that the majority of persons with alcoholism who seek treatment meet the lifetime criteria for one or more psychiatric disorders in addition to alcoholism. Most common among these co-occurring disorders are mood disorders, other substance dependence,

antisocial personality disorder, and anxiety disorders (Hesselbrock et al. 1985; Powell et al. 1982; Ross et al. 1988).

Medications that have been used as treatment for anxiety and depression in the postwithdrawal state include antidepressants, benzodiazepines and other anxiolytics, antipsychotics, and lithium. In general, the indications for use of these medications in alcoholic patients are similar to those for use in nonalcoholic patients with psychiatric illness. However, following careful differential diagnosis, the choice of medications should take into account the increased potential for adverse effects when the medications are prescribed to alcoholic patients. For example, adverse effects can result from pharmacodynamic interactions with medical disorders commonly present in alcoholic patients, as well as from pharmacokinetic interactions with medications prescribed to treat these disorders (Sullivan and O'Connor 2004).

A recent meta-analysis included 14 prospective, parallel-group, double-blind, randomized placebo-controlled trials of antidepressants for a co-occurring substance use disorder and unipolar depression (Nunes and Levin 2004). The majority of the studies reviewed (i.e., eight of the 14 studies) focused on alcohol dependence. Eight studies (six involving alcohol-dependent patients) showed a significant or near-significant advantage for the active medication over placebo. The principal measure of effect size was the standardized difference between mean scores on the Hamilton Depression Rating Scale. The pooled effect size on this measure was 0.38 (95% CI = 0.18–0.58), which is in the small-to-moderate range of effect sizes. There was a trend for the medication effect to be larger for studies of alcohol dependence. The most robust predictor of medication response was the magnitude of the placebo response, such that studies with a placebo response rate greater than 25% showed no advantage for the active medication, and those with a placebo response rate smaller than 25% yielded effects in the moderate-to-large range. Moderator analysis also showed that diagnosis of depression after a week of abstinence was associated with better antidepressant response, and the presence of a larger proportion of women in the study sample, the use of SRIs (compared with tricyclic or other antidepressants), and a concurrent psychosocial intervention were associated with poorer medication response. Reductions in substance use behavior were associated with the magnitude of the antidepressant response. Specifically, studies that showed a moderate depression effect size (i.e., greater than 0.5) yielded a substance use effect size that was also moderate, and

smaller depression effects were associated with no beneficial effects on substance use behavior.

The authors concluded that antidepressants exert a modest beneficial effect for patients with combined depressive disorder and substance use disorder. They also emphasized that antidepressants are not a stand-alone treatment for depressed alcoholic patients and that concurrent therapy directly targeting the substance use disorder is also indicated.

Recently, Hernandez-Avila et al. (2004) compared nefazodone with placebo in a small sample of alcohol-dependent subjects with current major depression. Although there were greater reductions in anxiety and depressive symptoms in the nefazodone group, compared with the placebo group, the effects did not reach statistical significance. Nonetheless, the nefazodone-treated subjects showed a significantly greater reduction in heavy drinking days and in total drinks than did the subjects who received placebo. Although nefazodone may be useful in depressed alcoholic patients, its association with a limited number of cases of idiosyncratic hepatic failure limits its clinical utility.

Consistent with the conclusion drawn by Nunes and Levin (2004) of the need for treating both the mood disorder and the substance use disorder in depressed substance abusers, there is growing interest in the use of combination pharmacotherapy for co-occurring alcohol dependence and depression. In a 12-week, open-label study, 14 depressed alcoholic patients who had continued to drink despite receiving antidepressants and chemical dependence counseling were treated with 50 mg/day of naltrexone (Salloum et al. 1998). The addition of naltrexone was associated with a substantial decrease in alcohol consumption and in the urge to drink alcohol in the presence of the usual triggers. There was also a trend toward decreased depressive symptoms and improved overall functioning. Similarly, a recent small study (Petrakis et al. 2004) showed that the addition of naltrexone to antipsychotic treatment among schizophrenic patients with co-occurring alcohol abuse or dependence reduced the number of drinking days and heavy drinking days. Large, placebo-controlled trials examining this approach are needed.

In summary, despite evidence that most instances of postwithdrawal depression spontaneously remit within a few days to several weeks of abstinence from alcohol (Brown and Schuckit 1988; Schuckit 1983), persistent depression requires treatment. SRIs have become the first-line treatment for depression

because they have a more favorable side-effect profile than many other antidepressants. SRIs do not have the anticholinergic, hypotensive, or sedative effects of the tricyclic antidepressants, nor do they have the adverse cardiovascular effects of the tricyclics, which in overdose can be lethal; thus the potential for deliberate self-poisoning is limited with SRIs (Lynskey 1998). However, SRIs can exacerbate the tremor, anxiety, and insomnia often experienced by recently detoxified alcoholic patients. Furthermore, the findings of Nunes and Levin (2004) suggested that for the treatment of depression among patients with a substance use disorder, SRIs may be less efficacious than other antidepressants.

Benzodiazepines and other anxiolytics. Although benzodiazepines are widely used in the treatment of acute alcohol withdrawal, most nonmedical personnel involved in the treatment of alcoholism are opposed to the use of medications that can induce any variety of dependence to treat the anxiety, depression, and sleep disturbances that can persist for months following withdrawal. Researchers have debated the pros and cons of the use of benzodiazepines for the management of anxiety or insomnia in alcoholic patients and other substance abuse patients during the postwithdrawal period (Ciraulo and Nace 2000; Posternak and Mueller 2001).

Despite the risks of benzodiazepine dependence and overdose among alcoholic patients beyond the period of acute withdrawal, there may be a role for the judicious use of benzodiazepines in treating these patients. To the degree that early relapse, which commonly disrupts alcoholism treatment, is a result of continued withdrawal-related symptoms (e.g., anxiety, depression, insomnia) that can be suppressed by low doses of benzodiazepines, retention in treatment could be enhanced by the use of benzodiazepines (Kissin 1977). Moreover, for some patients, benzodiazepine dependence, if it does occur, may be more benign than alcoholism.

These important potential benefits must be weighed against the risk both of benzodiazepine overdose and of physical dependence on such drugs. Although benzodiazepines alone are comparatively safe, even in overdose, their combination with other brain depressants (including alcohol) can be lethal. Although there is little doubt that alcoholic patients are more vulnerable to dependence on benzodiazepines, compared with persons without alcoholism, the probability of abuse and dependence may be lower than is generally believed (Bliding 1978; Ciraulo et al. 1990; Marks 1978). However, dependence on

both alcohol and benzodiazepines may increase depressive symptoms (Schuckit 1983), and co-occurring alcohol and benzodiazepine dependence may be more difficult to treat than alcoholism alone (Sokolow et al. 1981).

The benzodiazepines currently available for clinical use vary substantially in pharmacokinetics, acute euphoriant effects, and frequency of reported dependence. It is likely, therefore, than not all benzodiazepines have the same potential for abuse. Diazepam, lorazepam, and alprazolam may have greater abuse potential than chlordiazepoxide and clorazepate (Wolf et al. 1990). Similarly, oxazepam has been reported to produce low levels of abuse (Bliding 1978). Jaffe et al. (1983) found that in recently detoxified alcoholic patients, halazepam produces minimal euphoria even at a supratherapeutic dosage. The development of partial agonist and mixed agonist/antagonist compounds at the benzodiazepine receptor complex may offer an advantage over approved benzodiazepines for use in alcoholic patients.

Buspirone, a nonbenzodiazepine anxiolytic, appears to exert its effects largely by means of its partial agonist activity at serotonergic autoreceptors. It is comparable in efficacy to diazepam in the relief of anxiety and associated depression in outpatients with moderate-to-severe anxiety (Goldberg and Finnerty 1979; Jacobson et al. 1985). However, buspirone is less sedating than diazepam or clorazepate, does not interact with alcohol to impair psychomotor skills, and does not appear to have abuse liability (Griffith et al. 1986; Mattila et al. 1982; Seppala et al. 1982), making it more suitable than benzodiazepines for treatment of anxiety symptoms among alcoholic patients. In contrast to benzodiazepines, however, buspirone does not have acute anxiolytic effects, nor is it useful in the treatment of alcohol withdrawal.

Four placebo-controlled, double-blind trials of buspirone to treat anxiety symptoms among alcoholic patients have been reported. An early, double-blind, placebo-controlled trial of buspirone in alcoholic patients showed significantly greater retention in treatment and greater decreases in alcohol craving, anxiety, and depression scores in buspirone-treated patients (Bruno 1989). Both groups showed significant declines in alcohol consumption during the study, with no greater effect among buspirone-treated patients. In a placebo-controlled trial of buspirone among abstinent alcoholic patients with co-occurring generalized anxiety disorder, Tollefson et al. (1992) found greater treatment retention and greater reductions in anxiety among buspirone-treated subjects. Although buspirone-treated patients also showed greater im-

provement on a subjective global measure of drinking outcome, measures of alcohol consumption were not reported in this study. Kranzler et al. (1994) also found that anxious alcoholic patients showed a better response to buspirone than to placebo in terms of retention in treatment. The active drug also delayed relapse to heavy drinking and during a 6-month posttreatment follow-up period it reduced the number of drinking days. The beneficial effects of buspirone on both anxiety and drinking were most evident among the patients with the highest baseline anxiety scores. In contrast, a study of anxious, severely alcohol-dependent patients found buspirone to have no advantage over placebo on anxiety or drinking measures (Malcolm et al. 1992). Although there appears to be a role for buspirone in the treatment of anxiety symptoms in alcoholic patients, it is unclear which clinical features can be used to identify individuals for whom buspirone may be most efficacious.

Lithium. Although early studies of lithium, including some that used placebo controls (Kline et al. 1974; Merry et al. 1976), showed that lithium-treated patients experienced fewer days of pathological drinking, the rates of attrition in these studies were high. In a subsequent placebo-controlled study, adherence to the medication regimen, irrespective of medication group, was associated with abstinence in alcoholic patients who were not selected for coexisting depression (Fawcett et al. 1987). Furthermore, treatment-adherent patients who were taking active medication and who had therapeutic lithium serum levels (0.4 mEq/L or greater) were abstinent more often than were treatment-adherent subjects with subtherapeutic lithium levels. After the first 6 months, however, even subjects who had been adherent to treatment early in the study tended to stop taking their medication. Nevertheless, the association between early treatment adherence and sobriety persisted, suggesting that the beneficial effects of lithium are greatest in the early months after detoxification. The beneficial effect of lithium did not appear to be mediated by an antidepressant effect, because it did not affect mood in the patients who were depressed.

Dorus and colleagues (1989) conducted a multicenter, double-blind, placebo-controlled trial in depressed and nondepressed alcoholic veterans. A total of 457 male alcoholic patients, of whom approximately one-third were depressed, were randomly assigned to receive either 600–1,200 mg/day of lithium or a comparable number of placebo capsules. No significant differ-

ences between the two groups were found on any of a variety of outcome measures, including number of drinking days, alcohol-related hospitalizations, and severity of depression. The lack of efficacy was observed for both the depressed and the nondepressed groups. This large, carefully conducted trial suggested that lithium should be reserved for the treatment of alcoholic patients with co-occurring bipolar disorder. A subsequent study, in which there was no advantage to lithium over placebo in alcoholic patients who were not selected for a co-occurring psychiatric disorder yielded results consistent with this conclusion (Fawcett et al. 2000).

Conclusion

In general, with the exception of the central role that benzodiazepines play in the treatment of alcohol withdrawal, the use of medications that have been approved for alcoholism rehabilitation remains very limited. A survey of nearly 1,400 addiction physicians showed that they prescribed disulfiram to only 9% of their alcoholic patients and that naltrexone was prescribed for only slightly higher proportion of patients (13%) (Mark et al. 2003). These results contrast with findings for antidepressants, which were prescribed to 44% of alcoholic patients. Although nearly all of these physicians had heard of both disulfiram and naltrexone, their self-reported level of knowledge of these medications was much lower than that of antidepressants.

Although continuing developments in the United States, Europe, and Australia suggest that the use of medications may eventually contribute substantially to alcoholism rehabilitation efforts, many questions must be addressed before medications are likely to be widely employed for this indication. In addition to the issues discussed earlier in regard to specific agents (e.g., What is the optimal duration of use for naltrexone?), the safety and efficacy of medications to treat alcohol dependence must be examined with adequate statistical power in women, in different ethnic/racial groups, and in adolescent and geriatric samples. In addition, studies of cost-effectiveness and cost-benefit must support the routine coverage of pharmacological treatments for alcoholism under standard medical insurance plans.

The treatment of co-occurring psychiatric symptoms among alcoholic patients, which can be beneficial in relapse prevention, is an area in which considerable clinical and research interest already exists (Kranzler and Tinsley

2004). Anxiolytics with little abuse potential, such as buspirone, and antidepressants that have a benign side-effect profile and may reduce ethanol intake warrant careful evaluation in the treatment of anxious and depressed alcoholic patients.

However, the relationship between substance use and psychiatric symptoms is complex (Kranzler and Tinsley 2004; Meyer 1986). Despite ameliorating persistent mood and anxiety symptoms, medications that are prescribed to alcoholic patients with such co-occurring symptoms will not necessarily reduce alcohol consumption once a significant degree of alcohol dependence has developed, even if pathological mood states were important in the initiation of heavy drinking. The neuroadaptive changes and the complex learning that constitute the dependence syndrome (Edwards and Gross 1976) do not resolve simply because one major contributing factor is brought under control. The challenge for those treating alcoholic patients is to combine efficacious medications with empirically based psychological interventions and, when feasible, with self-help group participation.

The medications that have been most widely studied in alcohol rehabilitation are naltrexone and acamprosate. Results from the COMBINE Study, as well as results of Phase III trials of depot naltrexone formulations, will be available in the near future and will provide important new information on the use of these medications in alcohol rehabilitation. In addition, other promising medications, such as the anticonvulsant topiramate (Johnson et al. 2003), are being evaluated in multicenter trials. As the research literature on the use of medications to treat alcohol dependence grows, it will be possible to assess the utility of different medication combinations and a variety of psychotherapies. Ongoing efforts to match medications with specific subgroups of alcoholic patients, based on clinical or genetic characteristics, remain a promising strategy.

Combining medications with self-help group participation may represent a particular challenge. Abstinence-oriented groups such as Alcoholics Anonymous may be willing to work with physicians around the issue of proper dosage, adherence, and early detection of side effects of disulfiram, the use of which is supportive of these groups' goal of total abstinence. However, these groups may be less supportive of other pharmacotherapies for alcoholism, the focus of which is harm reduction through reduced drinking, rather than abstinence.

As evidence accumulates showing that a number of medications are efficacious for the treatment of co-occurring psychopathology and/or the prevention of relapse in alcoholic patients, the therapeutic options available to physicians in treating these patients will increase. As these developments unfold, it is crucial that efforts be directed to enhancing the acceptability of pharmacotherapy to the alcoholism treatment community as a standard ingredient in alcoholism rehabilitation.

References

Allen JP, Litten RZ: Techniques to enhance compliance with disulfiram. Alcohol Clin Exp Res 16:1035–1041, 1992

Allgaier C: Ethanol sensitivity of NMDA receptors. Neurochem Int 41:377–382, 2002

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised. Washington, DC, American Psychiatric Association, 1987

Amit Z, Brown Z, Sutherland A, et al: Reduction in alcohol intake in humans as a function of treatment with zimelidine: implications for treatment, in Research Advances in New Psychopharmacological Treatments for Alcoholism. Edited by Naranjo CA, Sellers EM. Amsterdam, Elsevier, 1985

Angelone SM, Bellini L, Di Bella D, et al: Effects of fluvoxamine and citalopram in maintaining abstinence in a sample of Italian detoxified alcoholics. Alcohol Alcohol 33:151–156, 1998

Anton RF, Moak DH, Latham PK, et al: Posttreatment results of combining naltrexone and cognitive-behavior therapy for the treatment of alcoholism. J Clin Psychopharmacol 21:72–77, 2000

Anton RF, Pettinati H, Zweben A, et al: A multi-site dose ranging study of nalmefene in the treatment of alcohol dependence. J Clin Psychopharmacol 24:421–428, 2004

Aragon CM, Stotland LM, Amit Z: Studies on ethanol-brain catalase interaction: evidence for central ethanol oxidation. Alcohol Clin Exp Res 15:165–169, 1991

Arizzi MN, Correa M, Betz AJ, et al: Behavioral effects of intraventricular injections of low doses of ethanol, acetaldehyde, and acetate in rats: studies with low and high rate operant schedules. Behav Brain Res 147:203–210, 2003

Azrin NH, Sisson RW, Meyers R, et al: Alcoholism treatment by disulfiram and community reinforcement therapy. J Behav Ther Exp Psychiatry 13:105–112, 1982

Babor TF, Kranzler HR, Lauerman RL: Social drinking as a health and psychosocial risk factor: Anstie's limit revisited, in Recent Developments in Alcoholism, Vol 5. Edited by Galanter M. New York, Plenum, 1987, pp 373–402

Babor TF, Kranzler HR, Hernandez-Avila CA, et al: Alcohol use disorders, in Psychiatry, 2nd Edition. Edited by Tasman A, Kay J, Lieberman JA. Philadelphia, PA, WB Saunders, 2003, pp 936–972

Bailly D, Servant D, Blandin N, et al: Effects of beta-blocking drugs in alcohol withdrawal: a double-blind comparative study with propranolol and diazepam. Biomed Pharmacother 46:419–424, 1992

Balldin J, Berggren U, Engel J, et al: Effect of citalopram on alcohol intake in heavy drinkers. Alcohol Clin Exp Res 18:1133–1136, 1994

Behar KL, Rothman DL, Petersen KF, et al: Preliminary evidence of low cortical GABA levels in localized 1H-MR spectra of alcohol-dependent and hepatic encephalopathy patients. Am J Psychiatry 156:952–954, 1999

Besson J, Aeby F, Kasas A, et al: Combined efficacy of acamprosate and disulfiram in the treatment of alcoholism: a controlled study. Alcohol Clin Exp Res 22:573–579, 1998

Bliding A: The abuse potential of benzodiazepines with special reference to oxazepam. Acta Psychiatr Scand Suppl 274:111–116, 1978

Bonnet U, Banger M, Leweke FM, et al: Treatment of acute alcohol withdrawal with gabapentin: results from a controlled two-center trial. J Clin Psychopharmacol 23:514–519, 2003

Bouza C, Magro A, Munoz A, et al: Efficacy and safety of naltrexone and acamprosate in the treatment of alcohol dependence: a systematic review. Addiction 99:811–828, 2004

Brady KT, Myrick H, Henderson S, et al: The use of divalproex in alcohol relapse prevention: a pilot study. Drug Alcohol Depend 67:323–330, 2002

Brewer C: How effective is the standard dose of disulfiram? a review of the alcohol-disulfiram reaction in practice. Br J Psychiatry 144:200–202, 1984

Brewer C, Meyers RJ, Johnsen J: Does disulfiram help to prevent relapse in alcohol abuse? CNS Drugs 14:329–341, 2000

Brown SA, Schuckit MA: Changes in depression among abstinent alcoholics. J Stud Alcohol 49:412–417, 1988

Bruno F: Buspirone in the treatment of alcoholic patients. Psychopathology 22 (suppl 1): 49–59, 1989

Calton JL, Wilson WA, Moore SD: Reduction of voltage-dependent currents by ethanol contributes to inhibition of NMDA receptor-mediated excitatory synaptic transmission. Brain Res 816:142–148, 1999

Carlezon WA Jr, Nestler EJ: Elevated levels of GluR1 in the midbrain: a trigger for sensitization to drugs of abuse? Trends Neurosci 25:610–615, 2002

Carlsson C, Fasth BG: A comparison of the effects of propranolol and diazepam in alcoholics. Br J Addict Alcohol Other Drugs 71:321–326, 1976

Carta M, Ariwodola OJ, Weiner JL, et al: Alcohol potently inhibits the kainate receptor-dependent excitatory drive of hippocampal interneurons. Proc Natl Acad Sci U S A 100:6813–6818, 2003

Chen CC, Lu RB, Chen YC, et al: Interaction between the functional polymorphisms of the alcohol-metabolism genes in protection against alcoholism. Am J Hum Genet 65:795–807, 1999

Chester JA, Cunningham CL: GABA(A) receptor modulation of the rewarding and aversive effects of ethanol. Alcohol 26:131–143, 2002

Chick J: Safety issues concerning the use of disulfiram in treating alcohol dependence. Drug Saf 20:427–435, 1999

Chick J, Gough K, Falkowski W, et al: Disulfiram treatment of alcoholism. Br J Psychiatry 161:84–89, 1992

Chick J, Lehert P, Landron F, et al: Does acamprosate improve reduction of drinking as well as aiding abstinence? J Psychopharmacol 17:397–402, 2003

Chrostek L, Jelski W, Szmitkowski M, et al: Gender-related differences in hepatic activity of alcohol dehydrogenase isoenzymes and aldehyde dehydrogenase in humans. J Clin Lab Anal 17:93–96, 2003

Ciraulo DA, Jaffe JH: Tricyclic antidepressants in the treatment of depression associated with alcoholism. J Clin Psychopharmacol 1:146–150, 1981

Ciraulo DA, Nace E: Benzodiazepine treatment of anxiety or insomnia in substance abuse patients. Am J Addict 9:276–284, 2000

Ciraulo DA, Barnhill JG, Jaffe JH, et al: Intravenous pharmacokinetics of 2-hydroxyimipramine in alcoholics and normal controls. J Stud Alcohol 51:366–372, 1990

Ciraulo DA, Knapp CM, LoCastro J, et al: A benzodiazepine mood effect scale: reliability and validity determined for alcohol-dependent subjects and adults with a parental history of alcoholism. Am J Drug Alcohol Abuse 27:339–347, 2001

Collins MA: Tetrahydropapaveroline in Parkinson's disease and alcoholism: a look back in honor of Merton Sandler. Neurotoxicology 25:117–120, 2004

COMBINE Study Research Group: Testing combined pharmacotherapies and behavioral interventions in alcohol dependence: rationale and methods. Alcohol Clin Exp Res 27:1107–1122, 2003a

COMBINE Study Research Group: Testing combined pharmacotherapies and behavioral interventions for alcohol dependence (the COMBINE study): a pilot feasibility study. Alcohol Clin Exp Res 27:1123–1131, 2003b

Covault C, Gelernter J, Hesselbrock V, et al: Allelic and haplotypic association of GABRA2 with alcohol dependence. Am J Med Genet B Neuropsychiatr Genet 129:104–109, 2004

Cowen MS, Chen F, Lawrence AJ: Neuropeptides: implications for alcoholism. J Neurochem 89:273–285, 2004

Cowley DS: Alcohol abuse, substance abuse, and panic disorder. Am J Med 92(suppl): 41S–48S, 1992

Cowley DS, Roy-Byrne PP, Radant A, et al: Eye movement effects of diazepam in sons of alcoholic fathers and male control subjects. Alcohol Clin Exp Res 18:324–332, 1994

Davis KM, Wu JY: Role of glutamatergic and GABAergic systems in alcoholism. J Biomed Sci 8:7–19, 2001

de Waele JP, Papachristou DN, Gianoulakis C: The alcohol-preferring C57BL/6 mice present an enhanced sensitivity of the hypothalamic beta-endorphin system to ethanol than the alcohol-avoiding DBA/2 mice. J Pharmacol Exp Ther 261:788–794, 1992

de Waele JP, Kiianmaa K, Gianoulakis C: Spontaneous and ethanol-stimulated in vitro release of beta-endorphin by the hypothalamus of AA and ANA rats. Alcohol Clin Exp Res 18:1468–1473, 1994

Dobrydnjov I, Axelsson K, Berggren L, et al: Intrathecal and oral clonidine as prophylaxis for postoperative alcohol withdrawal syndrome: a randomized double-blinded study. Anesth Analg 98:738–744, 2004

Dorus W, Ostrow DG, Anton R, et al: Lithium treatment of depressed and nondepressed alcoholics. JAMA 262:1646–1652, 1989

Dundon W, Lynch KG, Pettinati HM, et al: Treatment outcomes in type A and B alcohol dependence 6 months after serotonergic pharmacotherapy. Alcohol Clin Exp Res 28:1065–1073, 2004

Edenberg HJ, Dick DM, Xuei X, et al: Variations in GABRA2, encoding the alpha 2 subunit of the GABA(A) receptor, are associated with alcohol dependence and with brain oscillations. Am J Hum Genet 74:705–714, 2004

Edwards G, Gross MM: Alcohol dependence: Provisional description of a clinical syndrome. Br Med J 1:1058–1061, 1976

Egli M: Peptides: their role in excess alcohol drinking and their promise as a therapeutic tool. Physiol Behav 79:89–93, 2003

Farde L, Pauli S, Litton JE, et al: PET-determination of benzodiazepine receptor binding in studies on alcoholism. EXS 71:143–153, 1994

Farren CK, Ziedonis D, Clare AW, et al: D-Fenfluramine-induced prolactin responses in postwithdrawal alcoholics and controls. Alcohol Clin Exp Res 19:1578–1582, 1995

Favazza AR, Martin P: Chemotherapy of delirium tremens: a survey of physicians' preferences. Am J Psychiatry 131:1031–1033, 1974

Fawcett J, Clark DC, Aagesen CA, et al: A double-blind, placebo-controlled trial of lithium carbonate therapy for alcoholism. Arch Gen Psychiatry 44:248–256, 1987

Fawcett J, Kravitz HM, McGuire M, et al: Pharmacological treatments for alcoholism: revisiting lithium and considering buspirone. Alcohol Clin Exp Res 24:666–674, 2000

Feldman DJ, Pattison EM, Sobell LC, et al: Outpatient alcohol detoxification: initial findings on 564 patients. Am J Psychiatry 132:407–412, 1975

Foddai M, Dosia G, Spiga S, et al: Acetaldehyde increases dopaminergic neuronal activity in the VTA. Neuropsychopharmacology 29:530–536, 2004

Frezza M, di Padova C, Pozzato G, et al: High blood alcohol levels in women: the role of decreased gastric alcohol dehydrogenase activity and first-pass metabolism. N Engl J Med 322:95–99, 1990

Fuller RK, Branchey L, Brightwell DR, et al: Disulfiram treatment of alcoholism: a Veteran's Administration cooperative study. JAMA 256:1449–1455, 1986

Garbutt JC, West SL, Carey TS, et al: Pharmacological treatment of alcohol dependence: a review of the evidence. JAMA 281:1318–1325, 1999

Garbutt JC, Kranzler HR, O'Malley SS, et al: Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence. JAMA 293:1617–1625, 2005

Gerra G, Caccavari R, Delsignore R, et al: Effects of fluoxetine and Ca-acetyl-homotaurinate on alcohol intake in familial and nonfamilial alcohol patients. Curr Ther Res 52:291–295, 1992

Gianoulakis C, Beliveau D, Angelogianni P, et al: Different pituitary beta-endorphin and adrenal cortisol response to ethanol in individuals with high and low risk for future development of alcoholism. Life Sci 45:1097–1109, 1989

Gianoulakis C, Krishnan B, Thavundayil J: Enhanced sensitivity of pituitary beta-endorphin to ethanol in subjects at high risk of alcoholism. Arch Gen Psychiatry 53:250–257, 1996

Goldberg HL, Finnerty RJ: The comparative efficacy of buspirone and diazepam in the treatment of anxiety. Am J Psychiatry 136:1184–1187, 1979

Goldman D: Recent developments in alcoholism:genetic transmission. Recent Dev Alcohol 11:231–248, 1993

Goldstein DB, Hungund BL, Lyon RC: Increased surface glycoconjugates of synaptic membranes in mice during chronic ethanol treatment. Br J Pharmacol 78:8–10, 1983

Gorelick DA, Paredes A: Effect of fluoxetine on alcohol consumption in male alcoholics. Alcohol Clin Exp Res 16:261–265, 1992

Grant BF, Harford TC, Dawson DA, et al: Prevalence of DSM-IV alcohol abuse and dependence: United States, 1992. Alcohol Health and Research World 18:243–248, 1994

Grant BF, Harford TC: Comorbidity between DSM-IV alcohol use disorders and major depression: results of a national survey. Drug Alcohol Depend 39:197–206, 1995

Grant BF, Dawson DA, Stinson FS, et al: The 12-month prevalence and trends in DSM-IV alcohol abuse and dependence: United States, 1991–1992 and 2001–2002. Drug Alcohol Depend 74:223–234, 2004a

Grant BF, Stinson FS, Dawson DA, et al: Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Arch Gen Psychiatry 61:807–816, 2004b

Griffith JD, Jasinski DR, Casten GP, et al: Investigation of the abuse liability of buspirone in alcohol-dependent patients. Am J Med 80(suppl 3B):30–35, 1986

Hayashida M, Alterman Al, McLellan T, et al: Comparative effectiveness and costs of inpatient and outpatient detoxification of patients with mild-to-moderate alcohol withdrawal syndrome. N Engl J Med 320:358–365, 1989

Heinala P, Alho H, Kiianmaa K, et al: Targeted use of naltrexone without prior detoxification in the treatment of alcohol dependence: a factorial double-blind, placebo-controlled trial. J Clin Psychopharmacol 21:287–292, 2001

Heinz A, Schafer M, Higley JD, et al: Neurobiological correlates of the disposition and maintenance of alcoholism. Pharmacopsychiatry 36(suppl 3):S255–S258, 2003

Heinz A, Goldman D, Gallinat J, et al: Pharmacogenetic insights to monoaminergic dysfunction in alcohol dependence. Psychopharmacology (Berl) 174:561–570, 2004

Hernandez-Avila CA, Modesto-Lowe V, Feinn R, et al: Nefazodone treatment of comorbid alcohol dependence and major depression. Alcohol Clin Exp Res 28:433–440, 2004

Hesselbrock MN, Meyer RE, Keener JJ: Psychopathology in hospitalized alcoholics. Arch Gen Psychiatry 42:1050–1055, 1985

Hodge CW, Kelley SP, Bratt AM, et al: 5-HT_{3A} receptor subunit is required for 5-HT_3 antagonist-induced reductions in alcohol drinking. Neuropsychopharmacology 29:1807–1813, 2004

Hundt W, Holter SM, Spanagel R: Discriminative stimulus effects of glutamate release inhibitors in rats trained to discriminate ethanol. Pharmacol Biochem Behav 59: 691–695, 1998

Iwata N, Cowley DS, Radel M, et al: Relationship between a $GABA_A$ alpha $_6$ Pro385Ser substitution and benzodiazepine sensitivity. Am J Psychiatry 156:1447–1449, 1999

Jacobson AF, Dominguez RA, Goldstein B, et al: Comparison of buspirone and diazepam in generalized anxiety disorder. Pharmacotherapy 5:290–296, 1985

Jaffe JH, Ciraulo DA, Nies A, et al: Abuse potential of halazepam and diazepam in patients recently treated for acute alcohol withdrawal. Clin Pharmacol Ther 34: 623–630, 1983

Johnson BA, Ait-Daoud N: Neuropharmacological treatments for alcoholism: scientific basis and clinical findings. Psychopharmacology (Berl) 149:327–344, 2000

Johnson BA, Roache JD, Javors MA, et al: Ondansetron for reduction of drinking among biologically predisposed alcoholic patients: a randomized controlled trial. JAMA 284:963–971, 2000

Johnson BA, Ait-Daoud N, Bowden CL, et al: Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. Lancet 361:1677–1685, 2003

June HL, Foster KL, McKay PF, et al: The reinforcing properties of alcohol are mediated by $GABA_{A1}$ receptors in the ventral pallidum. Neuropsychopharmacology 28:2124–2137, 2003

Kabel DI, Petty F: A double blind study of fluoxetine in severe alcohol dependence: adjunctive therapy during and after inpatient treatment. Alcohol Clin Exp Res 20:780–784, 1996

Kahkonen S, Bondarenko BB: L-type Ca2+ channels mediate cardiovascular symptoms of alcohol withdrawal in humans. Prog Neuropsychopharmacol Biol Psychiatry 28:45–48, 2004

Kahkonen S: Alcohol withdrawal changes cardiovascular responses to propranolol challenge. Neuropsychobiology 47:192–197, 2003

Kessler RC, McGonagle KA, Zhao S, et al: Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Arch Gen Psychiatry 51:8–19, 1994

Kessler RC, Crum RM, Warner LA, et al: Lifetime co-occurrence of DSM-III-R alcohol abuse and dependence with other psychiatric disorders in the National Comorbidity Study. Arch Gen Psychiatry 54:313–321, 1997

Kiefer F, Jahn H, Tarnaske T, et al: Comparing and combining naltrexone and acamprosate in relapse prevention of alcoholism: a double-blind, placebo-controlled study. Arch Gen Psychiatry 60:92–99, 2003

Kissin B: Medical management of the alcoholic patient, in The Biology of Alcoholism, Vol 5. Treatment and Rehabilitation of the Chronic Alcoholic. Edited by Kissin B, Begleiter H. New York: Plenum, 1977, pp 55–103

Kline NS, Wren JC, Cooper TB, et al: Evaluation of lithium therapy in chronic and periodic alcoholism. Am J Med Sci 268:15–22, 1974

Koob GF, Roberts AJ, Schulteis G, et al: Neurocircuitry targets in ethanol reward and dependence. Alcohol Clin Exp Res 22:3–9, 1998

Kranzler HR (ed): The Pharmacology of Alcohol Abuse. New York, Springer-Verlag, 1995

Kranzler HR: Pharmacotherapy of alcoholism: gaps in knowledge and opportunities for research. Alcohol Alcohol 35:537–547, 2000

Kranzler HR, Anton RF: Implications of recent neuropsychopharmacologic research for understanding the etiology and development of alcoholism. J Consult Clin Psychol 62:1116–1126, 1994

Kranzler HR, Rosenthal RN: Dual diagnosis: alcoholism and co-morbid psychiatric disorders. Am J Addict 12 (suppl 1):S26–S40, 2003

Kranzler HR, Tinsley JA (eds): Dual Diagnosis: Substance Abuse and Comorbid Medical and Psychiatric Disorders, 2nd Edition. New York, Marcel Dekker, 2004

Kranzler HR, Van Kirk J: Efficacy of naltrexone and acamprosate for alcoholism treatment: a meta-analysis. Alcohol Clin Exp Res 25:1335–1341, 2001

Kranzler HR, Babor TF, Lauerman R: Problems associated with average alcohol consumption and frequency of intoxication in a medical population. Alcohol Clin Exp Res 14:119–126, 1990

Kranzler HR, Del Boca F, Korner P, et al: Adverse effects limit the usefulness of fluvoxamine for the treatment of alcoholism. J Subst Abuse Treat 10:283–287, 1993

Kranzler HR, Burleson JA, Del Boca FK, et al: Buspirone treatment of anxious alcoholics: a placebo-controlled trial. Arch Gen Psychiatry 51:720–731, 1994

Kranzler HR, Burleson JA, Korner P, et al: Placebo-controlled trial of fluoxetine as an adjunct to relapse prevention in alcoholics. Am J Psychiatry 152:391–397, 1995

Kranzler HR, Burleson JA, Brown J, et al: Fluoxetine treatment seems to reduce the beneficial effects of cognitive-behavioral therapy in type B alcoholics. Alcohol Clin Exp Res 20:1534–1541, 1996

Kranzler HR, Tennen H, Penta C, et al: Targeted naltrexone treatment in early problem drinkers. Addict Behav 22:431–436, 1997

Kranzler HR, Modesto-Lowe V, Nuwayser ES: A sustained-release naltrexone preparation for treatment of alcohol dependence. Alcohol Clin Exp Res 22:1074–1079, 1998

Kranzler HR, Armeli S, Tennen H, et al: Targeted naltrexone for early problem drinkers. J Clin Psychopharmacol 23:294–304, 2003a

Kranzler HR, Pierucci-Lagha A, Feinn R, et al: Effects of ondansetron in early- vs late-onset alcoholics: a prospective, open-label study. Alcohol Clin Exp Res 27:1150–1155, 2003b

Kranzler HR, Wesson DR, Billot L: Naltrexone depot for treatment of alcohol dependence: a multicenter, randomized, placebo-controlled clinical trial. Alcohol Clin Exp Res 28:1051–1059, 2004

Krystal JH, Cramer JA, Krol WF, et al: Naltrexone in the treatment of alcohol dependence. N Eng J Med 345:1734–1739, 2001

Krystal JH, Petrakis IL, Limoncelli D, et al: Altered NMDA glutamate receptor antagonist response in recovering ethanol-dependent patients. Neuropsychopharmacology 28:2020–2028, 2003a

Krystal JH, Petrakis IL, Mason G, et al: *N*-methyl-D-aspartate glutamate receptors and alcoholism: reward, dependence, treatment, and vulnerability. Pharmacol Ther 99: 79–94, 2003b

Lai CL, Chao YC, Chen YC, et al: No sex and age influence on the expression pattern and activities of human gastric alcohol and aldehyde dehydrogenases. Alcohol Clin Exp Res 24:1625–1632, 2000

Landabaso MA, Iraurgi I, Sanz J, et al. Naltrexone in the treatment of alcoholism: two-year follow up results. Eur J Psychiatry 13:97–105, 1999

Lane JD, Stinson FS, Bertolucci D: Trends in alcohol-related fatal traffic crashes, United States, 1977–95 (Surveillance Report No 42). Rockville, MD, National Institute on Alcohol Abuse and Alcoholism, 1997

Lhuintre JP, Moore ND, Saligaut C, et al: Ability of calcium bis acetyl homotaurinate, a GABA agonist, to prevent relapse in weaned alcoholics. Lancet 1:1014–1016, 1985

Litten RZ, Allen J, Fertig J: Pharmacotherapies for alcohol problems: a review of research with focus on developments since 1991. Alcohol Clin Exp Res 20:859–876, 1996

Littleton J: Acamprosate in alcohol dependence: how does it work? Addiction 90:1179–1188, 1995

Littleton J, Zieglgansberger W: Pharmacological mechanisms of naltrexone and acamprosate in the prevention of relapse in alcohol dependence. Am J Addict 12 (suppl 1):S3–S11, 2003

Lynskey MT: The comorbidity of alcohol dependence and affective disorders: treatment implications. Drug Alcohol Depend 52:201–209, 1998

Malcolm R, Ballenger JC, Sturgis ET, et al: Double-blind controlled trial comparing carbamazepine to oxazepam treatment of alcohol withdrawal. Am J Psychiatry 146:617–621, 1989

Malcolm R, Anton RF, Randall CL, et al: A placebo-controlled trial of buspirone in anxious inpatient alcoholics. Alcohol Clin Exp Res 16:1007–1013, 1992

Malcolm R, Myrick H, Roberts J, et al: The effects of carbamazepine and lorazepam on single versus multiple previous alcohol withdrawals in an outpatient randomized trial. J Gen Intern Med 17:349–355, 2002

Mann K, Lehert P, Morgan MY: The efficacy of acamprosate in the maintenance of abstinence in alcohol-dependent individuals: results of a meta-analysis. Alcohol Clin Exp Res 28:51–63, 2004

Mark TL, Kranzler HR, Song X, et al: Physicians' opinions about medications to treat alcoholism. Addiction 98:617–626, 2003

Marks J: The Benzodiazepines: Use, Misuse, Abuse. Lancaster, England, MTP Press, 1978

Mason B, Goodman A: Acamprosate: new preclinical and clinical research. Presented at the 23rd Annual Scientific Meeting of the Research Society on Alcoholism, Denver, CO, June 24–29, 2000

Mason BJ, Ritvo EC, Morgan RO, et al: A double-blind, placebo-controlled pilot study to evaluate the efficacy and safety of oral nalmefene HCL for alcohol dependence. Alcohol Clin Exp Res 18:1162–1167, 1994

Mason BJ, Salvato FR, Williams LD, et al: A double-blind, placebo-controlled study of oral nalmefene for alcohol dependence. Arch Gen Psychiatry 56:719–724, 1999

Matsuzawa S, Suzuki T, Misawa M: Involvement of mu-opioid receptor in the salsolinol-associated place preference in rats exposed to conditioned fear stress. Alcohol Clin Exp Res 24:366–372, 2000

Mattila MJ, Aranko K, Seppala T: Acute effects of buspirone and alcohol on psychomotor skills. J Clin Psychiatry 43:56–60, 1982

McMahon T, Andersen R, Metten P, et al: Protein kinase C epsilon mediates upregulation of N-type calcium channels by ethanol. Mol Pharmacol 57:53–58, 2000

Merry J, Reynolds CM, Bailey J, et al: Prophylactic treatment of alcoholism by lithium carbonate. Lancet 2:481–482, 1976

Meyer RE: How to understand the relationship between psychopathology and addictive disorders: another example of the chicken and the egg, in Psychopathology and Addictive Disorders. Edited by Meyer RE. New York, Guilford, 1986, pp 3–16

Monteiro MG, Klein JL, Schuckit MA: High levels of sensitivity to alcohol in young adult Jewish men: a pilot study. J Stud Alcohol 52:464–469, 1991

Mueller TI, Stout RL, Rudden S, et al: A double-blind, placebo-controlled pilot study of carbamazepine for the treatment of alcohol dependence. Alcohol Clin Exp Res 21:86–92, 1997

Myers RD, Melchior CL: Differential actions on voluntary alcohol intake of tetrahydroisoquinolines or a beta-carboline infused chronically in the ventricle of the rat. Pharmacol Biochem Behav 7:381–392, 1977

Naranjo CA, Sellers EM: Clinical assessment and pharmacotherapy of the alcohol withdrawal syndrome, in Recent Developments in Alcoholism, Vol 4. Edited by Galanter M. New York, Plenum, 1986

Naranjo CA, Sellers EM, Chater K, et al: Non-pharmacological interventions in acute alcohol withdrawal. Clin Pharmacol Ther 34:214–219, 1983

Naranjo CA, Sellers EM, Roach CA, et al: Zimelidine-induced variations in alcohol intake by nondepressed heavy drinkers. Clin Pharmacol Ther 35:374–381, 1984

Naranjo CA, Sellers EM, Sullivan JT, et al: The serotonin uptake inhibitor citalopram attenuates ethanol intake. Clin Pharmacol Ther 41:266–274, 1987

Naranjo CA, Sullivan JT, Kadlec KE, et al: Differential effects of viqualine on alcohol intake and other consummatory behaviors. Clin Pharmacol Ther 46:301–309, 1989

Naranjo CA, Kadlec KE, Sanhueza P, et al: Fluoxetine differentially alters alcohol intake and other consummatory behaviors in problem drinkers. Clin Pharmacol Ther 47:490–498, 1990

Naranjo CA, Poulos CX, Bremner KE, et al: Citalopram decreases desirability, liking, and consumption of alcohol in alcohol-dependent drinkers. Clin Pharmacol Ther 51:729–739, 1992

Naranjo CA, Bremner KE, Lanctot KL: Effects of citalopram and a brief psychosocial intervention on alcohol intake, dependence, and problems. Addiction 90:87–99, 1995

Nunes EV, Levin FR. Treatment of depression in patients with alcohol or other drug dependence: a meta-analysis. JAMA 291:1887–1896, 2004

O'Malley SS, Jaffe AJ, Chang G, et al: Naltrexone and coping skills therapy for alcohol dependence: a controlled study. Arch Gen Psychiatry 49:894–898, 1992

O'Malley SS, Jaffe AJ, Chang G, et al: Six-month follow-up of naltrexone and psychotherapy for alcohol dependence. Arch Gen Psychiatry 53:217–224, 1996a

O'Malley SS, Jaffe AJ, Rode S, et al: Experience of a "slip" among alcoholics treated with naltrexone or placebo. Am J Psychiatry 153:281–283, 1996b

O'Malley SS, Rounsaville BJ, Farren C, et al: Initial and maintenance naltrexone treatment for alcohol dependence using primary care vs specialty care: a nested sequence of 3 randomized trials. Arch Intern Med 163:1695–1704, 2003

Pandey SC, Carr LG, Heilig M, et al: Neuropeptide Y and alcoholism: genetic, molecular, and pharmacological evidence. Alcohol Clin Exp Res 27:149–154, 2003

Petrakis IL, Trevisan L, Boutros NN, et al: Effect of tryptophan depletion on alcohol cue-induced craving in abstinent alcoholic patients. Alcohol Clin Exp Res 25: 1151–1155, 2001

Petrakis IL, Buonopane A, O'Malley S, et al: The effect of tryptophan depletion on alcohol self-administration in non-treatment-seeking alcoholic individuals. Alcohol Clin Exp Res 26:969–975, 2002

Petrakis IL, O'Malley S, Rounsaville B, et al: Naltrexone augmentation of neuroleptic treatment in alcohol abusing patients with schizophrenia. Psychopharmacology (Berl) 172:291–297, 2004

Pettinati HM, Volpicelli JR, Kranzler HR, et al: Sertraline treatment for alcohol dependence: interactive effects of medication and alcoholic subtype. Alcohol Clin Exp Res 24:1041–1049, 2000

Petty F, Kramer GL, Davis LL, et al: Plasma gamma-aminobutyric acid (GABA) predicts outcome in patients with alcohol dependence. Prog Neuropsychopharmacol Biol Psychiatry 21:809–816, 1997

Pierucci-Lagha A, Feinn R, Modesto-Lowe V, et al: Effects of rapid tryptophan depletion on mood and urge to drink in patients with co-morbid major depression and alcohol dependence. Psychopharmacology (Berl) 171:340–348, 2004

Porjesz B, Begleiter H, Wang K, et al: Linkage and linkage disequilibrium mapping of ERP and EEG phenotypes. Biol Psychol 61:229–248, 2002

Posternak MA, Mueller TI: Assessing the risks and benefits of benzodiazepines for anxiety disorders in patients with a history of substance abuse or dependence. Am J Addict 10:48–68, 2001

Powell BJ, Penick EC, Othmer E, et al: Prevalence of additional psychiatric syndromes among male alcoholics. J Clin Psychiatry 43:404–407, 1982

Quertemont E, Grant KA: Role of acetaldehyde in the discriminative stimulus effects of ethanol. Alcohol Clin Exp Res 26:812–817, 2002

Radel M, Goldman D: Pharmacogenetics of alcohol response and alcoholism: the interplay of genes and environmental factors in thresholds for alcoholism. Drug Metab Dispos 29:489–494, 2001

Regier DA, Farmer ME, Rae DS, et al: Comorbidity of mental disorders with alcohol and other drug abuse: results from the Epidemiologic Catchment Area (ECA) Study. JAMA 264:2511–2518, 1990

Reoux JP, Saxon AJ, Malte CA, et al: Divalproex sodium in alcohol withdrawal: a randomized double-blind placebo-controlled clinical trial. Alcohol Clin Exp Res 25:1324–1329, 2001

Rodd-Henricks ZA, McKinzie DL, Melendez RI, et al: Effects of serotonin-3 receptor antagonists on the intracranial self-administration of ethanol within the ventral tegmental area of Wistar rats. Psychopharmacology (Berl) 165:252–259, 2003

Ross HE, Frederick B, Glaser MD, et al: The prevalence of psychiatric disorders in patients with alcohol and other drug problems. Arch Gen Psychiatry 45:1023–1031, 1988

Rubio G, Jimenez-Arriero MA, Ponce G, et al: Naltrexone versus acamprosate: one year follow-up of alcohol dependence treatment. Alcohol Alcohol 36:419–425, 2001

Ryabinin AE, Criado JR, Henriksen SJ, et al: Differential sensitivity of c-Fos expression in hippocampus and other brain regions to moderate and low doses of alcohol. Mol Psychiatry 2:32–43, 1997

Ryabinin AE, Bachtell RK, Freeman P, et al: ITF expression in mouse brain during acquisition of alcohol self-administration. Brain Res 890:192–195, 2001

Saadatmand F, Stinson FS, Grant FB, et al: Liver cirrhosis mortality in the United States, 1970–94 (Surveillance Report No 45). Rockville, MD, National Institute on Alcohol Abuse and Alcoholism, 1997

Salloum IM, Cornelius JR, Thase ME, et al: Naltrexone utility in depressed alcoholics. Psychopharmacol Bull 34:111–115, 1998

Schuckit M: Alcoholic patients with secondary depression. Am J Psychiatry 140:711–714, 1983

Seeman P: The membrane actions of anesthetics and tranquilizers. Pharmacol Rev 24:583–655, 1972

Seppala T, Aranko K, Mattila MJ, et al: Effects of alcohol on buspirone and lorazepam actions. Clin Pharmacol Ther 32:201–207, 1982

Smith BR, Amit Z: The role of gamma-aminobutyric acid (GABA) in the regulation of ethanol and acetaldehyde self-administration. Prog Neuropsychopharmacol Biol Psychiatry 9:759–763, 1985

Sokolow L, Welte J, Hynes G, et al: Multiple substance use by alcoholics. Br J Addict 76:147–158, 1981

Srisurapanont M, Jarusuraisin N: Opioid antagonists for alcohol dependence. Cochrane Database Syst Rev (2):CD001867, 2002

Stinson FS, DeBakey SF: Alcohol-related mortality in the United States, 1979–1988. Br J Addict 87:777–783, 1992

Streeton C, Whelan G: Naltrexone, a relapse prevention maintenance treatment of alcohol dependence: a meta-analysis of randomized controlled trials. Alcohol Alcohol 36:544–552, 2001

Substance Abuse and Mental Health Services Administration: Results from the 2002 National Survey on Drug Use and Health: National Findings (DHHS Publ No SMA 03-3836). Rockville, MD, Substance Abuse and Mental Health Services Administration, 2003. Available at http://oas.samhsa.gov/nhsda/2k2nsduh/Results/2k2Results.htm#chap3. Accessed November 5, 2004.

Sullivan LE, O'Connor PG: Medical disorders in substance abuse patients, in Dual Diagnosis and Psychiatric Treatment: Substance Abuse and Comorbid Disorders, 2nd Edition. Edited by Kranzler HR, Tinsley JA. New York, Marcel Dekker, 2004, pp 515–553

Sun F, Tsuritani I, Yamada Y: Contribution of genetic polymorphisms in ethanol-metabolizing enzymes to problem drinking behavior in middle-aged Japanese men. Behav Genet 32:229–236, 2002

Swift RM: Drug therapy for alcohol dependence. N Engl J Med 340:1482–1490, 1999

Thiele TE, Marsh DJ, Ste Marie L, et al: Ethanol consumption and resistance are inversely related to neuropeptide Y levels. Nature 396:366–369, 1998

Thiele TE, Miura GI, Marsh DJ, et al: Neurobiological responses to ethanol in mutant mice lacking neuropeptide Y or the Y5 receptor. Pharmacol Biochem Behav 67: 683–691, 2000

Thiele TE, Koh MT, Pedrazzini T: Voluntary alcohol consumption is controlled via the neuropeptide Y Y1 receptor. J Neurosci 22:RC208, 2002

Thiele TE, Navarro M, Sparta DR, et al: Alcoholism and obesity: overlapping neuropeptide pathways? Neuropeptides 37:321–337, 2003

Thomasson HR, Crabb DW, Edenberg HJ, et al: Low frequency of the ADH2*2 allele among Atayal natives of Taiwan with alcohol use disorders. Alcohol Clin Exp Res 18:640–643, 1994

Tiihonen J, Ryynanen O-P, Kauhanen J, et al: Citalopram in the treatment of alcoholism: a double-blind placebo-controlled study. Pharmacopsychiatry 29:27–29, 1996

Tollefson GD, Montague-Clouse J, Tollefson SL: Treatment of comorbid generalized anxiety in a recently detoxified alcohol population with a selective serotonergic drug (buspirone). J Clin Psychopharmacol 12:19–26, 1992

Tu GC, Israel Y: Alcohol consumption by orientals in North America is predicted largely by a single gene. Behav Genet 25:59–65, 1995

U.S. Department of Health and Human Services: Eighth Special Report to the U.S. Congress on Alcohol and Health (NIH Publ No 94-3699). Washington, DC, U.S. Department of Health and Human Services, 1994

Verheul R, Lehert P, Geerlings PJ, et al: Predictors of acamprosate efficacy: results from a pooled analysis of seven European trials including 1485 alcohol-dependent patients. Psychopharmacology (Berl) Aug 19, 2004 (epub ahead of print)

Volkow ND, Wang GJ, Begleiter H, et al: Regional brain metabolic response to lorazepam in subjects at risk for alcoholism. Alcohol Clin Exp Res 19:510–516, 1995

Volkow ND, Wang GJ, Overall JE, et al: Regional brain metabolic response to lorazepam in alcoholics during early and late alcohol detoxification. Alcohol Clin Exp Res 21:1278–1284, 1997

Volpicelli J, O'Brien C, Alterman A, et al: Naltrexone in the treatment of alcohol dependence. Arch Gen Psychiatry 49:867–880, 1992

Volpicelli JR, Watson NT, King AC, et al: Effect of naltrexone on alcohol "high" in alcoholics. Am J Psychiatry 152:613–615, 1995

Wirkner K, Eberts C, Poelchen W, et al: Mechanism of inhibition by ethanol of NMDA and AMPA receptor channel functions in cultured rat cortical neurons. Naunyn Schmiedebergs Arch Pharmacol 362:568–576, 2000

Wolf B, Iguchi MY, Griffiths RR: Sedative/tranquilizer use and abuse in alcoholics currently in outpatient treatment: incidence, pattern and preference, in Problems of Drug Dependence 1989. NIDA Research Monograph No 95. DHHS Publ No ADM-90-a663). Edited by Harris LS. Washington, DC, U.S. Government Printing Office, 1990, pp 376–377

Wong DF, Maini A, Rousset OG, et al: Positron emission tomography—a tool for identifying the effects of alcohol dependence on the brain. Alcohol Res Health 27:161–173, 2003

Woodward JJ: Ethanol and NMDA receptor signaling. Crit Rev Neurobiol 14:69–89, 2000

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Opioids

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A Brief History

In the mid-nineteenth century, it was the custom for doctors to frequently prescribe morphine (first isolated from opium by Friedrich Serturner in 1806) and other opium preparations. Morphine did not have a major impact on medical practice until the invention of the hypodermic needle in 1840. "Soldiers illness" was recognized after the Civil War when more than 50,000 veterans became dependent on morphine as a result of treatment for combat injuries (Musto 1987). The public also had ready access to opium and purified drugs in grocery stores and pharmacies. Medicinal mixtures and nostrums, usually unlabelled as to contents, often contained opium or morphine. By the end of the century, many physicians had come to recognize that chronic use of morphine was a disorder (morphinism), although others in society

viewed it as a vice. An early response to this growing problem was the establishment of morphine maintenance clinics in 44 American cities. After the passage of the Harrison Narcotics Act in 1914, legal use of opioids was restricted, all of the morphine maintenance clinics were closed, and opioids were no longer available except by prescription. Within a few years, increasing numbers of people were using opioids obtained illicitly. Some U.S. Supreme Court decisions at this time appeared to support the position that the prescription of an opioid to an addict was not the proper practice of medicine and was, therefore, illegal. Physicians who prescribed opioids to addicts were tried and censored, and more than 3,000 were imprisoned. By the early 1920s, people who were dependent on opioids often were denied hospital treatment for medical problems.

During the decades between 1930 and 1960, it was recognized that the opioid dependence itself needed to be treated, but prolonged hospitalization was essentially the only treatment recommended and available. In the late 1950s, the first therapeutic community for drug addicts was established. In the early 1960s, California and New York initiated compulsory commitment for treatment. At about the same time, Dole and Nyswander (1965) showed that maintenance on daily doses of methadone led to reduction in heroin use and in associated criminal activity. The use of narcotic antagonists for treatment of opioid dependence was also tried at this time. By the 1970s, concern about the increasing number of heroin addicts, along with the recognition that many opioid addicts could return to active, law-abiding participation in society during and after treatment, led to expansion of community-based treatment programs and increases in resources for research (Jaffe 1989). There has since been extensive research in areas related to opioid dependence, from the characterization of opioid receptors and second messengers to the psychosocial and pharmacological treatment of people with opioid dependence.

Prevalence and Natural History

Prevalence and Patterns of Opioid Use and Dependence

The National Survey on Drug Use and Health found that 1.6% of persons over age 12 years reported using heroin at some time in their lives (Substance

Abuse and Mental Health Services Administration 2004). However, less than 0.1% reported use during the preceding month. In urban areas, the rate of heroin use among men is approximately three times that among women. Use further increased in the 1990s with the availability of cheap, very high quality heroin. From 1999 to 2000, heroin mentions in U.S. emergency departments increased 15%, from 82,192 to 94,804 (Substance Abuse and Mental Health Services Administration 2001). Data from the 2003 National Survey on Drug Use and Health indicated that approximately 119,000 Americans reported current heroin use (Substance Abuse and Mental Health Services Administration 2004). Among past-year users 189,000 were classified with dependence on heroin. Heroin abusers are predominantly white (90%) and employed full-time (more than 50%), and almost 89% have a high school diploma or more advanced education (Honer et al. 2001). The greatest use of heroin was reported in the 21- to 25-year age group (2.0% reported lifetime use) and in the 35-year and older age group (1.8% reported lifetime use). Some areas of the country, such as Boston, have reported dramatic increases in heroin use and overdoses in adolescents and young adults associated with increased availability of inexpensive, high-potency heroin that often contains toxic adulterants (Community Epidemiology Work Group 2003).

Misuse of other opioids is far more common than heroin use. As is true for use of heroin, nonmedical use of opioids other than heroin is predominantly a problem of young adults. The prevalence of nonmedical use of "pain relievers" was reported as 8.6% for lifetime use and 1.2% for use in the past month among persons age 12 years or older. The highest rates were among 18- to 20-year-olds and 21- to 25-year-olds (15.8% and 13.7%, respectively, reported lifetime use) (Substance Abuse and Mental Health Services Administration 2004). Lifetime use also varies by race and socioeconomic class. College graduates are less likely to use opioids than are high school dropouts. Health professionals have higher use than others with comparable education. Data from the Drug Abuse Warning Network showed an increase in emergency department mentions of total narcotic analgesics/combinations from approximately 29,000 in the last half of 1997 to more than 56,000 in the first half of 2002 (Substance Abuse and Mental Health Services Administration 2004).

Opioid dependence rarely results from the prescribing of opioids temporarily for treatment of acute pain or pain of terminal illness. Even use in chronic

pain does not inevitably lead to opioid abuse and dependence. In a study of chronic opioid use to treat nonmalignant pain, problems developed in only two of 38 patients, both of whom had a prior history of drug abuse (Portenoy and Foley 1986). If patients are properly screened and treatment is monitored, opioids can be vital drugs for analgesia of chronic pain that is not responsive to nonopioid treatment.

The analgesic pentazocine (Talwin) and the antihistamine tripelennamine (a blue tablet), known as "Ts and blues," produce an effect that is both opioid-like and reinforcing when they are injected intravenously in combination. In the late 1970s, use of this combination became a significant problem in certain urban areas of the United States. In 1983, the oral preparation of Talwin was replaced with Talwin Nx, a pentazocine-naloxone combination that includes 0.5 mg of the opioid antagonist naloxone. At this dose, naloxone is inactive orally, but if it is injected intravenously, it blocks some of the effects of pentazocine. Although there continued to be some reports of abuse of Talwin Nx (Reed and Schnoll 1986), the reformulation significantly reduced pentazocine abuse (Baum et al. 1987).

A controlled-release oral formulation of oxycodone hydrochloride (OxyContin) introduced in the late 1990s has become popular with young opioid abusers. When the tablet is crushed or chewed, there is a rapid release of intoxicating, and sometimes fatal, amounts of oxycodone. Many pain patients have also found it difficult to terminate the use of this drug and have progressed to illicit drug use. Withdrawal from oxycodone is protracted and very difficult for some patients. In 2001, the National Household Survey on Drug Abuse reported that approximately 957,000 individuals age 12 years or older had used oxycodone nonmedically at least once in their lives. This number reflected a dramatic increase from estimates reported in 1999 (221,000 users) and 2000 (399,000 users) (Substance Abuse and Mental Health Services Administration 2004). Other controlled-release opioids, including hydromorphone (Palladone), have been released with a monitoring plan approved by the U.S. Food and Drug Administration (FDA) to detect abuse (Angst et al. 2001).

Although many who experiment with opioids experience euphoria or symptom relief with the first use, some experimenters use these drugs only a few times and then avoid further use because of an awareness of the risks or because of unpleasant side effects such as nausea or vomiting. Even for those

who become dependent, the most common pattern in Western cultures where the drug is illegal is one of alternating periods of use and abstinence, whether voluntary or brought about by external pressure. Many opioid-dependent individuals recover without ever having formal treatment. Addicts who voluntarily abstain often state they do so simply because they are tired of their lifestyles of constant drug seeking and frequent encounters with the law. Opioid addicts who do not seek treatment have less psychopathology, fewer legal problems, and more adequate social functioning, but not less drug dependence (Rounsaville and Kleber 1985b).

For those who do seek treatment, the average time from dependence to first treatment is approximately 2–3 years. Initial treatment typically involves detoxification, with little or no aftercare. Without supervision, as many as two-thirds of these individuals will relapse, most within the first few months after detoxification.

Factors Influencing Course and Treatment Outcomes

The lifestyles of opioid addicts in Great Britain and the United States who are involved in treatment are far from uniform. Some, such as health professionals who have become dependent on opioids, may hold jobs; other "loners" live mainly on legitimate earnings supplemented by some criminal activities or live on welfare. The stereotypical "junkies" socialize within an addict subculture and earn their income primarily from illegal activities, including drug dealing (Stimson and Oppenheimer 1982). For those who are arrested, the time from first use to first arrest ranges from 6 months to 5 years. "Maturing out" (or stopping opioid use as an overall result of the passage of time) is less likely for addicts involved in crime and drug dealing (Anglin et al. 1986).

There have been several long-term follow-up studies of addicts who sought treatment from publicly supported programs. In one study, selected daily opioid users who entered treatment in 1969–1974 were followed up 12 years after initial treatment; 24% of the male addicts had used opioids daily during the previous year, and 25% reported they had never returned to daily opioid use (Simpson and Marsh 1986; Simpson et al. 1982). Of the entire sample, 35% never relapsed after they had quit. During the previous year, 13% bad been arrested, and 29% had spent time in jail or prison.

In another study, more than 10,000 drug addicts who entered treatment during 1979–1981 were interviewed, and a sample of these individuals was reinterviewed 3–5 years later (Hubbard et al. 1989). Heroin use declined during and following treatment. For those who stayed in treatment, the rate of regular use of heroin declined from 63.5% before treatment to 17.5% 3–5 years later. A 33-year follow-up of 581 opioid addicts who had been treated in the California Civil Addict Program between 1962 and 1964 reported a very high mortality rate of 49% (Hser et al. 2001). Of the 242 individuals interviewed at follow-up, 20.7% had positive urine tests for heroin, an additional 9.5% refused a urine test, and 14% were incarcerated. The authors concluded that for most of these subjects, heroin dependence was a lifelong condition that had a severe impact on their health and social functioning. By the end of the 33-year follow-up period only 25% had achieved abstinence; for most of those years, less than 6% of the subjects were in treatment at any one time.

In general, physicians and other health professionals with opioid dependence have a remarkably good prognosis when their license to practice is made contingent on continued abstinence and their abstinence monitored by random urine tests. Most studies report abstinence rates of 65%–75% 1–2 years after initial treatment (Herrington et al. 1982). Somewhat lower success rates have been reported for anesthesia residents. One study reported that only 34% of parenteral opioid abusers in residency training for anesthesia successfully reentered training, compared with 70% of anesthesiology residents who abused other substances (Menk et al. 1990).

Currently, there are no reliable means to predict an individual's long-term prognosis as measured by drug use, work, crime, and psychological adjustment. Although the achievement of even temporary abstinence is associated with improvement in a number of factors (legal problems in particular), simply attaining abstinence does not ensure complete psychosocial adjustment. Therefore, other problem areas must be addressed as well. In general, outcome in a particular area (e.g., work or crime) is best predicted by past behavior with respect to that area (Kosten et al. 1987a; Rounsaville et al. 1987).

Medical Complications and Life Expectancy

Before 1980, the mortality rate among younger addicts was up to 20 times higher than that among control subjects; it was 2–3 times higher for older ad-

dicts (Joe and Simpson 1987). The higher mortality rate was related to factors such as overdose, suicide, homicide, and infection. About 1%–1.5% of addicts who sought treatment died each year (Joe and Simpson 1987; Oppenheimer et al. 1994; Stimson and Oppenheimer 1982). Some studies suggested that with the spread of human immunodeficiency virus (HIV) infection, which is transmitted among opioid users by needle sharing and sexual contact, these figures have risen (Sanchez-Carbonell and Seus 2000; Quaglio et al. 2001). The authors of a recent study in Sweden reported a 20% mortality rate during a 1-year period in a group of opioid addicts who served as the control group in double-blind, placebo-controlled buprenorphine maintenance study (Kakko et al. 2003). None of these individuals were eligible for methadone maintenance under Swedish law because they had been dependent on opioids for less than 4 years. They were all given buprenorphine detoxification (as the initial phase of an intended 1-year placebo arm of the maintenance trial) and were offered intensive outpatient counseling services. These results dramatically pointed out the shortcomings and risks of detoxification and outpatient counseling, even for addicted individuals with a relatively short history of dependence.

Infections are common with use of intravenously injected opioids (Francis 2003). Approximately 28% of new HIV infections occur in users of injection drugs, including opioids (Cooper et al. 2003). It has been estimated that between 29% and 57% of those in methadone clinics in the northeastern region of the United States are HIV positive (Brown et al. 1993; Des Jarlais et al. 1998). The lethality and prevalence of HIV are the basis of the argument for the controversial practice of distributing clean needles to addicts. A study by Ball et al. (1988b) indicated that standard methadone maintenance significantly reduces needle sharing. Other transmittable infections include hepatitis and malaria (Bastos et al. 1999). Hepatitis C now infects 79% of injection drug users in the United States (Centers for Disease Control 1998). Between 75% and 85% of these cases will go on to chronic infection, 20% will develop cirrhosis, and 1%–5% will die each year from chronic liver disease. In some methadone clinics, the annual death rate from hepatitis C has surpassed that from AIDS. Tuberculosis is more common in heroin addicts than in the general population. Other infectious complications include endocarditis, meningitis, brain abscess, and septicemia.

Embolic phenomena may occur from particulate matter such as talc or

starch when pills are used for injections or if drugs are filtered through cigarette filters or cotton. Pulmonary emboli may result in pulmonary hypertension and right ventricular failure. Septic emboli may be a cause of staphylococcal pneumonitis.

Most heroin addicts have lymphadenopathy (Carbone et al. 1998; Tirelli et al. 1986). Vein sclerosis and contaminant-related lymphatic obstruction may cause extremity edema. Ulceration and other dermatologic changes are often present in those who "skin pop."

Pharmacology

The term *opioid* refers to any exogenous substance that acts as an agonist at any of several receptors. Opioid antagonists are drugs that bind to a receptor but produce no actions. The poppy plant, *Papaver somniferum*, from which opium is obtained, is grown in many areas of the world. Morphine constitutes 10% of opium, and codeine can be obtained directly from opium. Semisynthetic opioids such as heroin and oxycodone are obtained directly or indirectly from morphine. There are other distinct chemical classes of drugs with opioid actions, including the methadones.

Central nervous system effects of opioids include analgesia, sedation, "mental clouding" (apathy and difficulty concentrating), mood changes, nausea, and vomiting. In abstinent addicts, euphoria is greater and mental clouding is less pronounced than in normal subjects. Tolerance develops to these effects with chronic use. Opioids acutely inhibit gonadotropin-releasing hormone and corticotropin-releasing hormone secretion, but tolerance develops with chronic use. Therefore, male methadone patients who have been maintained for more than a year with stable doses generally have been found to have normal levels of cortisol, luteinizing hormone, and testosterone (for general references, see Gutstein and Akil 2001).

Major gastrointestinal effects include decreased gut motility and changes in secretion of gastric and intestinal fluids. Morphine and most μ receptor agonists cause pupillary constriction. Some tolerance to this effect may develop, but addicts with high opioid levels will still have miosis. Respiratory depression is the usual cause of death from opioid overdose.

After rapid intravenous injection of an opioid, the user experiences warm skin flushing and a "rush" that lasts about 45 seconds. In one retrospective study

(Seecof and Tennant 1987), the most common feelings associated with the rush were pleasure, relaxation, and satisfaction. Although at one time the rush was classically reported to be similar to a sexual orgasm, in a study of the phenomenon such a feeling was reported in only 18% of men and 10% of women (Seecof and Tennant 1987).

Opioids are easily absorbed subcutaneously and intramuscularly, as well as from the gastrointestinal tract, nasal mucosa (e.g., when heroin is used as snuff), and lung (e.g., when opium is smoked). About 90% of the excretion of morphine occurs during the first 24 hours, but traces are detectable in urine for more than 48 hours. Heroin (diacetylmorphine) is hydrolyzed to monoacetylmorphine, which is then hydrolyzed to morphine. Morphine and monoacetylmorphine are responsible for the pharmacologic effects of heroin. Heroin produces effects more rapidly than morphine because it is more lipid soluble and therefore crosses the blood-brain barrier faster. In the urine, heroin is detected as free morphine and morphine glucuronide (Gutstein and Akil 2001; Jaffe et al. 2004).

Opioid Receptors

Three distinct classes of opioid receptor have been identified: the μ, δ, and κ opioid receptors. Opioid receptors are activated by several classes of endogenous peptides, including the endorphins, enkephalins, endomorphins, and dynorphins. There is extensive overlap in the amino acid composition of these receptors. Endogenous opioid peptides differ in their affinity for the different opioid receptor types. β-Endorphin and met-enkephalin have greater affinities for the μ and δ receptors than for the κ receptor, whereas the affinity of dynorphins is greater for the κ receptor than it is for the μ and δ receptors. Endomorphins are selective potent μ receptor agonists (Zadina et al. 1999).

Preclinical evidence indicates that opioid drugs such as morphine produce their pharmacologic effects primarily through interactions with the μ receptor. These effects include analgesia, respiratory depression, mood elevation, constipation, immunosuppression, and physical dependence. The administration of κ receptor agonists may lead to the production of both analgesia and dysphoria. Mixed agonist/antagonist agents such as pentazocine and nalbuphine have effects at the κ receptor, as does the drug levorphanol.

Three distinct opioid receptor genes have been identified, namely the *MOR* (μ), *KOR* (κ), and *DOR* (δ) genes. Although only one μ receptor gene

has been identified, there is some evidence that μ receptor subtypes might exist as a consequence of variations in the splicing of the messenger RNA produced from *MOR* (Bare et al.1994; Pan et al. 2003). The functional differences that may exist between these receptor subtypes remain to be determined. In addition to splice variants, several allelic variants of *MOR* have been identified, including several single nucleotide polymorphisms. Attempts have made to establish associations between single nucleotide polymorphisms and heroin intake (Shi et al. 2002; Tan et al. 2003), but additional evidence is required before firm associations are established. It is clear, however, that single nucleotide polymorphisms can alter the effects of opioid agonists on the μ receptor. The *A118G* polymorphism of the μ receptor is one example. This polymorphism appears to increase the affinity of the human μ receptor for β-endorphin in vitro (Bond et al. 1998) and to decrease the adverse effects produced by the morphine metabolite morphine-6-glucuronide (Lotsch et al. 2002; Skarke et al. 2003).

Opioid receptors are coupled to guanine nucleotide–binding proteins (G proteins). The binding of agonists with the opioid receptor leads to the activation of several effector systems by G-protein subunits. The acute administration of opioid agonists leads to the inhibition of adenylyl cyclases, calcium conductance, and neurotransmitter release (most notably release of γ-aminobutyric acid and substance P) from vesicles (Williams et al. 2001). Other effects of opioid agonists include G-protein activation of inwardly rectifying potassium conductance, activation of protein kinase C, and initiation of the mitogen-activated protein kinase (MAPK) cascade.

High densities of μ receptors are found in the dorsal horn of the spinal cord, brain stem, thalamus, and cortex, where they can modulate the intensity of incoming pain signals. Within the mesolimbic system μ receptors may play a role in regulating reward-motivated behaviors. The reinforcing actions of opioid agonists are produced, at least in part, by the induction of dopamine release by these agents in the nucleus accumbens, a mesolimbic structure implicated in mediating the effects of rewarding stimuli on behavior (Nestler et al. 2001).

Mechanisms of Tolerance and Dependence

Receptor desensitization, internalization, and/or down-regulation may play a role in the development of tolerance to opioid receptor agonists (Clark et al.

2003; Potenza et al. 1999; Stafford et al. 2001; Yabaluri and Medzihradsky 1997). Binding with β-arrestin leads to uncoupling of the receptor from G proteins, resulting in receptor desensitization. Tolerance to the analgesic effects of morphine, which is reliably seen after the chronic administration of this agent, is attenuated in mutant animals that have the β-*arrestin-2* gene deleted (Bohn et al. 2000). Internalization of uncoupled opioid receptors below the plasma membrane surface may be mediated by the protein dynamin (Li et al. 1999; Patel et al. 2002). These receptors may be dephosphorylated and recycled to the cell surface in a sensitized state or they may undergo degradation within the cells. Opioid receptor down-regulation is a decrease in receptor density.

Opioids differ in the mechanism by which tolerance is produced, although the clinical implications of these differences are yet unknown. For example, opioid receptor down-regulation is produced by some opioid agonists, but most notably not by morphine (Williams et al. 2001). Internalization of receptors, on the other hand, does not appear to occur in vivo or in vitro following chronic exposure to morphine, although it does occur after prolonged treatment with agents such as methadone, L-α-acetylmethadol (LAAM), or etorphine (Keith et al. 1998; Williams et al. 2001). These differences may be related to the disparate effects of these opioid agonists on trafficking proteins such as dynamin (Patel et al. 2002). The clinical implications of the finding that methadone and LAAM can produce receptor internalization, while morphine does not, remain to be established.

Tolerance may involve a reduction in the inhibitory effects of morphine on cyclic adenosine monophosphate (cAMP) activity. The acute administration of opioid agonists such as morphine decreases the activity of cAMP second messenger pathways through inhibition of adenylyl cyclase activity; however, following chronic exposure to morphine, this inhibitory effect is lost in many brain areas (Nestler et al. 2001). Once morphine treatment is discontinued, rebound activity may occur in the cAMP pathway. This increase in activity may lead to enhanced phosphorylation of cAMP response element binding protein (CREB), which in turn alters transcription of a number of genes in brain regions associated with withdrawal (Delfs et al. 2000; Shaw-Lutchman et al. 2002). Symptoms of physical withdrawal following morphine administration are reduced in mice mutated to produce only residual levels of CREB (Maldonado et al. 1996).

Preclinical studies indicate that the administration of *N*-methyl-D-aspartate (NMDA) receptor (a type of glutamate receptor) antagonists can block the development of morphine-induced tolerance and dependence (Maldonado et al. 1996). Opioids may alter the activity of NMDA receptors by activating protein kinase C (Chen and Huang 1991). This enzyme phosphorylates the NMDA receptor, which leads to an increase in the permeability of the receptor to calcium. Clinical evidence indicates that administration of the NMDA antagonist memantine attenuates symptoms of physical dependence in heroin addicts (Bisaga et al. 2001). Clinical trials are being conducted to establish whether the administration of the NMDA antagonist dextromethorphan can block the development of tolerance in individuals being treated with morphine for pain.

Etiology of Opioid Dependence

Multiple factors interact in complex ways to result in opioid dependence. It is difficult to delineate, even for a specific individual, the precise etiology of dependence. In addition, each of the etiologic factors discussed in this section may play variable roles in initiation of use, maintenance of use, relapse, and recovery. Keeping in mind all of these potential factors is essential when formulating a treatment plan for each individual.

Opioids can be reinforcing by directly inducing pleasurable effects or by reducing aversive affects or the experience of noxious stimuli. They may reduce pain or anxiety and, for some users, decrease boredom, relieve the experience of intense aggression, and increase self-esteem. Social approval among peers may be a factor in initial opioid use. The rituals of injecting opioids often become associated with a "high," so that even an occasional placebo injection may still elicit pleasurable effects. Even after tolerance has developed to some of the effects of opioids, the rush may still be experienced briefly after an intravenous injection. Animal studies indicate that low doses of opioids lower the threshold for producing reinforcing (pleasurable) effects by means of self-administration of electrical currents to certain brain regions (Kornetsky 2004). Tolerance to this effect does not seem to occur. The experience of withdrawal relief also contributes to repeated opioid use. Because of heroin's brief duration of action, withdrawal occurs several times a day, and its repeated relief leads to a strongly reinforced behavior pattern.

The paraphernalia and setting associated with drug use can become cues indicating that a high or relief of distress is possible. Craving or desire to use the drug is increased in the presence of such stimuli. Withdrawal symptoms may also become conditioned to such stimuli. The addict may experience conditioned withdrawal as an increase in craving or desire to use opioids (McLellan et al. 1986; Meyer and Mirin 1979; Wikler 1980). However, the most intense craving appears to be elicited by conditions associated with opioid use rather than those associated with withdrawal. The role that conditioned phenomena play in relapse and perpetuation of use is presently unknown; however, work in research settings suggested that these phenomena may be clinically important and that their extinction may be helpful in treatment (Childress et al. 1988).

Psychosocial and environmental factors play a major role in the development and recovery from opioid dependence; however, a detailed discussion is beyond the scope of this chapter. In general, the use of such drugs as marijuana and alcohol precedes the use of opioids (Clayton and Voss 1981; Kandel and Faust 1975). Although one cannot predict definitively which users will proceed to opioid use, those who do generally have low self-esteem, disrupted families, and/or difficult relationships with their parents. The increased availability of opioids in inner cities of major urban centers contributes to initiation of use and relapse. It is particularly difficult to avoid use and relapse in areas with high unemployment, poor school systems, and high crime rates, because living in such an area may contribute to the very affects opioid use temporarily relieves.

Brief experimentation with illicit opioids rarely leads to dependence, but persons who use opioids commonly escalate to daily use, at least once per month for at least a brief period. Among Vietnam War–era soldiers, experimentation with opioids was widespread; 73% of the soldiers who used opioids at least five times became dependent; however, 88% of enlisted men who became addicted to heroin did not become readdicted at any time in the 3 years after return, and 56% did not use opioids at all during that time (Robins et al. 1975).

Epidemiological studies and treatment facilities report a high prevalence of anxiety, affective disorders, bipolar disorder, and alcoholism, as well as antisocial personality, among individuals with opioid dependence (Cacciola et al. 2001; Callaly et al. 2001; Hien et al. 2000; Krausz et al. 1998; Krausz et al. 1999; Marsden et al. 2000; Milby et al. 1996; Regier et al. 1990; Roozen et al. 2003).

A biological etiology underlying opioid dependence was postulated by Dole and Nyswander (1967), who suggested that a preexisting metabolic deficiency could lead to dependence or that changes induced by opioid use could perpetuate dependence. Dole (1988) later hypothesized that opioid receptor dysfunction is a primary etiologic factor. Recent research efforts have focused on the hypothesis that individuals with a genetic vulnerability to opioid abuse have defects in the genes for the opioid peptides and receptors. Variants of the μ and δ receptors have positive associations with opioid and/or alcohol addiction. However, the associations are weak, suggesting that either the opioid system plays a relatively small part in the genesis of these disorders or, alternatively, that combinations of opioid system polymorphisms may be necessary to demonstrate a relationship (Mayer and Höllt 2001). Antisocial personality and alcoholism are more common in opioid users. Because both of these disorders appear to be influenced by genetic factors, it is possible that a more robust link with genetic factors in opioid abuse may someday be established.

Clinical Aspects of Tolerance and Withdrawal

Tolerance

Some degree of tolerance to the euphorigenic effects of heroin in addicts may develop in 1–2 weeks (Meyer and Mirin 1979). Therefore, the addict who desires a rush or a high progressively increases the dose. Although some build up to extraordinarily high doses, there is always a dose capable of causing death from respiratory depression. Physical dependence and tolerance occur more rapidly in former addicts; morphine addicts can reach a dose of 500 mg/day within 10 days of resumption of use. Tolerance largely disappears after withdrawal; addicts have unwittingly taken fatal doses by returning to their previous doses after detoxification. Receptor up-regulation may occur with chronic administration of opioid antagonists and may render addicts treated with these agents more sensitive to opioids when the antagonists are discontinued.

Withdrawal

Administration of sufficient doses of an opioid antagonist after only a single therapeutic dose of morphine results in withdrawal phenomena (Bickel et al. 1987; Heishman et al. 1989; Jones 1979). Some degree of physical dependence

develops in people who are given opioids regularly for more than a few days. However, very few become chronic users. Physical dependence and the presence of tolerance and withdrawal symptoms thus cannot be viewed as the only causes of continued use and relapse. However, the presence of physical dependence clearly contributes to difficulty with or fear of withdrawing and to the tendency to relapse.

Intensity of withdrawal depends on the following factors, including 1) dose of the opioid used (however, increasing beyond the equivalent of 500 mg/day of morphine does not significantly increase severity), 2) duration of use, 3) rate of removal of opioids from receptors, and 4) extent of continuous use. Generally, the character of the signs and symptoms is opposite to that of the acute agonist effects. For example, constipation occurs during acute treatment, and bowel hypermotility occurs with withdrawal. Individual sensitivity may affect the nature of the withdrawal syndrome. For example, stomach cramps predominate in some, muscle aches in others. Withdrawal from different agents that have similar profiles of receptor activity generally has similar characteristics. Also, generally, the shorter the duration of action of the drug, the more severe is the withdrawal syndrome, the more rapid the onset of symptoms, and the shorter the total duration of the symptoms. With short-acting drugs such as heroin and morphine, early symptoms may occur between 8 and 12 hours after the last dose. Severe syndromes peak 48–72 hours after the last dose. In some individuals, subjective symptoms predominate over objective signs. Untreated, the acute phase of morphine or heroin withdrawal lasts 7–10 days. Withdrawal from κ agonists (e.g., nalorphine) is generally mild and of a qualitatively distinct character. The onset of withdrawal with longer-acting drugs such as methadone or LAAM can be delayed until 1–3 days after the last dose. Peak symptoms often may not occur until days 3–5. Withdrawal from methadone includes complaints of pain, which patients state originates from muscle or bone. Meperidine withdrawal develops within 3 hours after the last dose, peaks in 5–12 hours, and generally ends in 4–5 days. With meperidine, subjective symptoms, such as craving and restlessness, may be much more severe than the autonomic changes. Codeine withdrawal is comparatively less severe.

A protracted abstinence syndrome may follow the acute opioid withdrawal syndrome and last for many weeks (Martin et al. 1973). In one study of heroin addicts detoxified with methadone, withdrawal distress peaked at day 20,

the final day of methadone detoxification, and it was not until day 40 that addicts' symptom scores reached normal levels (Gossop et al. 1987). During this phase, there may be excessive somatic concerns, decreased stress tolerance, poor self-image, and disturbed sleep. Opioid effects are especially reinforcing at this time, perhaps providing one explanation for early relapse (Cushman and Dole 1973; Martin et al. 1973).

Formerly, ratings of withdrawal severity from drugs such as heroin, morphine, and methadone were made with the Himmelsbach Scale (Himmelsbach 1941), which emphasized "objective" or measurable signs over subjective reports. With such a system, the sequence of signs observed was as shown in Table 2–1. However, more recent work giving greater weight to subjective aspects of withdrawal distress has shown that drug users experience mood changes, fatigue, dysphoria, and vague discomforts many hours before such signs as lacrimation or yawning can be detected. When buprenorphine, a partial μ agonist, is withdrawn, no changes are observed by using the Himmelsbach Scale, but a withdrawal syndrome is readily measured with an opioid withdrawal symptom checklist (Fudala et al. 1990; Wesson and Ling 2003).

Table 2–1. Signs and symptoms of opioid withdrawal

Early	Middle	Late
Lacrimation	Restless sleep	Increased severity of earlier symptoms
Yawning	Dilated pupils	Tachycardia
Rhinorrhea	Anorexia	Nausea
Sweating	Gooseflesh	Vomiting
	Restlessness	Diarrhea
	Irritability	Abdominal cramps
	Tremor	Increased blood pressure
		Mood lability
		Depression
		Muscle spasms
		Weakness
		Bone pain

Source. Adapted from Ciraulo and Ciraulo 1988.

Personality variables, state of mind at time of withdrawal, and expectations of severity of symptoms all may affect withdrawal severity (Kleber 1981). One study found that merely providing addicts information about the withdrawal syndrome resulted in lower levels of withdrawal symptoms (Green and Gossop 1988). Naloxone rapidly induces a severe withdrawal syndrome, which peaks within 30 minutes and then declines rapidly. Until the antagonist is eliminated, only partial suppression of the withdrawal syndrome is possible, and then only by using very high opioid doses, which may cause respiratory depression when naloxone is metabolized.

Treatment Approaches

Treatment approaches include 1) short-term detoxification, usually with methadone, buprenorphine, or clonidine; 2) opioid substitution therapy, consisting of maintenance treatment with methadone, LAAM, or buprenorphine; 3) antagonist treatment with naltrexone; 4) the therapeutic community; and 5) outpatient drug-free treatment, which may include formal relapse prevention programs. Some private residential chemical dependency programs emphasizing a 12-step approach to recovery also offer treatment to opioid-dependent individuals. Therapists in each of these settings may have experience ranging from prior dependence and experiential training to advanced degrees in the health professions. An addict often has experience with more than one treatment modality in his or her career. For example, the user may first be detoxified, then relapse, enter methadone maintenance, eventually be detoxified from methadone, and finally continue successfully with outpatient drug-free treatment. It is often difficult to ascertain for such individuals what the key ingredient for recovery was.

Opioid Detoxification

Methadone

At present in the United States, methadone is the most commonly used drug to treat withdrawal symptoms. Detoxification can be accomplished over a period as long as 6 months in an ambulatory methadone maintenance program or as brief as several days in a hospital setting. The goal in brief detoxification is to make the experience less distressing, but the suppression of all with-

drawal symptoms should not be expected. If the daily opioid dose is known, one can administer the pharmacologically equivalent methadone dose. The drawback to this approach is that the published equivalencies of oral methadone vary markedly. For example, one source cited reported equivalencies of oral morphine to oral methadone ranging from 4:1 to 14:1 (Gordon et al. 1999), although it may be as low as 2.5:1 (Ripamonte et al. 1998). Caution should be used when dosing is guided by equivalency tables. As a consequence of methadone's longer duration of action and oral efficacy, it is possible to suppress withdrawal with the lower doses of oral methadone than would be predicted from the published analgesic equivalency ratios.

For patients taking street heroin, the initial dose of methadone is usually 15–20 mg orally. If withdrawal symptoms or signs persist, one may repeat the dose in a few hours. Although some addicts with access to pure drugs (not uncommon in some U.S. cities) may require higher doses, generally 40 mg/day of methadone is adequate. Once a stabilizing dosage has been found, methadone can be reduced about 10%–20% per day to achieve full detoxification within 5–10 days. The rate of decrease can be more rapid if clonidine is used (see the next section on clonidine). To facilitate compliance in outpatient detoxification, the treatment period may need to be prolonged. Reasonable tapering schedules are 10% per week from high doses and 3% per week from doses less than 20 mg/day (Senay et al. 1977).

Relapse rates after detoxification are very high. Although extension of the withdrawal period for up to 6 months does not appear to improve outcome (Sees et al. 2000), patients who have received methadone maintenance and who have a good therapeutic relationship have more successful outcomes.

Clonidine

Clonidine, an α_2 agonist used primarily as an antihypertensive, is another agent now commonly used for detoxification (Table 2–2). Since the late 1970s, clonidine repeatedly has been shown to suppress many of the autonomic symptoms of the withdrawal syndrome (Gold et al. 1978; Kleber et al. 1985). Patients taking opioids can be transitioned to taking oral clonidine in doses starting at 0.1–0.2 mg three times per day (up to 0.6 mg/day). Doses greater than 1.0 mg/day are not recommended for outpatient settings. Clonidine should be given for approximately 10 days for heroin detoxification and for 14 days for individuals who are discontinuing methadone. Limiting the use

Table 2–2. Protocol for administration of clonidine for detoxification from short-acting opioids and methadone

	Detoxification	
Day	From short-acting opioid (heroin, oxycodone)	From methadone (25 mg or less)
1	0.3–0.6 mg/day (includes 0.1-mg test dose)	0.3–0.6 mg/day (includes 0.1-mg test dose)
2	0.4–0.8 mg/day	0.4–0.6 mg/day
3–6	0.6–1.2 mg/day, then reduce daily dose by 50% each subsequent day; daily reductions should not exceed 0.4 mg	0.5–0.8 mg/day
6–10		0.6–1.2 mg/day, then reduce daily dose by 50% each subsequent day; daily reductions should not exceed 0.4 mg

Note. Clonidine alone may not adequately treat insomnia, diarrhea, muscle aches, restlessness, irritability, or other withdrawal symptoms, which may require other medications. For this reason many programs use lower doses of clonidine than outlined in this table, in combination with oral opioids.
Source. Adapted from Kleber and Kosten 1984.

of clonidine on an outpatient basis are two major side effects: hypotension, which may be marked, and sedation. Although not currently approved by the FDA, lofexidine, another α_2 agonist, has been used extensively in Europe for detoxification. Compared with clonidine, it is less likely to produce hypotension or sedation (Strang et al. 1999).

Detoxification is more successful when the patient is transitioned from a stable methadone dose with the support of ongoing therapy than when the patient comes directly from the street for detoxification from heroin. Some practitioners believe that detoxification with clonidine can be more rapid than with methadone, at least on an outpatient basis. One important limitation of clonidine is that, although it suppresses autonomic signs of withdrawal, subject-reported symptoms, such as lethargy, restlessness, insomnia, and craving, are not well relieved (Charney et al. 1981; Jasinski et al. 1985). Anxiety may

be alleviated with benzodiazepines, and some data suggested that low-dose propranolol may reduce restlessness (Roehrich and Gold 1987).

Clonidine has been used in combination with naltrexone to facilitate rapid withdrawal as well as to ease rapid transition to treatment with the antagonist. Patients usually begin by taking both clonidine and a very low dose of naltrexone on day 1. Clonidine is given in divided doses, adjusted for severity of withdrawal, to a dosage of up to 2–2.5 mg/day. The dosage of naltrexone is gradually increased to 50–150 mg/day by approximately day 5 or 6; 80%–90% of patients are able to complete the transition to naltrexone in less than 1 week (Charney et al. 1986; Kleber et al. 1987; Vining et al. 1988). In one of the few randomized trials comparing some of the newer detoxification protocols, O'Connor et al. (1997) reported that patients detoxified with a combination of clonidine, naltrexone, and buprenorphine had fewer withdrawal symptoms than those treated with clonidine or with clonidine plus naltrexone.

Buprenorphine

Since the late 1990s buprenorphine has been recognized as an effective agent for opioid detoxification. The intramuscular formulation approved for pain (Buprenex) has been used successfully in inpatient detoxification programs (Umbricht et al. 2003). Although never approved by the FDA for this purpose, several protocols for intramuscular buprenorphine were used clinically for opioid detoxification. A common protocol was 0.6 mg im every 4 hours on day 1, 0.6 mg im every 6 hours on day 2, and 0.6 mg im every 8 hours on day 3, a regimen that followed some research protocols (Umbricht et al. 2003). Other clinical protocols recommended 0.3–0.6 mg im tid on day 1, 0.15–0.3 mg im tid on day 2, and 0.15 mg im bid on day 3. Some research protocols used higher doses (Cheskin et al. 1994). With the recent FDA approval of sublingual buprenorphine (Subutex) for the office-based treatment of opioid dependence, it is likely that this medication will become one of the standard options for use in detoxification. The optimal withdrawal protocol is now being studied; until the results are known, most clinicians are following the guidelines for buprenorphine induction outlined in Table 2–3 and described in the discussion of buprenorphine maintenance therapies in the subsequent section on long-term treatment. Buprenorphine is clearly preferred by many addicts as a medication for detoxification. In one study, sublingual buprenorphine appeared to be as effective as methadone in a 7-week detoxification (Bick-

el et al. 1987). Buprenorphine withdrawal syndrome appears to be quite mild, with few subjects requesting drugs for relief (Fudala et al. 1990; Jasinski et al. 1978; Kosten and Kleber 1988; Mello and Mendelson 1980). After 6 weeks of treatment with 8 mg of buprenorphine sublingually daily, withdrawal was measurable by a symptom checklist and appeared to peak at about 72 hours after the last dose. No increase in withdrawal symptoms was observed with the Himmelsbach Scale, which emphasizes physiological signs and symptoms (Fudala et al. 1990). The low severity of buprenorphine withdrawal seems to facilitate rapid induction of naltrexone after buprenorphine discontinuation (Kosten and Kleber 1988).

Ultrarapid detoxification employs general anesthesia and opioid antagonists to accomplish withdrawal more quickly (Alvarez and Carmen del Rio 1999; Bell et al. 1999; Brewer et al. 1998; Brewer and Maksoud 1997; Gerra et al. 2000; Kleber 1998; Rabinowitz et al. 1998; San and Arranz 1999; Shreeram et al. 2001; Stephenson 1997; Strang et al. 1997). Its efficacy and safety are being studied.

Agonist Replacement

Despite evidence documenting the effectiveness of methadone maintenance and other types of opioid substitution therapy (Ball and Ross 1991) and therapeutic communities (DeLeon 1985), there is still considerable controversy about the most effective treatment for opioid dependence. Each patient needs to be evaluated extensively, with attention paid to a number of factors, including 1) motivation for a particular type of treatment, 2) presence of psychopathology, 3) presence of other substance abuse, 4) availability and feasibility of various types of treatment, and 5) success or failure of prior treatments. More often than not, a combination of treatment methods is practiced. Even for programs focused on the use of a medication, counseling and/or psychotherapy must play a critical role. In addition, the necessity for acute detoxification must always be assessed before determining appropriate long-term treatment. Detoxification alone is usually unsuccessful in preventing relapse, so strong efforts must be made to interest the detoxifying addict in further treatment.

Opioid Substitution Therapy

Methadone Maintenance

Methadone maintenance was first introduced in 1964 by Dole and Nyswander (1965). The basis for use of methadone is that high doses alleviate craving

and induce cross-tolerance to other opioids so that heroin-induced euphoria is blocked. In theory, individuals receiving methadone maintenance would have no need to use heroin or to be involved with the various maladaptive behaviors needed to maintain heroin addiction. Results with more psychologically disturbed and less-motivated patients than those treated by Dole and Nyswander, however, were less dramatic than they originally demonstrated (Sells 1979). Nevertheless, methadone maintenance does reduce heroin use, nonopioid drug use, health problems, and crime (e.g., Ball and Ross 1991, Ball et al. 1988a; Gerstein and Harwood 1990; Sees et al. 2000; Senay 1985). Despite the benefits of methadone maintenance, some addicts have a negative attitude toward this approach and are often misinformed about methadone itself, factors that may lead to reluctance to enter into this form of treatment (Hunt et al. 1985–1986). In addition, some health professionals and members of the general public consider it a controversial treatment. Despite the extensive research documenting its efficacy, some believe its primary purpose is crime reduction; others see it as merely a substitution of one addiction for another.

Methadone is a μ receptor agonist with special properties that make it particularly useful as a maintenance agent. Reliably absorbed orally, it does not reach peak concentration until about 4 hours after administration and maintains a large extravascular reservoir (Kreek 1979). These properties minimize acute euphoric effects. The reservoir results in a plasma half-life of 1–2 days, so there are usually no rapid blood level drops that could lead to withdrawal syndromes between daily doses. Effective blood levels are in the range of 200–500 ng/mL. Trough levels of 400 ng/mL are considered optimal (Payte and Khouri 1993). There is wide variability among individuals in blood levels with identical doses (Kreek 1979), and some have inadequate levels even with doses as high as 200 mg/day (Tennant 1987; Tenore 2003).

Methadone is metabolized by enzymes in the cytochrome P450 system, primarily by CYP3A4 in the liver (Shinderman et al. 2003). Hepatic enzyme-inducing drugs such as phenobarbital, phenytoin, carbamazepine, isoniazid, rifampin, nevirapine, and vitamin C in large doses may markedly reduce serum methadone concentrations (Bell et al. 1988; Kreek 1979). Drugs that raise methadone levels include ketoconazole, fluconazole, sertraline, amitriptyline, paroxetine, fluvoxamine, fluoxetine, diazepam, alprazolam, and zidovudine, which implies that CYP2D6, CYP2C9, and CYP2C19, as well as

CYP3A4, may contribute to methadone metabolism. Even with adequate methadone plasma levels, some patients continue to abuse drugs, such as sedatives, possibly because they are seeking some form of intoxication rather than relief of opioid hunger (Bell et al. 1990). Relapse to illicit drug use is also common during periods of high stress, even in patients with adequate plasma levels.

Although tolerance develops as with all opioids, some pharmacologic effects of methadone may persist (Kreek 1983; also see earlier discussion of pharmacology). Euphoria and drowsiness are generally more pronounced in the first weeks of treatment. Some slight but measurable mood elevation occurs at about the time of peak plasma levels in patients who receive methadone chronically and may be one reason why some patients stay in treatment (McCaul et al. 1982). Effects to which tolerance may not develop fully include constipation, increased perspiration, and complaints of sexual dysfunction and decreased libido. (Opioid-induced endocrine effects usually resolve after a few months, but chronic use of opioids may lower testosterone and follicle-stimulating hormone levels. However, there is not a strong correlation between these levels and sexual dysfunction.) During the early months of treatment, there may be altered electroencephalogram (EEG) sleep patterns and insomnia. Although EEGs appear to normalize, sleep disturbance may persist. There is no evidence for long-term organ damage with methadone. At very high doses, methadone may prolong the QTc interval and lead to torsade de pointes (Krantz et al. 2002, 2003; Kornick et al. 2003).

Methadone maintenance programs usually are staffed by a part-time physician, nurse, and counselors of varying levels of training. Federal, state, and sometimes local regulations govern each program. Federal requirements regulate areas such as standards for admission, frequency of urine testing, methadone dosage, quantity of take-home medication, and treatment of pregnant addicts. Regulations stipulate that clients must be at least 18 years old (with some exceptions), have been addicted for most of the prior year, and have 1 year of "physiologic dependence." (These conditions are in contrast to the requirements for buprenorphine treatment, for which patients must meet the DSM-IV criteria for opioid dependence, which does not necessarily require current physiologic dependence.) Physiologic dependence is not a requirement for persons recently released from prison or a chronic care institution, provided they would have been eligible for methadone maintenance before

incarceration or institutionalization, or for selected patients who have previously been treated with methadone maintenance.

The maximum first-day dosage is 30 mg, with an additional 10 mg permitted if withdrawal symptoms persist after the initial dose. Patients initially return daily for each dose of methadone. Treatment is monitored by counselors, and because opioid addicts often underreport their drug use (Magura et al. 1987), random urine testing is required by federal regulation. After 90 days of methadone treatment, patients are eligible for weekend take-home doses, plus an additional day during the week if they have been drug free for the prior 30 days. After years of treatment, patients can qualify for up to six take-home doses per week, if they have been drug free for the previous year. Eventually patients who remain drug free can earn up to a 30-day supply of take-home doses.

Reasons for discharge from maintenance include persistent opioid or other substance use, sporadic attendance, and aggressive behavior at the clinic. Although such patients undermine the purpose of treatment and the treatment milieu, it is often difficult to discharge them because clinicians generally believe that they would likely do worse without treatment.

Although standard regulations and a common underlying philosophy result in many similarities among methadone maintenance programs, there are also a number of differences. Programs modeled after the original model of Dole and Nyswander (1965) tend to use a high dosage (80–120 mg/day) or more flexible dosing to ensure cross-tolerance and suppression of craving. Because illicit opioid use is seen as a response to a metabolic deficiency, indefinite continuation of methadone is felt to be the only way to preclude relapse. One group had good results with outpatient "medical maintenance" (Novick et al. 1988). Selected, highly successful methadone maintenance patients were seen in a physician's office every 28 days and given a take-home supply of methadone tablets up to a dosage of 100 mg/day. The percentage of patients who relapsed to heroin use, got into legal difficulty, or dropped out of treatment was very low. Another study randomly assigned 73 highly stable methadone maintenance patients to either routine methadone maintenance, medical maintenance in a methadone clinic setting, or medical maintenance in a physician's office (King et al. 2002). Although the patients did well in all three settings, the two groups of medical maintenance patients were more satisfied and initiated more new employment or family/social activities. Clini-

cians have reported concern about the potential for diversion and serious overdose in medical maintenance programs (Wesson 1988). This type of "medical maintenance" has not proven successful for unselected addict populations waiting for admission to standard methadone maintenance programs.

Other programs use a methadone dosage in the range of 20–60 mg/day and less flexible dosing. Although lower doses may reduce drug-seeking behaviors, these doses often are not high enough to prevent heroin-induced euphoria. Clients are viewed not as having a biological illness but rather as being responsible persons who will do best if gradually shifted from maintenance to detoxification. These programs are thus less tolerant of continued drug use and are more likely to discharge clients for problem behavior. Programs using lower doses generally had lower rates of retention in treatment (Brown et al. 1982–1983). In a study of six methadone clinics believed to be operating effectively, the percentage of patients who had used illicit injection drugs within the month before the interview ranged from 9% to 57% (Ball and Ross 1991; Ball et al. 1988a, 1988b). Even after adjustment for differences among patients, the factors associated with decreased intravenous drug use (in addition to higher methadone dosage) in that study were the quality of program leadership and services provided. Another factor to consider is variability within programs; some counselors are demonstrably more effective than others.

In addition to factors related to the treatment program, there are demographic and psychological correlates of retention. Clients who are employed, married, black, and older have longer retention times. Persons with criminal histories and higher levels of psychopathology tend to leave treatment sooner. Severity and duration of opioid use per se do not appear to correlate with retention.

Treatment outcome is, of course, determined by multiple factors. Duration and severity of use do not correlate with outcome. Many of the factors contributing to retention rates also affect treatment outcome. For example, patients with serious psychopathology or criminal backgrounds do less well. This is not to say, however, that such clients never improve. In one 2.5-year follow-up study, clients with criminal backgrounds showed significant improvement in substance abuse and in family, legal, and psychological problems (Kosten et al. 1987b). For clients with severe psychopathology, maintenance programs appear to be more helpful than therapeutic communities (see McLellan 1986). Opioid users with more criminality and less psychopathol-

ogy appear to prefer short-term detoxification to maintenance (Kosten et al. 1986b).

LAAM

LAAM (L-α-acetylmethadol or levomethadyl acetate) is a full agonist at the μ opioid receptor with pharmacologic properties similar to those of methadone. A number of studies have demonstrated that treatment with LAAM results in reduction of opioid use and beneficial effects comparable to those achieved with methadone (Ling et al. 1978; Tennant et al. 1986; Zangwell et al. 1986). However, retention rates are higher in patients who take methadone doses of 80–100 mg/day.

There is a great deal of individual variability in rates of conversion of LAAM to its various metabolites, so initiating treatment is more complicated for the clinician (Ling et al. 1978; Tennant et al. 1986). LAAM itself is an inactive prodrug. The two active metabolites (nor-LAAM and di-nor-LAAM) have half-lives of 2–3 days. It typically takes 14 days to establish fully effective blood levels. For that reason, LAAM may not adequately suppress opioid withdrawal during the first 48 hours of treatment. Other agents (e.g., methadone) may need to be used during this period (Tennant et al. 1986). Because of its long half-life, LAAM is dispensed three times per week. Clients need not attend the clinic daily, and, because no take-home doses are dispensed, there is less likelihood of diversion.

LAAM usually has been prescribed in doses of 20–140 mg (Ling et al. 1978; Tennant et al. 1986). The typical Monday-Wednesday-Friday dosing schedule is 100 mg–100 mg–140 mg. The maximum recommended doses are 140 mg–140 mg–140 mg or 130 mg–130 mg–180 mg (thrice-weekly schedule) or 140 mg every other day. For some patients LAAM "holds better" than methadone. There is evidence that LAAM may be particularly helpful for patients who do not respond to high-dose methadone because of low plasma levels (Tennant 1988). Others patients prefer LAAM to methadone because they can attend the clinic less often (Tennant et al. 1986; Trueblood et al. 1978). However, a few experience nervousness and stimulation while taking this drug.

Recent evidence that LAAM can prolong the QTc wave or induce a severe arrhythmia (torsade de pointes) has limited its clinical use (Katchman et al. 2002, Kang et al. 2003). All patients must have a screening electrocardiogram (ECG) before starting LAAM and again after 6 weeks of taking the drug.

LAAM is contraindicated for any patient with ECG abnormalities or any significant cardiac disease.

Buprenorphine

In 2002, the FDA approved sublingual buprenorphine (Subutex) and a combination sublingual tablet of buprenorphine/naloxone (Suboxone) for the office-based treatment of opioid dependence. Buprenorphine is a partial μ receptor agonist, with most of the properties of morphine. It is also a strong antagonist at the κ receptor. Administered at dosages of 4–24 mg/day sublingually, it attenuates or blocks opioid-induced euphoria. It is not clear whether this effect is a result of cross-tolerance or some other action at the receptor. Buprenorphine has a very high affinity for the μ receptor, and can precipitate withdrawal by displacing other opioids from the receptor. However, it also dissociates very slowly from the receptor. This feature probably accounts for both its long duration of action (24–48 hours) and its reduced capacity to produce opiate withdrawal. The efficacy of buprenorphine for the maintenance treatment of opioid dependence was demonstrated in a large, multicenter randomized clinical trial (Ling et al. 1998). In another randomized maintenance trial, buprenorphine (16–24 mg sublingually three times a week), high-dose methadone (60–100 mg/day), and LAAM (75–115 mg three times a week) were all shown to be effective in treating opioid dependence and were superior to low-dose methadone (20 mg/day) in clinic retention and suppression of opioid use (Johnson et al. 2000). An additional benefit of buprenorphine is that risk of overdose may be low. As a partial agonist, buprenorphine appears to have a ceiling effect as the dose is increased, so that respiratory depression greater than that caused by 30–60 mg of morphine is not produced (Jasinski et al. 1978).

The initial dose of buprenorphine should be given at least 12–24 hours after the last heroin dose, 24 hours after the last methadone dose, or 48 hours after the last LAAM dose (see Table 2–3). The methadone dosage of methadone maintenance patients should be reduced to 30 mg/day before the transfer to buprenorphine is attempted. Ideally patients should show clear evidence of opiate withdrawal before receiving the first dose of buprenorphine, to avoid the risk that buprenorphine will precipitate more severe withdrawal. For the first day, sublingual buprenorphine/naloxone doses of 2/0.5–4/1 mg can be given every 2–4 hours, up to a maximum total dose of 8/2 mg/day. On the

Table 2–3. Buprenorphine induction schedule

	Sublingual buprenorphine/naloxone tablets[a]		
	Day 1		
Patient type	**First dose**	**Supplemental dose**	**Day 2**
Not currently dependent	2/0.5 mg		4/1 mg
Dependent on heroin or pain medications	2/0.5 to 4/1 mg[b]	Redose every 1–2 hours, if withdrawal continues, up to a total of 8/2 mg	If the patient is still in withdrawal, give first-day dosage plus 2/0.5 to 4 /1 mg
Dependent on methadone (≤ 30 mg/day) or on LAAM (≤ 40 mg/every other day)[c]	2/0.5 mg[b]	Redose every 1–2 hours, if withdrawal continues, up to a total of 8/2 mg	If the patient is still in withdrawal, give first-day dosage plus 2/0.5 to 4 /1 mg; if oversedated, give < 8/2 mg

Note. LAAM = L-α-acetylmethadol (no longer available in the United States).
[a]Dose amounts consist of the buprenorphine dose (the number before the slash) and the naloxone dose (the number after the slash).
[b]Do not begin buprenorphine until patient shows evidence of opioid withdrawal.
[c]Patient should abstain from LAAM for ≥48 hours before first buprenorphine dose.
Source. Adapted from McNicholas and Howell 2000.

following days, the dose can be increased by 2/0.5–4/1 mg daily until the initial target maintenance dosage of 12/3–16/4 mg/day is reached. Most patients receive a maintenance dosage of 12/3–24/6 mg/day. After 1 week at a stable-dose patients can be shifted to three times a week dosing. Initiation of buprenorphine can be done by using either the buprenorphine-only tablet or the combination buprenorphine/naloxone tablet; however, only the combination tablet can be dispensed as a take-home medication.

The approval of buprenorphine for the office-based treatment of opioid dependence represents a major departure from the earlier methadone clinic system. Physicians with addiction specialist credentials or those who have completed 8 hours of approved training can become qualified to treat up to 30 patients in their private offices. Stable patients may be given prescriptions for up to a month of medication. The combination buprenorphine/naloxone tablet is expected to have minimal risk for diversion. When taken sublingually, as prescribed, naloxone has minimal biologic activity and does not interfere with the buprenorphine dose. However, if an attempt is made to inject the drug, the addict will experience the full antagonist effect of the naloxone.

It is anticipated that buprenorphine will be an acceptable treatment for younger addicts and for individuals with smaller habits and shorter histories of dependence, thus permitting earlier intervention in the course of the addiction. Clinical experience suggests that buprenorphine is less effective for individuals with larger opioid habits. Methadone or LAAM remains the preferred medication for those patients.

Detoxification From Maintenance Treatment

The factors that correlate with treatment success do not clearly apply to success after detoxification from methadone maintenance. Correlates of successful detoxification include 1) less criminal behavior; 2) more stable family; 3) more stable employment; 4) shorter drug history; 5) long maintenance with lower dosage; and 6) discharge status, with patient and staff consensus as opposed to unilateral discharge from treatment (Dole and Joseph 1978). In one study, addicts were followed an average of 2 years after detoxification (Stimmel et al. 1977). Although only 28% of the total sample remained abstinent, 83% of those who had fully completed treatment remained abstinent. Another study of 105 patients detoxified after methadone maintenance treatment documented an 82% relapse rate within 12 months (Ball and Ross 1991). These

studies suggest that clinicians should exercise caution when recommending detoxification, even for more successful maintenance patients.

When patients elect detoxification from maintenance, a very gradual reduction of dosage is preferred, with careful monitoring of drug craving and withdrawal symptoms. Three to 6 months is recommended for most elective detoxifications. As many as one-third of methadone maintenance clients have been found to have a marked fear of detoxification (Milby et al. 1986).

Clients who need to reenter treatment at a later date often do much better than during their original treatment, showing less dependence, criminality, and physical disability (Kosten et al. 1986b). Such findings indicate that intermittent treatment appears to be beneficial. Therefore, reentry does not necessarily indicate failure and may instead be one further step to eventual recovery. On the other hand, there is a high probability that those who discontinue methadone will resume intravenous drug use with attendant risks for hepatitis and HIV infection (Ball et al. 1988a, 1988b).

Opioid Antagonists

Originally, behavioral principles were the basis for the use of opioid antagonists to treat addiction. In theory, drug use that was once operantly reinforced by euphoria would no longer be reinforced if the patients were given high enough maintenance doses of an opioid antagonist. In addition, with no regular opioid use, there would be extinction of the association between withdrawal symptoms and the addict's environment (Wikler 1980). Studies of cyclazocine, naloxone, and naltrexone showed them all to be successful in blocking opioid effects, but addicts generally stayed in treatment only for an average of 6–8 weeks (Capone et al. 1986; Fram et al. 1989; Resnick et al. 1980).

Naltrexone (Trexan) is the only opioid antagonist currently in use for treatment of addiction. Naloxone is used to treat opioid overdose and to test for opioid addiction but has a short half-life and is relatively ineffective orally; cyclazocine's dysphoric side effects make it unacceptable (Resnick et al. 1980). Patients who are likely to continue to use naltrexone and to benefit from treatment are those who have established careers (e.g., health professionals) and family support and are well motivated. Up to 70% of such clients are abstinent at 1-year follow-up (Washton et al. 1984). Programs that utilize additional rehabilitative services have better results than those that provide minimal services. Successful treatment is also associated with taking naltrexone

for longer than 2 months (Capone et al. 1986). A multiclinic, double-blind study involving primarily heroin addicts had such a high attrition rate that conclusions could not be drawn (National Research Council 1978). A more recent study compared the effect of naltrexone alone versus naltrexone combined with either contingency management or family counseling (Carroll et al. 2001). Both study conditions improved retention and medication compliance, with the most significant effect seen in the subgroup that attended family counseling.

Naltrexone is orally effective and long-acting. It may be given daily in doses of 50 mg/day or three times a week, in doses of 100 mg on weekdays and 150 mg on a weekend day. An injectable depot formulation of naltrexone is being developed by several groups, but it is not yet commercially available. Some authors recommended that naltrexone should be started slowly and only after a waiting period (e.g., maximum starting dosage of 50 mg only after the patient is heroin free for 7 days or methadone free for 10 days, confirmed by a negative naloxone challenge) (Ginzburg 1984). However, there is a significant risk of relapse during such a waiting period. There has been some success with the rapid induction of naltrexone during clonidine detoxification from opioids (see earlier section on detoxification). Naltrexone may actually reduce protracted withdrawal symptoms in part because it may accelerate the return of normal central nervous system function (Charney et al. 1986).

At the doses used, there is blockage of the effects of as much as 25 mg of injected heroin. Toxicity in heroin addicts is low, but some reported subtle adverse effects of naltrexone such as decreased energy (Hollister et al. 1981). Nonaddicted obese subjects have been known to develop markedly elevated transaminase levels at doses of 300 mg/day (Mitchell et al. 1987). The inference has been drawn that high doses are potentially hepatotoxic (Pfohl et al. 1986), and the drug is contraindicated in liver failure or acute hepatitis.

Therapeutic Communities

Therapeutic communities are supervised communal drug-free living situations for opioid and nonopioid drug abusers. Because substance abuse is viewed as a disorder of the whole person, the goal is a dramatic alteration of the addict's entire lifestyle (DeLeon 1985). Addicts are expected to live in these communities for 6–18 months. Therefore, they are not indicated for people who have a strong intimate relationship or stable employment. The community is a surrogate fam-

ily in many ways. Treatment may include peer confrontation techniques in group and milieu settings as well as education and rehabilitation. The user is expected to be an active member of the community, whose existence depends on the involvement of all. The more responsibility one assumes, the more status, freedom, and comfortable living situation one may obtain.

Therapeutic communities vary a great deal in staffing and philosophy (Bale et al. 1984; DeLeon 1985), but all have some recovering addicts on staff. They are present not only because of some clients' belief that recovering addicts are needed to understand their situation but also because they are role models who provide hope for those who doubt they can change their lifestyles. Some therapeutic communities are becoming more aligned with a traditional psychiatric model, developing individual treatment plans and employing mental health professionals in key positions. Some are directed by psychiatrists.

At present, many clients are referred by the courts and thus are required to complete treatment. Another recent change has been that entrants appear to be more depressed and less intelligent and to have more behavioral problems than in the past (DeLeon 1985). Even in the past, when clients had to demonstrate high levels of motivation to gain admission, dropout rates were high (DeLeon 1985). About 50% of patients drop out within the first 3 months, and only about 15% of entrants complete a year of treatment.

High dropout rates notwithstanding, those who stay in treatment have excellent results. Clients remaining for 90 days or more do better than dropouts on legitimate employment, number of arrests, self-reported drug use, and antisocial behavior; these results hold true at 1- and 5-year follow-ups (Bale et al. 1984; DeLeon 1985). However, some research showed a negative correlation between duration of residence and outcome, particularly for clients with extensive psychiatric symptoms, who do comparatively poorly in therapeutic community settings (McLellan 1986).

Outpatient Drug-Free Treatment and Psychotherapy

Outpatient drug-free programs, like therapeutic communities, seek to achieve abstinence without the use of psychoactive medication. Programs range from unstructured drop-in centers with discussion groups and recreational activities to organized day treatment programs.

Individual psychotherapy in the context of other opioid addiction treatment such as methadone maintenance appears to be most helpful for patients with severe psychopathology. Methadone maintenance clients have been shown to do better with individual psychotherapy than with drug counseling alone; individual supportive-expressive psychotherapy plus drug counseling and individual cognitive-behavioral psychotherapy plus drug counseling were both superior to drug counseling alone at 12-month follow-up (Woody et al. 1987). Family therapy is often an adjunct treatment for opioid-dependent individuals (Kaufman 1986).

Opioid-Associated Problems

Pregnancy and Opioids

Opioid withdrawal is much more dangerous for the fetus than for the adult. Withdrawal in the pregnant addict can cause fetal death or miscarriage, especially during the first trimester, although there are insufficient experimental data to quantify risk (Luty et al. 2003; Jarvis and Schnoll 1995). Because continued heroin use or high-dose methadone maintenance can result in a severe neonatal withdrawal syndrome after delivery, many authorities recommend continued methadone maintenance (Kaltenbach et al. 1998). Although some recommend methadone maintenance dosages of 10–40 mg/day, these lower dosages are clearly less effective than those above 60 mg/day in suppressing illicit injection opioid use. In light of the risk of HIV and other infections associated with continued injection drug use, clinicians must consider several factors and individualize treatment for each patient. Estimates of the rate of neonatal withdrawal syndrome vary from 60% to 90% (Lacroix et al. 2004; Luty et al. 2003; Sharpe and Kuschel 2004). Studies suggest that the syndrome rarely requires treatment when the mother receives low methadone doses, but as many as 50% to 75% of neonates may require treatment if the mother is given high maintenance methadone doses (Lacroix et al. 2004; Sharpe et al. 2004). In severe cases, neonatal withdrawal is characterized by irritability, autonomic dysfunction, breathing problems, and poor feeding (Johnson et al. 2003). There appear to be no uniform long-term effects of maternal methadone maintenance on children followed up to 7 years of age (Rosen and Johnson 1985). When mothers are maintained with low metha-

done doses, neonatal withdrawal is usually mild and readily manageable with low-dose paregoric (Finnegan et al. 1984) or morphine (0.5 mg/kg/day in divided doses) (Kayemba-Kay's and Laclyde 2003). If pregnancy began when the woman was receiving high-dose methadone, there could be a slow taper of 1 mg every 3 days; however, published studies vary greatly in the length of withdrawal, with protocols lasting 12 days (Dashe et al. 1998), 2–8 weeks (Maas et al. 1990), and 21 days (Luty et al. 2003). If complete withdrawal is desired, it should occur during the second trimester. Although definitive evidence is lacking, some clinicians believe that first-trimester withdrawal is associated with miscarriage and that third-trimester withdrawal is associated with premature delivery.

Preliminary trials of buprenorphine in pregnant addicts indicated that the drug was well tolerated (Schindler et al. 2003) and that infants born to buprenorphine-maintained mothers had normal birth weight and normal Apgar scores and showed no evidence of neonatal abstinence syndrome (Fischer et al. 1998), although recent reports have established that a withdrawal syndrome may occur (Johnson et al. 2003). A comprehensive review of published data on pregnant women maintained with buprenorphine (0.4–24 mg sublingual daily) supported the safety of buprenorphine in pregnancy (Johnson et al. 2003). There are few data on the pharmacokinetics of buprenorphine during pregnancy, but it is known that the ratio of buprenorphine in plasma to buprenorphine in breast milk is 1:1, although because of poor oral bioavailability only 10%–25% of the buprenorphine in breast milk will be absorbed by the neonate, which has been insufficient to prevent a neonatal withdrawal syndrome (Auriacombe and Loustauneau 2000–2001). Contrary to early reports, a neonatal withdrawal syndrome does occur in infants whose mothers have taken buprenorphine (Johnson et al. 2003). A review of 349 buprenorphine-treated pregnant women found that 62% of infants had opioid withdrawal symptoms and 48% required treatment, with less than 10% treated in the neonatal intensive care unit (Johnson et al. 2003). It should be kept in mind that many of the mothers were using multiple drugs, so that other illicit substances may have caused the withdrawal syndrome. It is generally agreed that the neonatal withdrawal syndrome from buprenorphine is milder than that from methadone. It usually occurs within 12–48 hours of drug discontinuation, peaks at 72–96 hours, and may last 120–168 hours (Johnson et al. 2003). As with infants of

methadone-maintained patients, the withdrawal syndrome can be managed with paregoric or morphine.

Psychiatric Disorders

High levels of global severity of psychopathology adversely influence the course of opioid dependence as well as response to all forms of treatment. It is unclear whether specific diagnoses selectively influence outcome (Ciraulo et al. 2003; Kosten et al. 1986a; McLellan 1986; McLellan et al. 1983; Rounsaville et al. 1986b; Woody et al. 1984). Several studies have assessed prevalence of psychiatric disorders among opioid-dependent persons. In one study of 533 treated opioid addicts (Rounsaville et al. 1982), lifetime prevalence of Research Diagnostic Criteria (RDC) disorders (Spitzer et al. 1978) was assessed. The most common diagnoses, with percentages for men and women, respectively, were affective disorder (70.7%, 85.4%), with major depression the most prevalent (48.4%, 69.2%); alcoholism (37%, 26.9%); antisocial personality (29.5%, 16.9%); and anxiety disorders (13.2%, 25.4%), with phobic disorder the most prevalent (8.2%, 13.9%). The RDC require that the diagnosis of antisocial personality be independent of the need for drugs; with DSM-III criteria (American Psychiatric Association 1980), 54% of the population studied would have met the criteria for antisocial personality disorder. In this study, 70.3% met the criteria for a current episode of psychiatric disorder, the most common of which were major depression (23.8%), alcoholism (13.7%), and phobic disorder (9.2%).

Comparable findings for lifetime prevalence of psychiatric disorders were obtained in another study of 133 persons, which also found that 47% received a concurrent DSM-III diagnosis of substance abuse or dependence (Khantzian and Treece 1985). The most frequently abused substances were sedative-hypnotics (23%), alcohol (14%), and cannabis (13%). Similar rates of psychiatric disorders were found in other studies of drug abusers (Mirin et al. 1986; Woody et al. 1983). Although such diagnoses do not imply causality, and, in many cases, opioid dependence causes or exacerbates psychiatric problems, some causal link seems likely (Regier et al. 1990).

A later study used DSM-III-R criteria to assess 716 opioid abusers seeking methadone maintenance treatment (Brooner et al. 1997). In evaluations conducted 1 month after admission, psychiatric comorbidity was found in 47% of

the subjects (48% of the men and 47% of the women). The most common diagnoses were antisocial personality disorder (25.1%) and major depression (15.8%). Abuse of multiple drugs was common, with cocaine dependence being the most frequent comorbid substance abuse problem. These findings represent a significant change from earlier studies, in which alcoholism was the most common secondary substance abuse problem (Rounsaville et al. 1982).

Clinicians have more recently become more aware of elevated rates of posttraumatic stress disorder (PTSD) in both men and women with opioid dependence (Hien et al. 2000). A lifetime prevalence of PTSD of 20% in women and 11% in men was found in one sample of methadone maintenance patients (Villagomez et al. 1995). Patients often deny a PTSD history during initial assessment. They should be reassessed after they have had the opportunity to develop trust in their treating clinicians.

Alcoholism

Opioid-dependent people who abuse alcohol appear to have greater psychological difficulties and to lead more unstable lives than opioid addicts without alcohol problems (Barr and Cohen 1987). Affective disorders and alcoholism often coexist in this population (Mirin et al. 1986; Rounsaville et al. 1982). Alcoholism apparently mitigates against successful treatment of opioid addiction (Green and Jaffe 1977; Joseph and Appel 1985). Psychological treatment for alcoholism may be provided, and naltrexone or disulfiram (Antabuse) can be used safely with methadone, but it is difficult to determine if such measures are beneficial (Ling et al. 1983).

Polydrug Use

Many opioid users are also dependent on nonopioids (Krausz et al. 1998). As is true when the secondary substance is alcohol, those with combined addictions have greater psychiatric problems (Hartog and Tusel 1987; Kosten et al. 1987c). Those who abuse nonopioids also appear to have greater difficulties in treatment programs and have poorer treatment outcomes. In one retrospective self-report study, abuse of nonopioids and particularly of cocaine was higher during periods of active opioid addiction than during periods of nonaddiction (Nurco et al. 1988).

A 2.5-year follow-up study of opioid addicts in methadone maintenance treatment found that prevalence of cocaine use only slightly declined and that

severity of cocaine use in users actually increased, particularly in those with depressive disorders (Kosten et al. 1987c). These data, which were obtained during the rising phase of a major cocaine epidemic, indicate that methadone and counseling alone are insufficient to prevent or ameliorate cocaine use. Pilot data from one program suggested that desipramine can decrease cocaine craving in methadone-maintained patients (Kosten et al. 1988), but other programs have not observed similar beneficial results (Arndt et al. 1990).

Affective Disorders

Affective disorders are the most common psychiatric problems in opioid addicts and are frequently associated with an anxiety disorder (Callaly et al. 2001; Milby et al. 1996). Many patients have subsyndromal depressive symptoms, rather than major depression. However, even without specific treatment for depression, many patients report less depression within the first few months after beginning treatment for opioid dependence (Mirin et al. 1988). In one study, current depression was seen in 25.9% of a sample but in only 12.7% at 2.5-year follow-up (Rounsaville et al. 1986a). Depressed patients were found to improve about equally in outpatient drug-free therapy, therapeutic communities, and methadone maintenance, when no correction for severity of depression was made in the analysis (Ginzburg et al. 1984). However, some patients who have no symptoms initially may develop them during the course of treatment.

Lithium and mood-stabilizing anticonvulsants, which can be combined safely with methadone and naltrexone (although clinicians should monitor for drug-drug interactions), should be considered for patients with bipolar disorder. Controlled studies of antidepressants have yielded mixed results. Some studies have not shown that such treatment results in significant improvement beyond that seen with placebo (Kleber et al. 1983), but plasma samples were not obtained in that study to ensure therapeutic levels. In other studies, depressed patients receiving methadone maintenance responded better to doxepin than to placebo (Woody et al. 1975). If symptoms of major depression persist after a patient is stabilized while taking methadone, antidepressant treatment should be initiated. Nunes et al. (1998) showed a greater improvement in depression with imipramine treatment, compared with placebo, in a trial involving 137 methadone patients with primary or chronic depressive disorders that persisted during abstinence. Imipramine was also superior in

measures of self-reported drug use and craving, although abstinence was uncommon. Methadone impairs metabolism of tricyclic antidepressants, so that clinical responses or side effects may be seen with relatively low doses (Kosten et al. 1990; Maany et al. 1989). There have been mixed, but mostly negative, results for the use of selective serotonin reuptake inhibitors (SSRIs) in this population (Petrakis et al. 1998). In a randomized trial of fluoxetine, both the study group and the control group showed similar improvement in depressive symptoms (Dean et al. 2002). Hamilton and associates (2000) reported success using sertraline in methadone patients, but they noted that sertraline produced a increase in methadone plasma levels. Fluvoxamine and, to a lesser degree, fluoxetine inhibit methadone metabolism (Alderman and Frith 1999; Bertschy et al. 1996). The cytochrome P450 enzyme 3A4 (CYP3A4) plays a major role in methadone metabolism, and inhibitors of that enzyme (e.g., fluvoxamine) increase methadone levels. Paroxetine and fluoxetine may also increase methadone levels, suggesting that its metabolism is more complicated, perhaps involving CYP2D6, CYP2C9, and CYP2C19 (Jaffe et al. 2004).

Anxiety

Anxiety disorders are common in the population of opioid-addicted individuals; however, treatment studies are lacking. It is uncertain whether the frequency of anxiety disorders contributes to high rates of illicit use of benzodiazepines, which is common in methadone maintenance programs (Ross and Darke 2000). Increased toxicity has been observed when benzodiazepines are co-administered with some opioids (Borron et al. 2002; Caplehorn and Drummer 2002). Although there is an interesting report of clonazepam maintenance treatment for methadone maintenance patients who abuse benzodiazepines, further studies are needed (Bleich et al. 2002). Unfortunately, buspirone, which has low abuse liability, was not effective in an anxiety treatment study in opioid-dependent subjects (McRae et al. 2004). Current clinical practice is to prescribe SSRIs or other antidepressants that have anti-anxiety actions for these patients. Carefully controlled benzodiazepine prescribing is advocated by some practitioners.

Schizophrenia

Schizophrenia is seen in less than 1% of those treated for opioid dependence (Rounsaville et al. 1982). Opioids appear to have antidopaminergic effects

and thus may have an antipsychotic action. Antipsychotic medications can be used along with methadone, LAAM, buprenorphine, or naltrexone; however, drugs that prolong the QTc interval should be avoided.

Conclusion

Opioid dependence has been recognized as a problem in the United States since the end of the nineteenth century. In 1914, the Harrison Narcotics Act prohibited medical maintenance of addicts and effectively eliminated all treatment for opioid addiction. The problem, however, was not eliminated, and the number of addicts grew steadily over the next 50 years. The reintroduction of maintenance treatment with methadone in 1964 demonstrated that treated addicts could be returned to productive lives and ushered in a new era of scientific and medical interest in opioid addiction. Despite the successes of therapeutic communities and methadone treatment, less than 10% of the addicted population was ever engaged in treatment, and the problem continued to grow. The availability of cheap and very high quality heroin during the 1990s produced a new generation of abusers, many of whom became addicted by snorting heroin that was more than 90% pure. This group, combined with abusers of synthetic opioids such as oxycodone, has almost doubled the incidence of opioid-related problems in many urban areas in the past 15 years. The lifetime prevalence of heroin use has grown to 1.2% for individuals age 12 years and older, and the lifetime prevalence of the nonmedical use of pain medications has increased to 8.6% (Substance Abuse and Mental Health Services Administration 2004). Use patterns typically involve periods of alternating use and abstinence. Although many addicts recover without treatment, for those addicts who seek treatment, addiction is usually a lifelong condition (Hser et al. 2001).

There has been major progress in our understanding of the actions of the opioids and of the risk factors associated with dependence. Most opioid drugs act at the μ opioid receptor. Polymorphisms in the receptor gene can alter the effect of opioid agonists on the receptor and may be associated with an increased risk for dependence. Repeated use is driven by stimulation of the pleasure centers of the brain and by the drugs' capacity to reduce noxious stimuli such as pain or anxiety. Peer pressure and environmental factors are strongly associated with use patterns. Single-parent families, poor schools, and high

unemployment, as well as a family history of depression or antisocial personality disorder, are all associated with an increased risk for use and abuse.

Physiologic dependence as manifested by both tolerance and withdrawal appears after 1–2 weeks of regular use. Withdrawal is associated with both objective changes (elevated vital sign measures, dilated pupils, sweating, etc.) and subjective complaints such as dysphoria, fatigue, and craving. Options for the medical management of this syndrome include full agonists such as methadone, the partial agonist buprenorphine, and α_2-adrenergic agonists such as clonidine. Clonidine suppresses only the autonomic symptoms of withdrawal and has little effect on subjective complaints. Methadone and buprenorphine more effectively attenuate the full withdrawal syndrome. Regardless of the medication used, there is a very high rate of relapse after detoxification treatment. Techniques for rapid detoxification coupled with transition to opioid antagonist (naltrexone) treatment have done little to improve rates of long-term abstinence. Relapse is less likely in patients who were previously stable with methadone maintenance, have utilized professional counseling services, and are detoxified very slowly.

The last 50 years have seen the development of a range of treatment options. They include detoxification, usually followed by drug-free outpatient counseling; opioid-substitution therapy with methadone, LAAM, or buprenorphine; antagonist therapy; therapeutic communities; and 12-step programs. These choices remain controversial, despite clear evidence documenting the effectiveness of therapeutic communities and opioid substitution therapy. Success in methadone substitution therapy is associated with adequate dosage (80–120 mg/day) effects, extended time in treatment, provision of profession counseling services, and treatment for comorbid psychiatric conditions. Stable patients may be given up to a 30-day supply of take-home medication if they have been free from illicit drug use for more than 2 years. The partial opioid agonist buprenorphine, in a sublingual tablet combined with naloxone, was introduced in 2002, permitting opioid-substitution therapy in office-based settings. Buprenorphine is recommended for younger patients with smaller habits and shorter histories of dependence. Methadone is preferred for older addicts with larger habits.

The management of comorbid medical and psychiatric conditions has become an essential component of effective opioid addiction treatment. Hepatitis C has now surpassed AIDS as the most common cause of death in

methadone maintenance patients in many areas of the United States. Affective disorders, alcoholism, and antisocial personality disorder are the most common comorbid psychiatric conditions, followed by phobic disorder and posttraumatic stress disorder. By the late 1990s, concurrent cocaine abuse had replaced alcoholism as the most common secondary substance abuse problem. Although there have been relatively few studies of the treatment of these concurrent conditions, it appears that opioid addicts with concurrent affective disorders respond better to tricyclic antidepressants than they do to the SSRIs. Untreated concomitant psychopathology is the most common cause for failure in opioid addiction treatment.

The approval of buprenorphine for use in the private office setting represents a significant shift in public policy for the management of opioid dependence. It is hoped that the availability of buprenorphine in these settings will not only expand effective treatment options but will also engage younger patients who have traditionally avoided methadone treatment. This new treatment option, coupled with recognition of the need to treat comorbid psychiatric conditions, holds great promise for the development of a more effective treatment system for this major health problem.

References

Alderman CP, Frith PA: Fluvoxamine-methadone interaction. Aust N Z J Psychiatry 33:99–101, 1999

Alvarez FJ, Carmen del Rio M: Ultrarapid opiate detoxification: a look at what is happening in Spain. Addiction 94:1239–1240, 1999

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition. Washington, DC, American Psychiatric Association, 1980

Anglin MD, Brecht, ML, Woodward JA, et al: An empirical study of maturing out: conditional factors. Int J Addict 21:233–246, 1986

Angst MS, Drover DR, Lotsch J, et al: Pharmacodynamics of orally administered sustained-release hydromorphone in humans. Anesthesiology 94:63–73, 2001

Arndt I, Dorozynsky L, McLellan AT, et al: Desipramine treatment of cocaine abuse in methadone maintenance patients. NIDA Res Monogr Ser 95:322–323, 1990

Auriacombe M, Loustauneau A: Medical treatment of the pregnant heroin addict: review of the literature, in Pregnancy and Drug Misuse Update 2000. Proceedings: Seminar Organized by the Co-operation Group to Combat Drug Abuse and Illicit Trafficking in Drugs (Pompidou Group), Strasbourg, France, May 29–30, 2000. Strasbourg, France, Drugs and Addiction Council of Europe, 2000–2001, pp 39–74

Bale RN, Zarcone VP, VanStone WW, et al: Three therapeutic communities: a prospective controlled study of narcotic addiction treatment; process and two-year follow-up results. Arch Gen Psychiatry 41:185–191, 1984

Ball JC, Ross A: The Effectiveness of Methadone Maintenance Treatment. New York, Springer-Verlag, 1991

Ball J, Corty E, Bond H, et al: The reduction of intravenous heroin use, non-opiate use and crime during methadone maintenance treatment: further findings. NIDA Res Monogr 81:224–230, 1988a

Ball JC, Lange WR, Myers CP, et al: Reducing the risk of AIDS through methadone maintenance treatment. J Health Soc Behav 29:214–226, 1988b

Bare LA, Mansson E, Yang D: Expression of two variants of the human mu opioid receptor mRNA in SK-N-SH cells and human brain. FEBS Lett 354:213–216, 1994

Barr HL, Cohen A: Abusers of alcohol and narcotics: who are they? Int J Addict 22:525–541, 1987

Bastos FI, Barcellos C, Lowndes CM, et al: Co-infection with malaria and HIV in injecting drug users in Brazil: a new challenge to public health? Addiction 94:1165–1174, 1999

Baum C, Hsu JP, Nelson RC: The impact of the addition of naloxone on the use and abuse of pentazocine. Public Health Rep 102:426–429, 1987

Bell J, Seres V, Bowron P, et al: The use of serum methadone levels in patients receiving methadone maintenance. Clin Pharmacol Ther 43:623–629, 1988

Bell J, Bowron P, Lewis J, et al: Serum levels of methadone in maintenance clients who persist in illicit drug use. Br J Addict 85:1599–1602, 1990

Bell JR, Young MR, Masterman SC, et al: A pilot study of naltrexone-accelerated detoxification in opioid dependence. Med J Aust 171:26–30, 1999

Bertschy G, Eap CB, Powell K, et al: Fluoxetine addition to methadone in addicts: pharmacokinetic aspects. Ther Drug Monit 18:570–572, 1996

Bickel WK, Johnson RE, Stitzer ML, et al: A clinical trial of buprenorphine, I: comparison with methadone in the detoxification of heroin addicts, II: examination of its opioid blocking properties. NIDA Res Monogr 76:182–188, 1987

Bisaga A, Comer SD, Ward AS, et al: The NMDA antagonist memantine attenuates the expression of opioid physical dependence in humans. Psychopharmacology (Berl) 157:1–10, 2001

Bleich A, Gelkopf M, Weizman T, et al: Benzodiazepine abuse in a methadone maintenance treatment clinic in Israel: characteristics and a pharmacotherapeutic approach. Isr J Psychiatry Relat Sci 39:104–112, 2002

Bohn LM, Gainetdinov RR, Lin FT, et al: Mu-opioid receptor desensitization by beta-arrestin-2 determines morphine tolerance but not dependence. Nature 408:720–723, 2000

Bond C, LaForge KS, Tian M, et al: Single-nucleotide polymorphism in the human mu opioid receptor gene alters beta-endorphin binding and activity: possible implications for opiate addiction. Proc Natl Acad Sci U S A 95:9608–9613, 1998

Borron SW, Monier C, Risede P, et al: Flunitrazepam variably alters morphine, buprenorphine, and methadone lethality in the rat. Hum Exp Toxicol 21:599–605, 2002

Brewer C, Maksoud NA: Opiate detoxification under anesthesia. JAMA 278:1318–1319, 1997

Brewer C, Williams J, Rendueles EC, et al: Unethical promotion of rapid opiate detoxification under anaesthesia (RODA) (letter). Lancet 351(9097):218, 1998

Brooner RK, King VL, Kidorf M, et al: Psychiatric and substance abuse comorbidity among treatment-seeking opioid abusers. Arch Gen Psychiatry 54:71–80, 1997

Brown BS, Watters JK, Iglehart AS: Methadone maintenance dosage levels and program retention. Am J Drug Alcohol Abuse 9:129–139, 1982–1983

Brown LS, Hickson MJ, Ajuluchukwu DC, et al: Medical disorders in a cohort of New York City drug abusers: much more than HIV disease. J Addict Dis 12:11–27, 1993

Cacciola JS, Alterman AI, Rutherford MJ, et al: The relationship of psychiatric comorbidity to treatment outcomes in methadone maintained patients. Drug Alcohol Depend 61:271–280, 2001

Callaly T, Trauer T, Munro L, et al: Prevalence of psychiatric disorder in a methadone maintenance population. Aust N Z J Psychiatry 35:601–605, 2001

Caplehorn JR, Drummer OH: Fatal methadone toxicity: signs and circumstances, and the role of benzodiazepines. Aust N Z J Public Health 26:358–363, 2002

Capone T, Brahen L, Condren R, et al: Retention and outcome in a narcotic antagonist treatment program. J Clin Psychol 42:825–833, 1986

Carbone A, Manconi R, Poletti A, et al: A histopathologic study of persistent generalized lymphadenopathy in intravenous drug abusers. Pathol Res Pract 181:195–199, 1986

Carroll KM, Ball SA, Nich C, et al: Targeting behavioral therapies to enhance naltrexone treatment of opioid dependence. Arch Gen Psychiatry 58:755–761, 2001

Centers for Disease Control and Prevention: Recommendation for prevention and control of hepatitis (virus (HCV) infection and HCV-related chronic disease. MMWR Recommendations and Reports 47(RR19):1–39, 1998

Charney DS, Steinberg DE, Kleber HD, et al: The clinical use of clonidine in abrupt withdrawal from methadone. Arch Gen Psychiatry 38:1273–1277, 1981

Charney DS, Heninger OR, Kleber HD: The combined use of clonidine and naltrexone as a rapid, safe, and effective treatment of abrupt withdrawal from methadone. Am J Psychiatry 143:831–837, 1986

Chen L, Huang LY: Sustained potentiation of NMDA receptor-mediated glutamate responses through activation of protein kinase C by a mu opioid. Neuron 7:319–326, 1991

Cheskin LJ, Fudala PJ, Johnson RE: A controlled comparison of buprenorphine and clonidine for acute detoxification from opioids. Drug Alcohol Depend 36:115–121, 1994

Childress AR, McLellan AT, Ehrman R, et al: Classically conditioned responses in opioid and cocaine dependence: a role in relapse? NIDA Res Monogr 84:25–43, 1988

Ciraulo DA, Ciraulo AN: Substance abuse, in Handbook of Clinical Psychopharmacology. Edited by Tupin JP, Shader RI, Harnett DS. Northvale, NJ, Jason Aronson, 1988, p 143

Ciraulo DA, Piechniczek-Buczek J, Iscan EN: Outcome predictors in substance use disorders. Psychiatr Clin N Am 26:381–409, 2003

Clark MJ, Harrison C, Zhong H, et al: Endogenous RGS protein action modulates mu-opioid signaling through Galphao: effects on adenylyl cyclase, extracellular signal-regulated kinases, and intracellular calcium pathways. J Biol Chem 278: 9418–9425, 2003

Clayton RR, Voss HL: Young men and drugs in Manhattan: a causal analysis. NIDA Res Monogr 39:1–187, 1981

Community Epidemiology Workgroup: Epidemiologic Trends in Drug Abuse Advanced Report (NIH Publ No 04-5363). Bethesda, MD, National Institute on Drug Abuse, December 2003

Cooper OB, Brown TT, Dobs AS: Opiate drug use: a potential contributor to the endocrine and metabolic complications in human immunodeficiency virus disease. Clin Infect Dis 37(suppl 2):S132–S136, 2003

Cushman P, Dole VP: Detoxification of rehabilitated methadone-maintained patients. JAMA 226:747–752, 1973

Dashe JS, Jackson GL, Olscher DA, et al: Opioid detoxification in pregnancy. Obstet Gynecol 92:854–858, 1998

Dean AJ, Bell J, Mascord DJ, et al: A randomized, controlled trial of fluoxetine in methadone maintenance patients with depressive symptoms. J Affect Disord 72: 85–90, 2002

DeLeon G: The therapeutic community: status and evolution. Int J Addict 20:823–844, 1985

Delfs JM, Zhu Y, Druhan JP, et al: Noradrenaline in the ventral forebrain is critical for opiate withdrawal-induced aversion. Nature 403:430–434, 2000

Des Jarlais DC, Perlis T, Friedman SR, et al: Declining seroprevalence in a very large HIV epidemic: injecting drug users in New York City, 1991–1996. Am J Public Health 88:1801–1806, 1998

Dole VP: Implications of methadone maintenance for theories of narcotic addiction. JAMA 260:3025–3029, 1988

Dole VP, Joseph H: Long-term outcome of patients treated with methadone. Ann NY Acad Sci 311:181–189, 1978

Dole VP, Nyswander MN: A medical treatment for diacetylmorphine (heroin) addiction. JAMA 193:646–650, 1965

Dole VP, Nyswander MN: Heroin addiction: a metabolic disease. Arch Intern Med 120:19–24, 1967

Finnegan LP, Michael H, Leifer B, et al: An evaluation of neonatal abstinence treatment modalities. NIDA Res Monogr 49:282–288, 1984

Fischer G, Etzersdorfer P, Eder H, et al: Buprenorphine maintenance in pregnant opiate addicts. Eur Addict Res 4(suppl 1):32–36, 1998

Fram DH, Marmo J, Holden R: Naltrexone treatment: the problem of patient acceptance. J Subst Abuse Treat 6:119–122, 1989

Francis H: Substance abuse and HIV infection. Top HIV Med 11:20–24, 2003

Fudala PJ, Jaffe JH, Dax EM, et al: Use of buprenorphine in the treatment of opioid addiction, II: physiologic and behavioral effects of daily and alternate-day administration and abrupt withdrawal. Clin Pharmacol Ther 47:525–534, 1990

Gerra G, Zaimovic A, Rustichelli P, et al: Rapid opiate detoxification in outpatient treatment: relationship with naltrexone compliance. J Subst Abuse Treat 18:185–191, 2000

Gerstein DR, Harwood HJ (eds): Treating Drug Problems, Vol 1: A Study of the Evolution, Effectiveness, and Financing of Public and Private Drug Treatment Systems. Washington, DC, National Academy Press, 1990

Ginzburg HM: Naltrexone: its clinical utility (NIDA Treatment Research Report ADM-84-1358). Washington, DC, U.S. Government Printing Office, 1984

Ginzburg HM, Allison M, Hubbard RL: Depressive symptoms in drug abuse treatment clients: correlates, treatment and changes. NIDA Res Monogr 49:313–319, 1984

Gold MS, Redmond DE, Kleber HD: Clonidine in opiate withdrawal. Lancet 1:929–930, 1978

Gordon DB, Stevenson KK, Griffie J, et al: Opioid equianalgesic calculations. J Palliat Med 2:209–218, 1999

Gossop M, Bradley B, Phillips GT: An investigation of withdrawal symptoms shown by opiate addicts during and subsequent to a 21-day in-patient methadone detoxification procedure. Addict Behav 12:1–6, 1987

Green J, Jaffe JH: Alcohol and opiate dependence. J Stud Alcohol 38:1274–1293, 1977

Green L, Gossop M: Effects of information on the opiate withdrawal syndrome. Br J Addict 83:305–309, 1988

Gutstein HB, Akil H: Opioid analgesics, in Goodman and Gilman's The Pharmacological Basis of Therapeutics, 10th Edition. Edited by Hardman JG, Limbird LE, Gilman AG. New York, McGraw-Hill, 2001, pp 569–619

Hamilton SP, Nunes EV, Janal M, et al: The effect of sertraline on methadone plasma levels in methadone-maintained patients. Am J Addict 9:63–69, 2000

Hartog J, Tusel DJ: Valium use and abuse by methadone maintenance clients. Int J Addict 22:1147–1154, 1987

Herrington RE, Benzer DG, Jacobson GR, et al: Treating substance use disorders among physicians. JAMA 247:2253–2257, 1982

Heishman SJ, Stitzer ML, Bigelow GE, et al: Acute opioid physical dependence in postaddict humans: naloxone dose effects after brief morphine exposure. J Pharmacol Exp Ther 248:127–134, 1989

Hien DA, Nunes E, Levin FR, et al: Posttraumatic stress disorder and short-term outcome in early methadone treatment. J Subst Abuse Treat 19:31–37, 2000

Himmelsbach CK: The morphine abstinence syndrome, its nature and treatment. Ann Intern Med 15:829–839, 1941

Hollister LE, Johnson K, Bowkhabza, et al: Aversive effects of naltrexone in subjects not dependent on opiates. Drug Alcohol Depend 8:37–41, 1981

Honer J, Gordon SM, Snyderan R: Heroin-addicted patient characteristics and drug use histories (unpublished data). Wernersville, PA, Caron Foundation, 2001

Hser YI, Hoffman V, Grella CE, et al: A 33-year follow-up of narcotic addicts. Arch Gen Psychiatry 58:503–508, 2001

Hubbard RL, Marsden ME, Rachal JV, et al: Drug Abuse Treatment: A National Study of Effectiveness. Chapel Hill, University of North Carolina Press, 1989

Hunt DE, Lipton DS, Goldsmith DS, et al: "It takes your heart": the image of methadone maintenance in the addict world and its effect on recruitment into treatment. Int J Addict 20:1751–1771, 1985–1986

Jaffe JH: Drug dependence: opioids, nonnarcotics, nicotine (tobacco), and caffeine, in Comprehensive Textbook of Psychiatry, 5th Edition, Vol 1. Edited by Kaplan HI, Sadock BJ. Baltimore, Williams & Wilkins, 1989, pp 642–686

Jaffe J, Knapp CM, Ciraulo DA: Opiates: clinical aspects, in Substance Abuse: A Comprehensive Textbook. Edited by Lowinson JH, Ruiz P, Millman RB, et al. New York, Lippincott Williams and Wilkins, 2004, pp 158–165

Jarvis MA, Schnoll SH: Methadone use during pregnancy. NIDA Res Monogr 149:58–77, 1995

Jasinski DR, Pevnick JS, Griffith JD: Human pharmacology and abuse potential of the analgesic buprenorphine. Arch Gen Psychiatry 35:501–516, 1978

Jasinski DR, Johnson RE, Kocher TR: Clonidine in morphine withdrawal: differential effects on signs and symptoms. Arch Gen Psychiatry 42:1063–1066, 1985

Joe GW, Simpson DO: Mortality rates among opioid addicts in a longitudinal study. Am J Public Health 77:347–348, 1987

Johnson RE, Chutuape MA, Strain EC, et al: A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. N Engl J Med 343:1290–1297, 2000

Johnson RE, Jones HE, Fischer G: Use of buprenorphine in pregnancy: patient management and effects on the neonate. Drug Alcohol Depend 20(suppl 2):S87–S101, 2003

Jones RT: Dependence in non-addict humans after a single dose of morphine, in Endogenous and exogenous opiate agonists and antagonists. Edited by Way EL. New York, Pergamon, 1979, pp 557–560

Joseph H, Appel P: Alcoholism and methadone treatment: consequences for the patient and program. Am J Drug Alcohol Abuse 11:37–53, 1985

Kakko J, Svanborg KD, Kreek MJ, et al: 1-year retention and social functioning after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomized, placebo-controlled trial. Lancet 361(9358):662–668, 2003

Kaltenbach K, Berghella V, Finnegan L: Opioid dependence during pregnancy: effects and management. Obstet Gynecol Clin North Am 25:139–151, 1998

Kandel D, Faust R: Sequence and stages in patterns of adolescent drug use. Arch Gen Psychiatry 32:923–932, 1975

Kang J, Chen XL, Wang H, et al: Interactions of the narcotic 1-alpha-acetylmethadol with human cardiac K+ channels. Eur J Pharmacol 458:25–29, 2003

Katchman AN, McGroary KA, Kilborn MJ, et al: Influence of opioid agonists on cardiac human ether-a-go-go-related gene K(+) currents. J Pharmacol Exp Ther 303:688–694, 2002

Kaufman E: A contemporary approach to the family treatment of substance abuse disorders. Am J Drug Alcohol Abuse 12:199–211, 1986

Kayemba-Kay's S, Laclyde JP: Buprenorphine withdrawal syndrome in newborns: a report of 13 cases. Addiction 98:1599–1604, 2003

Keith DE, Anton B, Murray SR, et al: mu-Opioid receptor internalization: opiate drugs have differential effects on a conserved endocytic mechanism in vitro and in the mammalian brain. Mol Pharmacol 53:377–384, 1998

Khantzian EJ, Treece T: DSM-III psychiatric diagnosis of narcotic addicts: recent findings. Arch Gen Psychiatry 42:1067–1071, 1985

King VL, Stoller KB, Hayes M, et al: A multicenter randomized evaluation of methadone medical maintenance. Drug Alcohol Depend 65:137–148, 2002

Kleber HD: Detoxification from narcotics, in Substance Abuse: Clinical Problems and Perspectives. Edited by Lowinson J, Ruiz P. Baltimore, MD, Williams & Wilkins, 1981, pp 317–338

Kleber HD: Ultrarapid opiate detoxification. Addiction 93:1629–1633, 1998

Kleber HD, Kosten TR: Naltrexone induction: psychologic and pharmacologic strategies. J Clin Psychiatry 45:29–38, 1984

Kleber HD, Weissman MM, Rounsaville BJ, et al: Imipramine as treatment for depression in addicts. Arch Gen Psychiatry 40:649–653, 1983

Kleber HD, Riordan CE, Rounsaville BJ, et al: Clonidine in outpatient detoxification from methadone maintenance. Arch Gen Psychiatry 42:391–394, 1985

Kleber HD, Topazian M, Gaspari J, et al: Clonidine and naltrexone in the outpatient treatment of heroin withdrawal. Am J Drug Alcohol Abuse 13:1–17, 1987

Kornetsky C. Brain stimulation reward, morphine-induced stereotypy, and sensitization: implications for abuse. Neurosci Biobehav Rev 27:777–786, 2004

Kosten TR, Kleber HD: Buprenorphine detoxification from opioid dependence: a pilot study. Life Sci 42:635–641, 1988

Kosten TR, Rounsaville BJ, Kleber HD: A 2.5-year follow-up of depression, life crises, and treatment effects on abstinence among opioid addicts. Arch Gen Psychiatry 43:733–738, 1986a

Kosten TR, Rounsaville BJ, Kleber HD: A 2.5 year follow-up of treatment retention and reentry among opioid addicts. J Subst Abuse Treat 3:181–189, 1986b

Kosten TR, Rounsaville BJ, Kleber HD: Multidimensionality and prediction of treatment outcome in opioid addicts: 2.5-year follow-up. Compr Psychiatry 28:3–13, 1987a

Kosten TR, Rounsaville BJ, Kleber HD: Predictors of 2.5-year outcome in opioid addicts: pretreatment source of income. Am J Drug Alcohol Abuse 13:19–32, 1987b

Kosten TR, Rounsaville BJ, Kleber HD: A 2.5-year follow-up of cocaine use among treated opioid addicts. Arch Gen Psychiatry 44:281–284, 1987c

Kosten TR, Gawin F, Schumann B: Treating cocaine abusing methadone maintenance patients with desipramine. NIDA Res Monogr 81:237–241, 1988

Kosten TR, Gawin F, Morgan C, et al: Evidence for altered desipramine disposition in methadone-maintained patients treated for cocaine abuse. Am J Drug Alcohol Abuse 16:329–336, 1990

Kornick CA, Kilborn MJ, Santiago-Palma J, et al: QTc interval prolongation associated with intravenous methadone. Pain 105:499–506, 2003

Krantz MJ, Lewkowiez L, Hays H, et al: Torsade de pointes associated with very-high-dose methadone. Ann Intern Med 137:501–504, 2002

Krantz MJ, Kutinsky IB, Robertson AD, et al: Dose-related effects of methadone on QT prolongation in a series of patients with torsade de pointes. Pharmacotherapy 23:802–805, 2003

Krausz M, Degkwitz P, Kuhne A, et al: Comorbidity of opiate dependence and mental disorders. Addict Behav 23:767–783, 1998

Krausz M, Verthein U, Degkwitz P: Psychiatric comorbidity in opiate addicts. Eur Addict Res 5:55–62, 1999

Kreek MJ: Methadone in treatment: physiological and pharmacological issues, in Handbook on Drug Abuse. Edited by Dupont RL, Goldstein A, O'Donnell J. Washington, DC, U.S. Government Printing Office, 1979, pp 57–86

Kreek MJ: Health consequences associated with the use of methadone, in Research on the Treatment of Narcotic Addiction: State of the Art (NIDA Research Monograph ADM-83-1281). Edited by Cooper JR, Altman R, Brown BS, et al. Washington, DC, U.S. Government Printing Office, 1983, pp 456–482

Lacroix I, Berrebi A, Chaumerliac C, et al: Buprenorphine in pregnant opioid-dependent women: first results of a prospective study. Addiction 99:209–214, 2004

Li JG, Luo LY, Krupnick, JG, et al: U50,488H-induced internalization of the human kappa opioid receptor involves a beta-arrestin- and dynamin-dependent mechanism: kappa receptor internalization is not required for mitogen-activated protein kinase activation. J Biol Chem 274:12087–12094, 1999

Ling W, Klett CJ, Gillis RD: A cooperative clinical study of methadyl acetate. Arch Gen Psychiatry 35:345–353, 1978

Ling W, Weiss DG, Charuvastra VC, et al: Use of disulfiram for alcoholics in methadone maintenance programs. Arch Gen Psychiatry 40:851–854, 1983

Ling W, Charuvastra C, Collins JF, et al: Buprenorphine maintenance treatment of opiate dependence: a multi-center, randomized clinical trial. Addiction 93:475–486, 1998

Lotsch J, Zimmermann M, Darimont J, et al: Does the A118G polymorphism at the mu-opioid receptor gene protect against morphine-6-glucuronide toxicity? Anesthesiology 97:814–819, 2002

Luty J, Nikolaou V, Bearn J: Is opiate detoxification unsafe in pregnancy? J Subst Abuse Treat 24:363–367, 2003

Maany I, Dhopesh V, Arndt IO, et al: Increase in desipramine serum levels associated with methadone treatment. Am J Psychiatry 146:1611–1613, 1989

Maas U, Kattner E, Weingart-Jesse B, et al: Infrequent neonatal opiate withdrawal following maternal methadone detoxification during pregnancy. J Perinat Med 18:111–118, 1990

Magura S, Goldsmith D, Casriel C, et al: The validity of methadone clients' self-reported drug use. Int J Addict 22:727–749, 1987

Maldonado R, Blendy JA, Tzavara E, et al: Reduction of morphine abstinence in mice with a mutation in the gene encoding CREB. Science 273:657–659, 1996

Marsden J, Gossop M, Stewart D, et al: Psychiatric symptoms among clients seeking treatment for drug dependence. Intake data from the National Treatment Outcome Research Study. Br J Psychiatry 176:285–289, 2000

Martin WR, Jasinski DR, Haertzen CA, et al: Methadone: a reevaluation. Arch Gen Psychiatry 28:286–295, 1973

Mayer P, Höllt V: Allelic and somatic variations in the endogenous opioid system of humans. Pharmacol Ther 91:167–177, 2001

McCaul ME, Bigelow GE, Stitzer ML, et al: Short-term effects of oral methadone in methadone maintenance subjects. Clin Pharmacol Ther 31:753–761, 1982

McLellan AT: "Psychiatric severity" as a predictor of outcome from substance abuse treatments, in Psychopathology and Addictive Disorders. Edited by Meyer RE. New York, Guilford, 1986, pp 97–139

McLellan AT, Luborsky L, Woody GE, et al: Predicting responses to alcohol and drug abuse treatments: role of psychiatric severity. Arch Gen Psychiatry 40:620–625, 1983

McLellan AT, Childress AR, Ehrman R, et al: Extinguishing conditioned responses during opiate dependence treatment; turning laboratory findings into clinical procedures. J Subst Abuse Treat 3:33–40, 1986

McNicholas L, Howell EF: Buprenorphine Clinical Practice Guidelines, Field Review Draft November 17, 2000. Rockville, MD, U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Substance Abuse Treatment, Office of Pharmacologic and Alternative Therapies, 2000

McRae AL, Sonne SC, Brady KT, et al: A randomized, placebo-controlled trial of buspirone for the treatment of anxiety in opioid-dependent individuals. Am J Addict 13:53–63, 2004

Mello NK, Mendelson JH: Buprenorphine suppresses heroin use by heroin addicts. Science 207:657–659, 1980

Menk EJ, Baumgarten RK, Kingsley CP, et al: Success of reentry into anesthesiology training programs by residents with a history of substance abuse. JAMA 263: 3060–3062, 1990

Meyer RE, Mirin SM: The Heroin Stimulus: Implication for a Theory of Addiction. New York, Plenum, 1979

Milby JB, Gurwitch RH, Wiebe DJ, et al: Prevalence and diagnostic reliability of methadone maintenance detoxification fear. Am J Psychiatry143:739–743, 1986

Milby JB, Sims, MK, Khuder S, et al: Psychiatric comorbidity: prevalence in methadone maintenance treatment. Am J Drug Alcohol Abuse 22:95–107, 1996

Mirin SM, Weiss RD, Michael J: Family pedigree of psychopathology in substance abusers, in Psychopathology and Addictive Disorders. Edited by Meyer RE. New York, Guilford, 1986, pp 57–77

Mirin SM, Weiss RD, Michael J: Psychopathology in substance abusers: diagnosis and treatment. Am J Drug Alcohol Abuse 14:139–157, 1988

Mitchell JE, Morley JE, Levine AS, et al: High dose naltrexone therapy and dietary counseling for obesity. Biol Psychiatry 22:35–42, 1987

Musto DF: The American Disease: Origins of Narcotic Control, Expanded Edition. New York, Oxford University Press, 1987

National Research Council: Clinical evaluation of naltrexone treatment of opiate-dependent individuals: report of the National Research Council Committee on Clinical Evaluation of Narcotic Antagonists. Arch Gen Psychiatry 35:335–340, 1978

Nestler EJ, Hyman SE, Malenka RC: Molecular Neuropharmacology: A Foundation for Clinical Neuroscience. New York, McGraw Hill, 2001

Novick DM, Pascarelli EF, Joseph H, et al: Methadone maintenance patients in general medical practice: a preliminary report. JAMA 259:3299–3302, 1988

Nunes EV, Quitkin FM, Donovan SJ, et al.: Imipramine treatment of opiate-dependent patients with depressive disorders: a placebo-controlled trial. Arch Gen Psychiatry 55:153–160, 1998

Nurco DN, Kinlock TW, Hanlon TE, et al: Nonnarcotic drug use over an addiction career: a study of heroin addicts in Baltimore and New York City. Compr Psychiatry 29:450–459, 1988

O'Connor PG, Carroll KM, Shi JM, et al: Three methods of opioid detoxification in a primary care setting: a randomized trial. Ann Intern Med 127:526–530, 1997

Oppenheimer E, Tobutt C, Taylor C, et al: Death and survival in a cohort of heroin addicts from London clinics: a 22-year follow-up study. Addiction 89:1299–1308, 1994

Pan YX, Xu J, Mahurter L, et al: Identification and characterization of two new human mu opioid receptor splice variants, hMOR-1O and hMOR-1X. Biochem Biophys Res Commun 301:1057–1061, 2003

Patel MB, Patel CN, Rajashekara V, et al: Opioid agonists differentially regulate μ-opioid receptors and trafficking proteins in vivo. Mol Pharmacol 62:1464–1470, 2002

Payte J, Khouri E: Principles of methadone dose determination, in State Methadone Treatment Guidelines. Improvement Protocol (TIP) Series 1 (DHHS Publ No SMA-93-1991). Edited by Parrino MW. Rockville, MD, U.S. Department of Health and Human Services, Center for Substance Abuse Treatment; 1993

Petrakis I, Carroll KM, Nich C, et al: Fluoxetine treatment of depressive disorders in methadone-maintained opioid addicts. Drug Alcohol Depend 50:221–226, 1998

Pfohl DN, Allen JI, Atkinson RL, et al. Naltrexone hydrochloride (Trexan): a review of serum transaminase elevations at high dosage. NIDA Res Monogr 67:66–72, 1986

Portenoy PM, Foley KM: Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. Pain 25:171–186, 1986

Potenza MN, Gold SJ, Roby-Shemkowitz A, et al: Effects of regulators of G protein-signaling proteins on the functional response of the mu-opioid receptor in a melanophore-based assay. J Pharmacol Exp Ther 291:482–491, 1999

Quaglio G, Talamini G, Lechi A, et al: Study of 2708 heroin-related deaths in northeastern Italy 1985–98 to establish the main causes of death. Addiction 96:1127–1137, 2001

Rabinowitz J, Cohen H, Kotler M: Outcomes of ultrarapid opiate detoxification combined with naltrexone maintenance and counseling. Psychiatr Serv 49:831–833, 1998

Reed PA, Schnoll SH: Abuse of pentazocine-naloxone combination. JAMA 256:2562–2564, 1986

Regier DA, Farmer ME, Rae DS, et al: Comorbidity of mental disorders with alcohol and other drug abuse. JAMA 264:2511–2518, 1990

Resnick RB, Schuyten-Resnick E, Washton AM: Assessment of narcotic antagonists in the treatment of opioid dependence. Annu Rev Pharmacol Toxicol 20:463–474, 1980

Ripamonti C, Groff L, Brunelli C, et al: Switching from morphine to oral methadone in treating cancer pain: what is the equianalgesic dose ratio? J Clin Oncol 16:3216–3221, 1998

Robins LN, Helzer JE, Davis DH: Narcotic use in Southeast Asia and afterwards. Arch Gen Psychiatry 32:955–961, 1975

Roehrich H, Gold MS: Propranolol as adjunct to clonidine in opiate detoxification. Am J Psychiatry 144:1099–1100, 1987

Roozen HG, Kerhof AJ, van den Brink W: Experiences with an outpatient relapse program (community reinforcement approach) combined with naltrexone in the treatment of opioid-dependence: effect on addictive behaviors and the predictive value of psychiatric comorbidity. Eur Addict Res 9:53–58, 2003

Rosen TS, Johnson HL: Long-term effects of prenatal methadone maintenance. NIDA Res Monogr 59:73–83, 1985

Ross J, Darke S: The nature of benzodiazepine dependence among heroin users in Sydney, Australia. Addiction 95:1785–1793, 2000

Rounsaville BJ, Kleber HD: Untreated opiate addicts. Arch Gen Psychiatry 42:1072–1077, 1985b

Rounsaville BJ, Weissman MM, Kleber HD, et al: Heterogeneity of psychiatric diagnosis in treated opiate addicts. Arch Gen Psychiatry 39:161–166, 1982

Rounsaville BJ, Kosten TR, Kleber HP: Long-term changes in current psychiatric diagnoses of treated opiate addicts. Compr Psychiatry 27:480–498, 1986a

Rounsaville BJ, Kosten TR, Weissman MM, et al: Prognostic significance of psychopathology in treated opiate addicts. Arch Gen Psychiatry 43:739–745, 1986b

Rounsaville BJ, Kosten TR, Kleber HD: The antecedents and benefits of achieving abstinence in opioid addicts: a 2.5-year follow-up study. Am J Drug Alcohol Abuse 13:213–229, 1987

San L, Arranz B: Pros and cons of ultrarapid opiate detoxification. Addiction 94:1240–1241, 1999

Sanchez-Carbonell X, Seus L: Ten-year survival analysis of a cohort of heroin addicts in Catalonia: the EMETYST project. Addiction 95:941–948, 2000

Schindler SD, Eder H, Ortner R, et al: Neonatal outcome following buprenorphine maintenance during conception and throughout pregnancy. Addiction 98:103–110, 2003

Seecof R, Tennant FS: Subjective perceptions to the intravenous "rush" of heroin and cocaine in opioid addicts. Am J Drug Alcohol Abuse 12:79–87, 1987

Sees KL, Delucci KL, Masson C, et al: Methadone maintenance vs. 180-day psychosocially enriched detoxification for treatment of opioid dependence: a randomized controlled trial. JAMA 283:1303–1310, 2000

Sells SB: Treatment effectiveness, in Handbook on Drug Abuse. Edited by Dupont RE, Goldstein A, O'Donnell J. Washington, DC, U.S. Government Printing Office, 1979, pp 105–118

Senay EC: Methadone maintenance treatment. Int J Addict 20:803–821, 1985

Senay EC, Dorus W, Goldberg F, et al: Withdrawal from methadone maintenance: rate of withdrawal and expectation. Arch Gen Psychiatry 34:361–367, 1977

Sharpe C, Kuschel C: Outcomes of infants born to mothers receiving methadone for pain management in pregnancy. Arch Dis Child Fetal Neonatal Ed 89:F33–F36, 2004

Shaw-Lutchman TZ, Barrot M, Wallace T, et al: Regional and cellular mapping of cAMP response element-mediated transcription during naltrexone-precipitated morphine withdrawal. J Neurosci 22:3663–3672, 2002

Shreeram SS, McDonald T, Dennison S: Psychosis after ultrarapid opiate detoxification (letter). Am J Psychiatry 158:970, 2001

Shi J, Hui L, Xu Y, et al: Sequence variations in the mu-opioid receptor gene (OPRM1) associated with human addiction to heroin. Hum Mutat 19:459–460, 2002

Shinderman M, Maxwell S, Brawand-Arney M, et al: Cytochrome P4503A4 metabolic activity, methadone blood concentrations, and methadone doses. Drug Alcohol Dependence 69:205–211, 2003

Simpson DD, Marsh KL: Relapse and recovery among opioid addicts 12 years after treatment. NIDA Res Monogr 72:86–103, 1986

Simpson DD, Joe GW, Bracy SA: Six-year follow-up of opioid addicts after admission to treatment. Arch Gen Psychiatry 39:1318–1323, 1982

Skarke C, Darimont J, Schmidt H, et al: Analgesic effects of morphine and morphine-6-glucuronide in a transcutaneous electrical pain model in healthy volunteers. Clin Pharmacol Ther 73:107–121, 2003

Spitzer RL, Endicott J, Robins E: Research Diagnostic Criteria: rationale and reliability. Arch Gen Psychiatry 35:773–782, 1978

Stafford K, Gomes AB, Shen J, et al: μ-Opioid receptor downregulation contributes to opioid tolerance in vivo. Pharmacol Biochem Behav 69:233–237, 2001

Stephenson J: Experts debate merits of 1-day opiate detoxification under anesthesia. JAMA 277:363–364, 1997

Stimmel B, Goldberg J, Rotkopf E, et al: Ability to remain abstinent after methadone detoxification: a six year study. JAMA 237:1216–1220, 1977

Stimson GV, Oppenheimer E: Heroin Addiction: Treatment and Control in Britain. London, Tavistock, 1982

Strang J, Bearn J, Gossop M: Lofexidine for opiate detoxification: review of recent randomized and open controlled trials. Am J Addict 8:337–348, 1999

Strang J, Bearn J, Gossop M: Opiate detoxification under anaesthesia. BMJ 315:1249–1250, 1997

Substance Abuse and Mental Health Services Administration: Emergency Department Trends from the Drug Abuse Warning Network, Preliminary Estimates January–June, 2001 with Revised Estimates 1994–2000 (DHHS Publ No SMA-02-3634). Rockville, MD, Substance Abuse and Mental Health Services Administration, 2001

Substance Abuse and Mental Health Services Administration: Emergency Department Trends From the Drug Abuse Warning Network, Preliminary Estimates January–June 2002 (DHHS Publ No SMA 03-3779). Rockville, MD, Substance Abuse and Mental Health Services Administration, 2002a. Available at: http://dawninfo.samhsa.gov/old_dawn/pubs_94_02/edpubs/2002prelim/files/EDTrendPrelim02Text.pdf. Accessed July 3, 2003.

Substance Abuse and Mental Health Services Administration: Overview of Findings from the 2003 National Survey on Drug Use and Health (DHHS Publ No SMA-04-3963). Rockville, MD, Substance Abuse and Mental Health Services Administration, 2004

Tan EC, Tan CH, Karupathivan U, et al: Mu opioid receptor gene polymorphisms and heroin dependence in Asian populations. Neuroreport 14:569–572, 2003

Tennant FS: Inadequate plasma concentrations in some high-dose methadone maintenance patients. Am J Psychiatry 144:1349–1350, 1987

Tennant FS: LAAM maintenance for opioid addicts who cannot maintain with methadone. NIDA Res Monogr 81:294, 1988

Tennant FS, Rawson RA, Pumphrey E, et al: Clinical experiences with 959 opioid-dependent patients treated with levo-alpha-acetylmethadol (LAAM). J Subst Abuse Treat 3:195–202, 1986

Tenore PL: Guidance on optimal methadone dosing. Addiction Treatment Forum 12(2) Spring, 2003, p 3

Tirelli U, Vaccher E, Carbone A, et al: Lymphangiography and abdominal computerized tomography in persistent generalized lymphadenopathy. AIDS Res 2:149–153, 1986

Trueblood B, Judson BA, Goldstein A: Acceptability of methadyl acetate (L-AAM) as compared with methadone in a treatment program for heroin addicts. Drug Alcohol Depend 3:125–132, 1978

Umbricht A, Hoover DR, Tucker MJ, et al: Opioid detoxification with buprenorphine, clonidine, or methadone in hospitalized heroin-dependent patients with HIV infection. Drug Alcohol Depend 69:263–272, 2003

Villagomez RE, Meyer TJ, Lin MM, et al: Post-traumatic stress disorder among inner city methadone maintenance patients. Subst Abuse Treat 12:253–257, 1995

Vining E, Kosten TR, Kleber H: Clinical utility of rapid clonidine-naltrexone detoxification for opioid abusers. Br J Addict 83:567–575, 1988

Washton AM, Pottash AC, Gold MS: Naltrexone in addicted business executives and physicians. J Clin Psychiatry 45:39–41, 1984

Wesson DR: Revival of medical maintenance in the treatment of heroin dependence (editorial). JAMA 259:3314–3315, 1988

Wesson DR, Ling W: The Clinical Opiate Withdrawal Scale (COWS). J Psychoactive Drugs 35:253–259, 2003

Wikler A: Opioid Dependence: Mechanisms and Treatment. New York, Plenum, 1980

Williams JT, Christie MJ, Manzoni O: Cellular and synaptic adaptations mediating opioid dependence. Physiol Rev 81:299–343, 2001

Woody GE, O'Brien CR, Rickels K: Depression and anxiety in heroin addicts: a placebo-controlled study of doxepin in combination with methadone. Am J Psychiatry 132: 447–450, 1975

Woody GE, Luborsky L, McLellan AT, et al: Psychotherapy for opiate addicts: does it help? Arch Gen Psychiatry 40:639–645, 1983

Woody GE, McLellan AT, Luborsky L, et al: Severity of psychiatric symptoms as a predictor of benefits from psychotherapy: the Veterans Administration–Penn study. Am J Psychiatry 141:1172–1177, 1984

Woody GE, McLellan AT, Luborsky L, et al: Twelve-month follow-up of psychotherapy for opiate dependence. Am J Psychiatry 144:590–596, 1987

Yabaluri N, Medzihradsky F: Down-regulation of mu-opioid receptor by full but not partial agonists is independent of G protein coupling. Mol Pharmacol 52:896–902, 1997

Zadina JE, Martin-Schild S, Gerall AA, et al: Endomorphins: novel endogenous mu-opiate receptor agonists in regions of high mu-opiate receptor density. Ann N Y Acad Sci 897:136–144, 1999

Zangwell BC, McGahan P, Dorozynsky L, et al: How effective is LAAM treatment? clinical comparison with methadone. NIDA Res Monogr 67:249–255, 1986

3

Sedative-Hypnotics

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Drugs that are classified as sedative-hypnotics or anxiolytics represent a pharmacologically diverse group of compounds. Those that have abuse potential produce antianxiety effects that are on a continuum with their hypnotic actions. The liability for abuse is certainly correlated with these actions but also involves specific mood-elevating properties that can be detected with standardized scales of drug-induced changes in mood states (Ciraulo et al. 2001). Currently there is no classification scheme for these drugs that is either scientifically precise or universally accepted. In this chapter, we discuss benzodiazepines, selective γ-aminobutyric acid (GABA) A_1 (benzodiazepine$_1$)

Table 3–1. Approximate benzodiazepine dose equivalency

Generic name	Brand name	Dose (mg)
Alprazolam	Xanax	1
Chlordiazepoxide	Librium	25
Clonazepam	Klonopin	0.5–1.0
Clorazepate	Tranxene	15
Diazepam	Valium	10
Flurazepam	Dalmane	30
Lorazepam	Ativan	2
Oxazepam	Serax	30
Temazepam	Restoril	20
Triazolam	Halcion	0.25
Zaleplon	Sonata	10
Zolpidem	Ambien	10

receptor agonists (i.e., zaleplon and zolpidem), barbiturates, and other agents that are used less commonly clinically but are sometimes abused (Table 3–1). The role for pharmacotherapy involves selecting therapeutic agents with the lowest abuse potential and managing abstinence syndromes and overdose.

The definitions of abuse, dependence, and misuse subtly influence both research and clinical practice. The application of the DSM-IV-TR criteria (American Psychiatric Association 2000) for substance dependence is limited when considering therapeutic agents that are associated with both physiological dependence and clinical efficacy. Specifically, the development of a withdrawal syndrome with abrupt discontinuation does not distinguish benzodiazepines from antidepressants. Furthermore, unauthorized dosage changes (increases or decreases) are similar between antidepressants and benzodiazepines. Two of the DSM-IV-TR criteria for substance dependence—continued use despite known physiologic dependence and a desire to reduce use—do not indicate addiction in the context of a severe anxiety disorder. In our experience, most patients would prefer to stop taking a medication that is no longer necessary therapeutically. "Continued use in the presence of physiologic dependence" is an inappropriate criterion of misuse for benzodiazepines

because virtually all patients meet that criterion after several weeks of therapy. Long-term use is not equivalent to misuse, nor does patients' regulation of the dosage based on symptom severity represent abuse. Other DSM-IV-TR criteria for substance dependence are also inappropriate when applied to use of benzodiazepines. Even among drug addicts, spending a great deal of time obtaining benzodiazepines or giving up social activities as a consequence of use is extremely rare. On the other hand, a small but clinically significant group of patients has difficulty discontinuing benzodiazepines, and benzodiazepines are frequently misused by individuals who abuse other drugs or alcohol.

Benzodiazepines and Selective $GABA_{A1}$ Agonists

Prevalence of Misuse, Abuse, and Dependence

Clinical Experience

When benzodiazepines were initially introduced, they were not thought to cause dependence. Their introduction was heralded as a pharmacologic advance, in contradistinction to the barbiturates. It was therefore of considerable interest when Hollister et al. (1961) demonstrated physiologic dependence in humans after abrupt discontinuation of therapy with large doses of chlordiazepoxide for many months. This and other work led to the perspective that physiologic dependence did occur at high doses but not in regular, therapeutic clinical use. As concern grew over the rapid growth in sales of benzodiazepines in the 1960s, attention was paid to the potential of these drugs to be "addicting." As new information became available, the concept of the dose and exposure time needed to produce physiologic dependence changed. Busto et al. (1986a, 1986b) demonstrated a withdrawal syndrome following chronic use of several benzodiazepines at therapeutic doses, and an abstinence syndrome was precipitated in cats after a single dose of diazepam by using the benzodiazepine antagonist flumazenil (Rosenberg and Chiu 1985). Thus, the presence of a discontinuation or abstinence syndrome is not uncommon following chronic treatment and is not, in itself, a clinically useful concept of substance abuse or dependence. This distinction is crucial in considering both the literature and the clinical situations in which benzodiazepine use may come under scrutiny.

Survey Data

Prevalence of benzodiazepine use and abuse can be estimated by national and cross-national surveys of the general population and of populations in medical clinics, psychiatric institutions, and chemical dependency treatment units.

In the 2002 National Survey on Drug Use and Health, nonmedical use of prescription agents by individuals was defined as "taking drugs that were not prescribed for them or drugs they took only for the experience or feeling they caused" (Substance Abuse and Mental Health Services Administration 2003). Lifetime use of these agents was low. About 1% of the population over age 12 years reported illicit use of sedatives or tranquilizers in the month before the survey, with the highest percentage in the 18- to 25-year age group (1.8%); 2.5% reported past-year use, with the highest rate of use (5.4%) in the 18- to 25-year age group. In 2002, 6.2% of Americans reported past-year nonmedical use of psychotherapeutic drugs; 2.5% used sedatives or tranquilizers, compared with 4.7% who used pain relievers. Rates of first-time nonmedical use of prescription drugs over the past 35 years are shown in Figure 3–1. New user rates have increased in the past decade, with pain relievers having higher rates than sedatives and tranquilizers.

A number of surveys of medical use of benzodiazepine have been conducted over the last 30–35 years. A national survey of medical use in 1971 showed that 15% (20% of women and 8% of men) had taken at least one dose of a minor tranquilizer in the past year (Parry et al. 1973). A second survey conducted by the same group in 1979 demonstrated the use of a "tranquilizer" in 14.1% of women and 7.5% of men (11.1% for both men and women) (Mellinger and Balter 1981). A multinational survey done in 1981 showed prevalences of 17.6% in Belgium, 12.9% in the United States, and 7.4% in the Netherlands (Balter et al. 1984). The results of these studies are not directly comparable because of differences in how "tranquilizers" were defined. A 1984 survey evaluated chronic anxiolytic use in the United States and found that long-term users were more likely to be older and female and to have high levels of emotional distress and chronic somatic health problems (Mellinger et al. 1984). Although the study concluded that women were more likely than men to use anxiolytics, once men became users, they were at least as likely to become long-term users.

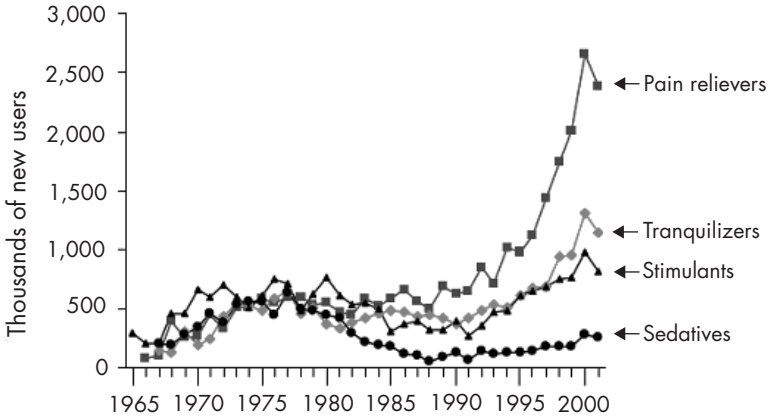

Figure 3–1. Annual numbers of new nonmedical users of psychotherapeutics: 1965–2001.
Source. From the results of the 2002 National Survey on Drug Use and Health (Substance Abuse and Mental Health Services Administration 2003).

Greenblatt et al. (1975) reported results of the Boston Collaborative Drug Surveillance Program, which showed that of 24,633 consecutive admissions to the general medical or surgical wards of 24 Boston hospitals, 14% of patients remembered having taken an antianxiety agent at least once in the preceding 3 months. It is interesting to note that no cases of physiological withdrawal symptoms were reported.

Marks (1978) reviewed published reports of benzodiazepine dependence in the literature from 1961 to 1977 and estimated that benzodiazepine dependence occurred in one case per 50 million patient-months of use. His assessment of risk has been criticized, however, because published case reports tend to occur less frequently than the phenomenon they describe. Benzodiazepine dependence case reports peaked between 1969 and 1973, about 10 years after the introduction of the drugs (Petursson and Lader 1981a).

In the absence of a diagnosis of substance abuse, most patients taking benzodiazepines continue to benefit from treatment over extended periods of

time, tend to reduce rather than escalate the dose, and do not show evidence of the behaviors associated with addiction to illicit drugs (Apsler and Rothman 1984; Bowden and Fisher 1980; Busto et al. 1986a; Caplan et al. 1985; Dunbar et al. 1989; Rickels and Schweizer 1993; Rickels et al. 1991; Romach et al. 1992, 1995; Salinsky and Dore 1987). The prevalence of benzodiazepine use among patients with chronic psychiatric disorders is reported to be 17%–36.9% (Cushman and Benzer 1980; Fleischhacker et al. 1986; Garvey and Tollefson 1986; Gottschalk et al. 1971; Hallstrom and Lader 1982; Samarasinghe et al. 1984; Schmidt et al. 1989; Wolf et al. 1989).

In summary, about 6.2% of the U.S. population over age 12 years reports nonmedical use of a "psychotherapeutic" in the previous year, with 2.5% reporting sedative/tranquilizer use. Between 7.4% and 17.6% of the general population use a benzodiazepine for medical purposes at least once during any given year, with only about 1% using the medication daily for 1 year or longer (Piper 1995). This finding can be compared with a 17%–36.9% *usage* rate and less than a 1% *abuse* rate among psychiatric patients. Of patients in treatment for substance dependence, 1.3%–9.2% include benzodiazepines among their multiple substances of abuse, but only a very small number (on the order of 0.2%) are dependent on benzodiazepines only. Studies of benzodiazepine use in alcoholic subjects indicate that between 3% and 41% are taking both drugs, with estimated rates of misuse of 10%–20% (Ashley et al. 1978; Bell et al. 1984; Busto et al. 1983; Ciraulo et al. 1988b; Johansson et al. 2003; Kania and Kofoed 1984; Kryspin-Exner 1966; Kryspin-Exner and Demel 1975; Rothstein et al. 1976; Schuckit and Morrissey 1979; Sokolow et al. 1981; Wiseman and Spencer-Peet 1985).

Medical Use

Medical use of benzodiazepines has been declining. Prescribing trends show an overall decline in the number of all benzodiazepine prescriptions written, with a market shift to increased prescribing of short elimination half-life agents (lorazepam, alprazolam), compared with long-elimination half-life agents (diazepam, chlordiazepoxide) (Ciraulo et al. 2004). In 2001, alprazolam was the most widely prescribed benzodiazepine (Ciraulo et al. 2004), and it also was the most widely prescribed psychiatric medication in that year for mood and anxiety disorders (Stahl 2002).

Most medical use is short-term (less than a month), with long-term users more likely to be older and female and to have high levels of psychological distress. Psychiatric patients have higher rates of benzodiazepine use than the general population but still have low rates of misuse. Benzodiazepines are rarely cited by treatment-seeking patients as the primary drug of abuse, with 0.2% of admissions attributed to primary sedative dependence (benzodiazepines or barbiturates), and of these, secondary alcohol abuse was reported in 34% and secondary marijuana abuse reported in 20% (Substance Abuse and Mental Health Services Administration 1999). Patients presenting for treatment of benzodiazepine dependence have high rates of psychiatric comorbidity, especially depression and anxiety, as well as polysubstance abuse (Busto et al. 1996; Romach et al. 1995).

Prevalence in Special Populations

Substance Abusers

A dramatically different pattern is found in surveys of drug abuse treatment facilities. Substance abuse treatment centers have reported that more than 20% of patients use benzodiazepines weekly or more frequently, with 30%–90% of opioid abusers reporting illicit use (Iguchi et al. 1993; Stitzer et al 1981). Methadone clinics reported that high proportions of urine samples are positive for benzodiazepines (Darke et al. 2003; Dinwiddie et al. 1996; Ross and Darke 2000; Seivewright 2001; Strain et al. 1991; Williams et al. 1996). The reasons for the high rates of benzodiazepine use in opioid addicts include self-medication of insomnia, anxiety, and withdrawal symptoms, as well as attempts to "boost" the euphoric effects of opioids.

There is some evidence of a synergistic effect on reinforcement with concurrent administration of benzodiazepines and opioids (Walker and Ettenberg 2003). Cocaine abusers are less likely than opioid abusers to abuse benzodiazepines, preferring alcohol and opioids as secondary drugs of abuse. The most common pattern of benzodiazepine misuse in these individuals is intermittent use of therapeutic or supratherapeutic doses to counter unwanted effects of cocaine.

Although estimates vary widely, approximately 10%–20% of individuals presenting for treatment of alcohol dependence may be using or abusing benzodiazepines (Ciraulo et al. 1988b; Ciraulo et al. 2004; Johansson et al. 2003;

Lejoyeux et al. 1998). Similar to opioid-dependent persons, these patients reported that they use benzodiazepines to self-medicate anxiety, insomnia, and alcohol withdrawal and, less commonly, to enhance the effects of ethanol. Approximately 16%–25% of patients presenting for treatment of anxiety disorders abuse alcohol (Kushner et al. 1990; Otto et al. 1992). Controversy exists concerning appropriate benzodiazepine prescribing in this population (Ciraulo and Nace 2000; Posternak and Mueller 2001).

The risk of benzodiazepine misuse in people with anxiety and alcoholism varies, depending on the population sampled. A prior history of alcohol dependence did not predict longer duration of use, higher doses, or more frequent prn doses of prescription benzodiazepines in a large outpatient clinical trial (Mueller et al. 1996). Sokolow et al. (1981) reported that over an 8-month period following alcohol detoxification, concurrent benzodiazepine use declined from 12.7% at admission to 8.1% at 8 months, suggesting that even in alcoholic patients there is a decreasing pattern of use over time. In patients entering a benzodiazepine discontinuation program, 40% of those with long-term use (averaging 70 months of daily use) had an alcohol use disorder. Of particular interest is the finding that typical use was at constant or decreasing therapeutic doses, with efforts to discontinue the medication and appropriate use for symptom control (see Busto et al. 1996; Romach et al. 1995 for details).

The subjective rewarding effects of alprazolam, and probably of other rapid-onset benzodiazepines, are greater among persons with alcoholism than among those without alcoholism (Ciraulo et al. 1988a; Ciraulo et al. 1988b). Differences in abuse potential may exist between individual benzodiazepines (Griffiths and Wolf 1990). For example, oxazepam and halazepam have a slower onset of positive mood effects than diazepam (Griffiths et al. 1984; Jaffe et al. 1983). The actual risk of benzodiazepine dependence among alcoholic patients is unclear because the methodological deficiencies of existing studies are substantial, but the risk in this group is probably higher than in the general population but lower than among opioid-dependent persons. There is a high likelihood that patients with alcoholism who receive benzodiazepines will take them inappropriately. On the other hand, anxiety disorder patients who are in stable recovery are at much lower risk of benzodiazepine abuse than nonabstinent or recently abstinent alcoholic patients (Posternak and Mueller 2001).

Elderly Patients

Elderly patients may be at risk for falls (Cumming et al. 1991; Cumming and Le Couteur 2003) and impaired cognition (Barker et al. 2004; Dealberto et al. 1997; Hanlon et al. 1998; McAndrews et al. 2003) from benzodiazepine toxicity. There is little evidence to suggest that elderly patients are more likely to misuse these drugs, although they do have higher rates of prescriptions than younger patients. Many studies have found an association between benzodiazepines and falls in the elderly (Cumming and Le Couteur 2003), but it should be noted that one study found that selective serotonin reuptake inhibitor (SSRI) antidepressants and narcotics were more likely than benzodiazepines to be associated with nonspine fractures in elderly patients (Ensrud et al. 2003). The reader is cautioned that the published literature on elderly patients often mistakenly views long-term use as equivalent to dependence or abuse. A study of elderly hospitalized patients over age 70 years who had been taking a benzodiazepine for an average of 3.6 years at a mean diazepam equivalent dose of 11 mg/day found that they had more severe personality pathology, anxiety, and dysthymia than a similar inpatient group not taking benzodiazepines (Petrovic et al. 2002). Although the most common interpretation of these and similar findings is that they support the position that benzodiazepines are prescribed appropriately for elderly patients, others have raised the question of whether chronic prescribing actually induces or worsens anxiety and depression. A study that reviewed insurance claims alleging benzodiazepine-induced behavioral toxicity showed that psychiatric symptoms most often represented preexisting psychopathology and were not the result of benzodiazepine use (Mattila-Evenden et al. 2001). Nonetheless, the issue requires further study.

Chronic Pain Patients

Several studies have reported that as many as 40%–60% of chronic pain patients receive benzodiazepines, even though these agents have limited effectiveness for most pain conditions (Fishbain et al. 1992; Hardo and Kennedy 1991; Hendler et al. 1980; King and Strain 1990a, 1990b; Kouyanou et al. 1997). The role of benzodiazepines in the treatment of pain is not straightforward; no doubt these medications help with sleep, anxiety, and dysphoria secondary to medical illness. Despite high rates of use, rates of misuse in one study were low, ranging from 3.2%–4.8% (Kouyanou et al. 1997). An in-

triguing recent finding is that some novel benzodiazepines may have direct effects on pain, either through actions as bradykinin B_1 receptor antagonists (Wood et al. 2003) or kappa (κ) receptor agonists (Anzini et al. 2003).

Overview of Neuropharmacology

The term *benzodiazepine* refers to drugs with a structural core consisting of a benzene ring fused to a diazepine ring. All benzodiazepines in clinical use also contain a 5-aryl substituent ring and a 1,4-diazepine ring, and so the term refers to the 5-aryl-l,4-benzodiazepines (Charney et al. 2001; Greenblatt et al. 1983a, 1983b; Harvey 1985). Variations on the benzodiazepine ring structure have produced the triazolo (e.g., alprazolam, triazolam, estazolam), 2-keto (e.g., diazepam), 3-hydroxy (e.g., lorazepam, oxazepam), and imidazo (e.g., midazolam) agents and other agents that produce sedative, hypnotic, anxiolytic, muscle relaxant, and anticonvulsant effects. Substantial controversy exists as to whether certain classes of benzodiazepines differ in efficacy (antipanic, antidepressant actions), severity of withdrawal syndromes, or abuse liability.

The two selective $GABA_{A1}$ receptor agonists currently marketed in the United States, zaleplon and zolpidem, are a pyrazolopyrimidine and a imidazopyridine, respectively. Both of these drugs are approved only for the short-term treatment of insomnia.

Benzodiazepines, the selective $GABA_{A1}$ agonists (zaleplon and zolpidem), barbiturates, and related compounds exert their actions at the $GABA_A$ receptor complex, a pentameric structure composed of alpha (α), beta (β), gamma (γ), and delta (δ) subunits forming a chloride channel (Atack 2003) (Figure 3–2). It is known that these (and other) subunits exist as a number of subtypes and can combine in many ways; however, comparatively few combinations have physiological relevance. The actions resulting from agonist binding at the $GABA_A$ receptor vary depending on the composition of the subunits. Benzodiazepine-sensitive $GABA_A$ receptors are composed of five subunits: two α subunits, two β subunits, and one γ subunit (Barnard et al. 1998). Benzodiazepines show activity at receptors that contain the γ_2 subunit. The benzodiazepine binding site lies at the interface of α and γ subunits (Stephenson et al. 1990). Diazepam has a high affinity for α_1, α_2, α_3, and α_5 subunits in the $GABA_A$ receptor, but not for the α_4 or α_6 subunits (Hadingham et al. 1993; Luddens et al. 1990; Wafford et al. 1996). The sedative effects of ben-

zodiazepines are associated with the presence of α_1 subunits in the $GABA_A$ receptor structure (the $GABA_{A1}$ receptor subtype) (McKernan et al. 2000), and the presence of α_2 units in this receptor may be required for the antianxiety effect (Low et al. 2000). Zaleplon and zolpidem act on and bind to $GABA_{A1}$ receptors more selectively than do classic benzodiazepines (Pritchett and Seeburg 1990; Sanna et al. 2002). These agents may act as hypnotic agents that, compared to the classic benzodiazepines, are less likely to produce antianxiety and anticonvulsant effects.

The different α subunits that are contained in $GABA_A$ receptors are distributed in a heterogeneous manner throughout the brain. $GABA_A$ receptors having the α_1 subunit are located predominantly in sensorimotor areas, cortical areas, the globus palidus, ventral thalamic complex, subthalamic nucleus, substantia nigra, and cerebellum in primates (Dennis et al. 1988). Positron emission tomography evidence suggests that high concentrations of $GABA_A$ receptors that contain the α_5 subunit exist in human limbic structures, including the hippocampus, septal region, amygdala, and anterior cingulate cortex (Lingford-Hughes et al. 2002).

Although barbiturates, benzodiazepines, and $GABA_{A1}$ selective agonists all increase chloride ion flux, the barbiturates both enhance GABA binding and directly activate the channel, and the benzodiazepines and $GABA_{A1}$ agonists act only to increase the actions of GABA and other direct GABA agonists such as GABA and muscimol (Charney et al. 2001). Benzodiazepines and the $GABA_{A1}$ agonists are allosteric modulators of the GABA binding site in the $GABA_A$ receptor complex. The duration of channel opening is increased by barbiturates, and benzodiazepines primarily increase the frequency of openings. Barbiturates also differ from benzodiazepines in that they do not require the γ subunit to produce their effects, and, in addition, they directly inhibit the excitatory α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) receptor, whereas benzodiazepines indirectly oppose the excitatory actions of glutamate by acting as positive modulators of GABA inhibitory activity (Saunders and Ho 1990). Benzodiazepines may also have effects on adenosine reuptake and the activity of calcium and sodium channels.

The precise mechanism through which benzodiazepines and barbiturates produce mood elevation remains to be elucidated. The mood-elevating effect of the benzodiazepines and barbiturates is probably mediated not only by acute increases in the actions of GABA but also by neural connections from

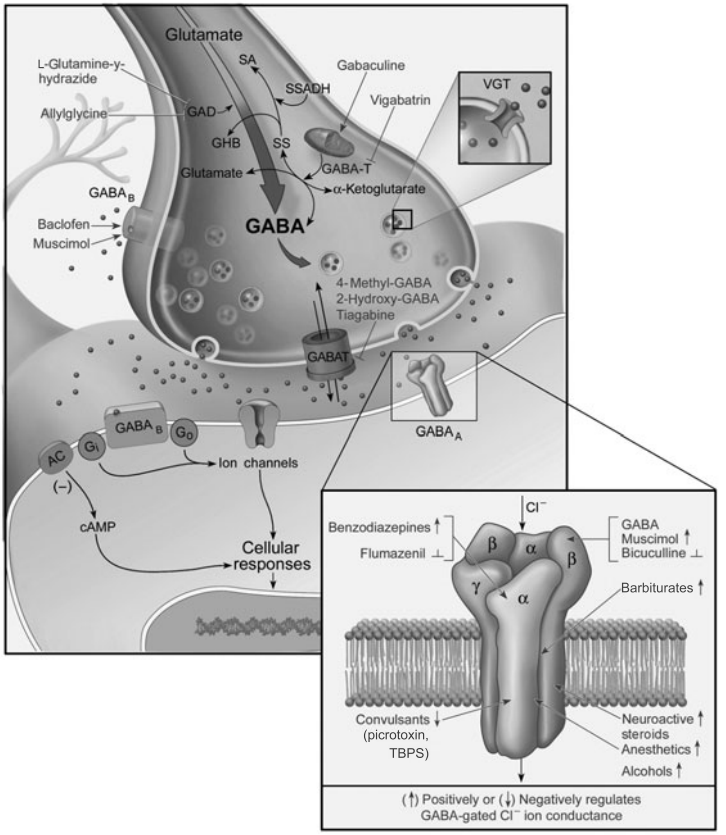

Figure 3–2. $GABA_A$ receptor.
Source. Reprinted from Szabo ST, Gould TD, Manji HK: "Neurotransmitters, Receptors, Signal Transduction, and Second Messengers in Psychiatric Disorders," in *The American Psychiatric Publishing Textbook of Psychopharmacology,* 3rd Edition. Edited by Schatzberg AF, Nemeroff CB. Washington, DC, American Psychiatric Publishing, Inc., 2004, p. 26. Copyright 2004, American Psychiatric Publishing, Inc. Used with permission.

GABAergic neurons. Depletion of dopamine from the nucleus accumbens may attenuate the rewarding effects of diazepam (Spyraki and Fibiger 1988), as may the administration of AMPA/kainate receptor antagonists (Gray et al. 1999). In addition to $GABA_A$ receptor antagonists, both dopamine and opioid receptor antagonists may block the rewarding actions of pentobarbital (Bossert and Franklin 2001). The rewarding effects of many commonly abused drugs including morphine and cocaine are associated with drug-induced increases in dopamine concentrations in the nucleus accumbens (Pontieri et al. 1995). However, the administration of benzodiazepines (DiChiara and Imperato 1988; Finlay et al. 1992) and higher doses of barbiturates (DiChiara and Imperato 1986) reduces rather than increases dopamine concentrations in the nucleus accumbens.

A number of benzodiazepine receptor ligands have been characterized and may exhibit one or more modes of action at the $GABA_A$ receptor (Ator 2003; Braestrup et al. 1983). They include 1) agonist action, in which ligands produce benzodiazepine-like effects (e.g., diazepam); 2) antagonist action, in which the ligands bind to benzodiazepine receptors and block the effects of agonists, as does flumazenil; and 3) inverse agonist actions, characterized by binding to the benzodiazepine receptor, resulting in effects that are opposite those of agonists. Examples of agents with the last mode of action are methyl beta-carboline-3-carboxylate, methyl 6,7-dimethoxy-4-ethyl-beta-carboline-3-carboxylate (DMCM), Ro 15–4513, and CGS 8216. A classification scheme proposed by Nutt and Linnoila (1988) divides ligands into agonists or inverse agonists and then subclassifies each as full or partial. This classification scheme is not absolute—a given benzodiazepine may have different actions depending on the composition of receptor subunits. For example, replacement of the γ_2 subunit with the γ_1 subunit reduces positive modulation and may result in an inverse agonist acting as a weak agonist (Barnard et al. 1998).

Pharmacodynamic tolerance to the psychomotor effects of benzodiazepines has been demonstrated after single or multiple doses (File 1985; Greenblatt and Shader 1978; Rosenberg and Chiu 1985). Pharmacodynamic tolerance to the anxiolytic effect (over a 6-month period) has not been demonstrated (Rickels et al. 1983), and clinical experience supports the view that many patients with anxiety disorders require long-term therapy with benzodiazepines or alternative antianxiety agents. An important clinical consequence of tolerance to sedative effects is observed in benzodiazepine overdoses, when patients may initially be

somnolent but may often wake up and recover while the serum level of the benzodiazepine active metabolite is very high and still rising.

Tolerance to the psychomotor impairment associated with lorazepam has been demonstrated in animal models (Miller et al. 1988a, 1988b), but it is our clinical impression that even though this impairment decreases with continued use in patients, it never completely remits. In most cases it does not persist at levels that cause significant difficulty in daily functioning. On the other hand, amnesic effects of benzodiazepines, especially the high-potency agents, seem to be a problem for some individuals whose occupations demand high levels of cognitive function. Using the lowest possible doses of these drugs during periods when cognitive performance is critical (e.g., test taking) is a successful therapeutic strategy.

The extent to which tolerance develops to the actions of either zaleplon or zolpidem is not yet clear. In contrast to triazolam, zolpidem was not associated with the development of behavioral tolerance to impairments of psychological performance produced by repeated administration (Stoops and Rush 2003). Several reports indicated that tolerance does not develop to the sleep-promoting effects of these agents over a 1-month period (Elie et al. 1999; Fry et al. 2000) and that significant rebound insomnia does not occur with the prolonged administration of these agents (Voderholzer et al. 2001). However, other evidence suggested that rebound insomnia may occur after zolpidem treatment (Elie et al. 1999; Fry et al. 2000). There are few data concerning the development of tolerance or dependence to either zaleplon or zolpidem when these agents are administered for periods of longer than a month.

Tolerance to benzodiazepines is pharmacodynamic, whereas barbiturates induce their own metabolism (pharmacokinetic tolerance) as well as induce changes in the function of receptor systems (pharmacodynamic tolerance). The exact mechanisms responsible for benzodiazepine tolerance, however, remain uncertain. Furthermore, although there is consensus that tolerance develops for such clinical effects as sedation and motor impairment, clinical experience suggests that antianxiety effects are long-lasting. It is well established that chronic administration of benzodiazepines in experimental models results in decreased GABA-stimulated chloride influx. Several mechanisms have been implicated in the development of tolerance to benzodiazepines. They include down-regulation of cortical benzodiazepine binding sites (Fahey et al.

2001), alterations in $GABA_A$ receptor subunit composition (Chen et al. 1999), and increased expression of AMPA (Allison and Pratt 2003; Van Sickle and Tietz 2002) and *N*-methyl-D-aspartate receptor subunits in the hippocampus (Perez et al. 2003).

Pharmacokinetics

Absorption by the oral route is essentially complete for benzodiazepines, except for clorazepate, which is decarboxylated in gastric secretions to *N*-desmethyldiazepam, which is absorbed. Diazepam and *N*-desmethyldiazepam are rapidly absorbed and will reach a peak in serum soon after ingestion (Greenblatt et al. 1983a, 1983b). Prazepam and halazepam are inactive or only slightly active prodrugs that are converted slowly to the active form. The rate of appearance in serum of *N*-desmethyldiazepam from prazepam is the slowest among the benzodiazepines. Some researchers believe that this property conveys lower abuse liability, although consensus does not exist on this question.

Some patients have reported sublingual use (particularly of lorazepam and alprazolam) to obtain a "high," presumably on the basis of faster absorption, although we rarely see either a high or a more rapid onset of action clinically. Although one group has found faster absorption of lorazepam by the sublingual route (Caille et al. 1983), a rigorous kinetic comparison of intravenous, intramuscular, oral, and sublingual routes failed to reveal significant differences between sublingual and oral administration in the fasted state (Greenblatt et al. 1982). Sublingual absorption may offer an increased rate of absorption in the postprandial state. In particular, alprazolam and triazolam may reach higher peak levels by means of the sublingual route. Although benzodiazepines are all highly lipophilic, the lipophilicity varies more than 50-fold among individual benzodiazepines (Harvey 1985). The more lipophilic drugs tend to enter the cerebrospinal fluid most rapidly, but in a study of diazepam, *N*-desmethyldiazepam, midazolam, lorazepam, alprazolam, flunitrazepam, and clobazam all attained peak cerebrospinal fluid concentrations within 15 minutes of intravenous administration (Arendt et al. 1983). Benzodiazepines and their active metabolites all bind to plasma proteins, and this binding correlates with lipophilicity—from 70% for alprazolam to 99% for diazepam (Harvey 1985).

Benzodiazepines are metabolized through the hepatic microsomal system. The cytochrome P450 3A4 (CYP3A4) isoform may mediate the metabolism of several benzodiazepines, including triazolam, alprazolam, and midazolam. The clearance of triazolam can be reduced by the administration of CYP3A inhibitors such as the antiretroviral agent ritonavir (Greenblatt et al. 2000). The metabolism of diazepam is catalyzed, in part, by the CYP2C19 isoform. All benzodiazepines ultimately undergo glucuronidation, and some require prior oxidative metabolism, either *N*-dealkylation or aliphatic hydroxylation. Oxidative metabolism is relatively more susceptible to impairment from certain population characteristics (e.g., aging), coadministration of other drugs (e.g., cimetidine, disulfiram), or disease states (e.g., cirrhosis) than is glucuronidation. The metabolism of the drugs that require only glucuronidation (e.g., oxazepam, lorazepam, temazepam) is less susceptible to these influences than that of the drugs that require oxidation (e.g., chlordiazepoxide, diazepam, clorazepate, prazepam, halazepam, flurazepam, triazolam, and alprazolam).

Benzodiazepines do not induce their own metabolism, and there is no evidence for the development of pharmacokinetic tolerance (Greenblatt and Shader 1986). The behavioral tolerance seen with chronic dosing is explicable entirely on the basis of pharmacodynamic tolerance (as described earlier in the overview of neuropharmacology).

Zaleplon and zolpidem are readily absorbed from the gastrointestinal tract. Zaleplon has low oral bioavailability (in the range of 30%), which is attributed to extensive presystemic extraction (Charney et al. 2001). The bioavailability of zolpidem is approximately 70% (Salva and Costa 1995). Both zaleplon and zolpidem are rapidly cleared from the plasma. The half-life of zaleplon is about 1 hour and that of zolpidem is approximately 2 hours (Greenblatt et al. 1998). The enzyme aldehyde oxidase mediates the extensive transformation of zaleplon into 5-oxo-zaleplon. Zolpidem, which is extensively metabolized in the liver, is a substrate of CYP3A enzymes (Pichard et al. 1995; von Moltke et al. 1999).

Etiologic Theories of Misuse, Abuse, and Dependence

Although many factors contribute to drug dependence and misuse, only the pharmacological origins of benzodiazepine dependence will be considered here. The capacity of a benzodiazepine to induce dependence is related to its

ability to produce a desired effect (a pleasant mood, relief of anxiety or dysphoria, and less commonly a "high") and to attempts to self-medicate an abstinence syndrome (physical dependence) from either the benzodiazepine or another abused substance (e.g., alcohol).

Benzodiazepines and similar agents occupy a position of intermediate abuse potential, compared with most other sedative-hypnotics (Griffiths and Weerts 1997). Animal models of abuse liability indicate that the reinforcing effects of benzodiazepines are less pronounced than are those of the barbiturates, opioids, and stimulants. Differences in abuse potential within the class have not been consistently demonstrated; however, most clinicians agree that benzodiazepines with a rapid onset and short duration of action pose the greatest risk in susceptible individuals.

Limited results from clinical laboratory evaluations suggested that the $GABA_{A1}$ agonists zaleplon (Rush et al. 1999b) and zolpidem (Rush et al. 1999a) produce effects that are consistent with abuse potential comparable to that of the benzodiazepine triazolam. The reported incidence of dependence on zolpidem in the medical literature is low, compared with that for benzodiazepines, and is characterized by use of high doses, often in individuals with a history of substance abuse (Hajak et al. 2003; Vartzopoulos et al. 2000).

Diazepam has a rapid onset of action in producing a euphoric effect, but as the desmethyl metabolite levels increase and the parent compound, diazepam, declines, the mood-elevating effect declines rapidly (Ciraulo et al. 1997; Jaffe et al. 1983). Benzodiazepines that are prodrugs for desmethyldiazepam, such as prazepam or halazepam, produce fewer euphoric effects (Jaffe et al. 1983; Orzack et al. 1982). Other pharmacokinetic factors influence the time course of withdrawal and by extension the proper medical management of the abstinence syndrome; however, there are no human data that clearly establish that the withdrawal syndrome is more severe with agents with a short versus long elimination half-life. The partial agonists (or, more accurately *partial positive modulators*) abecarnil and bretazenil consistently demonstrate lower abuse liability in animal models but still produce mood elevation on standardized scales assessing abuse liability in human subjects. Prior exposure to ethanol or sedative-hypnotic drugs may increase the reinforcing properties of benzodiazepines. Flunitrazepam is associated with a particularly disturbing form of abuse—surreptitious combination with beverage alcohol to induce amnesia and increase vulnerability to sexual assaults, so-called date rape.

Nonhuman primates will self-administer benzodiazepines and zolpidem (Weerts and Griffiths 1998), indicating that these agents produce moderate positive reinforcing effects (Ator 2002). Both drug-experienced and drug-naive animals will self-administer benzodiazepines, and the self-administration of these agents has been demonstrated to occur over periods lasting several months (Griffiths and Weerts 1997). Evidence that benzodiazepines produce positive reinforcing effects in humans is mixed and includes results of self-administration and choice studies (Griffiths and Weerts 1997). Benzodiazepines are less efficacious as reinforcers in humans than is pentobarbital (Griffiths et al. 1980), and diazepam may be a more efficacious reinforcer than oxazepam (Griffiths et al. 1984). The degree of reinforcing effects of benzodiazepines in humans appears to be determined by the psychiatric and substance use history of the subjects being tested. In a number of studies involving healthy volunteers, benzodiazepines, including diazepam (Johanson and de Wit 1992), lorazepam (de Wit et al. 1984), and triazolam (Roehrs et al. 1992), were not found to be reinforcers. In contrast, alprazolam (Ciraulo et al. 1988a; Ciraulo et al. 1989; Ciraulo et al. 1990; Ciraulo et al. 1996; Mumford et al. 1995a, 1995b), diazepam and triazolam (Roache and Griffiths 1989), and other agents clearly act as reinforcers in subjects with a history of drug abuse or alcoholism. Benzodiazepines also appear to have reinforcing effects in moderate drinkers (de Wit et al. 1989; Evans et al. 1996), and anxious individuals (Roache et al. 1996; Roache et al. 1997).

Physiological dependence develops with high doses and therapeutic doses of benzodiazepines. Difficulty discontinuing use can be related to the individual's inability to tolerate discontinuation symptoms or the return of the preexisting anxiety disorder. Physical dependence can also develop in primates treated with high doses of zolpidem (Ator et al. 2000; Richards and Martin 1998; Weerts and Griffiths 1998) and zaleplon (Ator et al. 2000; Weerts and Griffiths 1998).

Clinical Signs and Symptoms of Intoxication and Abstinence Syndrome

Intoxication

Benzodiazepines produce few pathognomonic signs of intoxication. Sedation, behavioral disinhibition, and occasional paradoxical excitation may all be

seen. Toxicity can occur after large single doses (as in some cases of abuse or in deliberate overdose) and by drug accumulation in persons with impaired metabolism. Three cardinal features of benzodiazepine toxicity are ataxia, diplopia, and impaired gag reflex. Level of consciousness may vary from light sedation to obtundation. Unless benzodiazepines are combined with other drugs (such as alcohol), the rate of mortality in persons with benzodiazepine intoxication is low. Tolerance develops rapidly, and it is not uncommon following single, large doses to see an initial period of sedation followed by apparent recovery while serum levels of active metabolites are still rising (Greenblatt et al. 1979). The competitive benzodiazepine antagonist flumazenil has been used to reverse benzodiazepine-induced sedation after surgery or diagnostic procedures (Brogden and Goa 1988).

Abstinence Syndrome

An abstinence syndrome after prolonged, high-dose administration was demonstrated with chlordiazepoxide (Hollister et al. 1961) and with diazepam (Hollister et al. 1963). This high-dose abstinence syndrome has been repeatedly confirmed and has been categorized by Smith and Wesson (1983) as either a minor withdrawal syndrome consisting of "anxiety, insomnia, and nightmares," or a major withdrawal syndrome consisting of "grand mal seizures, psychosis, hyperpyrexia, and possibly death" (p. 87).

An abstinence syndrome after long-term, low-dose treatment has also been described (Busto et al. 1986a; Covi et al. 1973; Petursson and Lader 1981b; Tyrer et al. 1981). Reported symptoms include muscle twitching, abnormal perception of movement, depersonalization or derealization, anxiety, headache, insomnia, diaphoresis, difficulty concentrating, tremor, fear, fatigue, lowered threshold to perception of sensory stimuli, and dysphoria.

A rebound sleep disturbance has been found after only 7–10 days of treatment with therapeutic doses of triazolam (Greenblatt et al. 1987). Others have described a withdrawal syndrome after substitution of a short-acting benzodiazepine for a long-acting benzodiazepine (Conell and Berlin 1983). Rebound insomnia may occur with zolpidem.

The clinician must be cautious in interpreting some of these symptoms (especially anxiety) in patients withdrawing from benzodiazepines. Anxiety, fearfulness, and dysphoria may represent symptoms that were treated by the benzodiazepine and unmasked on withdrawal.

Medical and Psychological Consequences of Abuse

There is no convincing evidence to suggest that there are adverse medical consequences of long-term benzodiazepine use. In one European study, patients with isolated benzodiazepine dependence showed a mortality rate greater than the general population but equivalent to the control group (nondependent patients with comparable psychiatric illnesses) (Piesiur-Strehlow et al. 1986). Virtually all reported medical morbidity and mortality result from the combination of benzodiazepines with other central nervous system (CNS) depressants in individual occurrences; for example, a person chronically abusing diazepam in high doses who then drinks alcohol may experience severe CNS depression resulting in respiratory depression or coma.

Anterograde amnesia has been well documented with a variety of benzodiazepines, and decrement in learning probably represents the single most significant drawback to medically indicated chronic use (Barker et al. 2004; Curran 1986; Lister 1985; Vermeeren et al. 1995). In persons with preexisting deficits in learning or orientation, the effect is magnified and may be a contraindication to use. The mechanism for memory impairment is unclear, but it may become further elucidated in studies with animal models. Preliminary data suggested that the benzodiazepine inverse agonists may enhance learning and memory (Maubach 2003; Venault et al. 1986). No studies have convincingly shown cognitive impairment that persisted after drug discontinuation and a reasonable period for withdrawal. Similarly, although some authorities have expressed concerns about structural CNS changes occurring with chronic benzodiazepine treatment, no adequately designed studies exist. In particular, alcohol intake and psychiatric comorbidity have often been ignored.

Protocols for Detoxification

Clinical situations in which detoxification is indicated can be grouped into three categories: 1) for patients who have been taking a maintenance therapeutic dosage for moderate to long periods of time and for whom a trial without medication is warranted, 2) for patients taking supratherapeutic doses (usually in the context of benzodiazepine dependence), and 3) for patients who use benzodiazepines as part of mixed substance dependence. Detoxification should be approached differently in each category.

Detoxification From Therapeutic Dosages

Patients may have been prescribed benzodiazepines for an acute problem that has since resolved, but the prescriptions were nonetheless renewed, for ill-defined reasons or for a diagnosed anxiety disorder. The unifying features in this group are that the patients have been using benzodiazepines at stable, therapeutic dosages, they have been obtaining them from legitimate sources, and they may or may not still be deriving clinical benefit from the medication. Determining continued benefit may be difficult and may require periodic tapering or discontinuation of the benzodiazepine. Return of symptoms during the taper may support continued treatment, but the clinician should also consider the possibility of a discontinuation syndrome.

Detoxification can usually be accomplished by using the same benzodiazepine that the patient is taking. Switching from a benzodiazepine with a short elimination half-life to one with a long elimination half-life may not be necessary if the tapering program is sufficiently long. If difficulty is encountered in tapering one benzodiazepine, however, then switching to another with a longer elimination half-life may be helpful. Substituting a medication with a shorter elimination half-life for one with a longer elimination half-life is not advised (Conell and Berlin 1983). Approximate dosage equivalencies of benzodiazepines are listed in Table 3–1.

We recommend an initial 10%–25% dose reduction, followed by careful observation of the patient for signs of the abstinence syndrome. Patients withdrawing from agents with a shorter elimination half-life (lorazepam, oxazepam) may have an earlier onset of symptoms, and withdrawal from longer half-life agents (clonazepam, diazepam) may not occur until several days after reducing the dose. Exceptions to this pattern do occur—some patients seem exquisitely sensitive to the rate of decline of drug levels and may have abstinence symptoms in the presence of therapeutic drug concentrations.

Clinical experience suggests that alprazolam can be particularly difficult to taper when lower doses are reached (e.g., tapering from 1 to 0 mg) (Ciraulo et al. 1990). One possible explanation for this is suggested by data from an animal model showing that alprazolam at doses of 0.02–0.05 mg/kg increases benzodiazepine receptor number above baseline (Miller et al. 1987). When difficulty is encountered in tapering the last 1–2 mg of alprazolam, the rate of dose reduction can be decreased to 0.25 mg/week, and/or adjunctive medication may

be employed, as described later in this chapter in the section on adjunctive medication strategies. We have not had extensive experience tapering the controlled-release preparation of alprazolam. However, one study found "moderate but transient levels of distress" in 48% of patients with panic disorder who were discontinued from the controlled-release formulation of alprazolam, compared to 10% of subjects in the placebo group (Schweizer et al. 1993).

There has been some interest in flumazenil as a treatment for benzodiazepine withdrawal (Gerra et al. 2002). Although of theoretical interest, this procedure is not recommended for clinical use. Because there is a body of literature on the topic, clinicians should have some familiarity with the rationale underlying its use in withdrawal. In healthy, nonanxious volunteers who have not been exposed to benzodiazepines, high doses of flumazenil inconsistently produce agonist effects (Darragh et al. 1983; Higgitt et al. 1986; Lupolover et al. 1984; Mintzer et al. 1999). Experimental evidence supported both an antagonist and agonist action for flumazenil, which may be dependent on dose and subject heterogeneity (Buldakova and Weiss 1997). Administration of flumazenil to benzodiazepine-tolerant individuals resulted in some symptoms of withdrawal (Griffiths et al. 1993), but one study found improvement in symptoms in long-term abstinent patients (Saxon et al. 1997). Further complicating the interpretation of the data are findings that subjects with panic disorder and generalized anxiety disorder can have different responses to flumazenil (Nutt et al. 1990).

Detoxification From High Dosages

Patients requiring detoxification from high or supratherapeutic dosages of benzodiazepines constitute a smaller number of patients, but they are at greater risk for life-threatening discontinuation symptoms, such as seizures, delirium, and psychoses. There has been more experience with inpatient detoxification in this group, but outpatient detoxification is possible if conducted slowly (5% reduction in dose per week), with frequent contact, and in the context of a therapeutic alliance with the patient. Often, such an alliance proves unworkable because the patient's impoverished control results in supplementation from outside sources or early exhaustion of prescribed supplies meant to be tapered. In these cases, as in the cases of patients with a history of seizures, delirium, or psychoses during previous detoxification attempts, inpatient detoxification is indicated.

In high-dosage detoxification, the risk of major adverse consequences requires that a smooth decline in plasma benzodiazepine level be achieved. Here, switching from the substance of abuse to diazepam or another long-acting benzodiazepine is recommended. The patient's medication should be switched to an equivalent dosage of a long-acting benzodiazepine given in divided daily doses (see Table 3–1), and the patient should be stabilized with this regimen for the first day (some clinicians use a stabilization period of 2–3 days). After stabilization, a 30% cut is made in the dose on day 2 (or on days 3–4 if a longer stabilization period is used), followed by a 5% cut on each day thereafter. This protocol will result in complete detoxification in about 2 weeks for most patients, but the rate of tapering should be slowed even further in the presence of diaphoresis, tremulousness, or elevated vital sign measurements. Hyperpyrexia is a grave sign and should prompt aggressive management. Supplemental benzodiazepine and supportive medical care are necessary in these instances. This protocol should serve as a guideline only, because individual patients vary in their sensitivity to withdrawal. True withdrawal is best distinguished from recurrence of anxiety by the development of new symptoms and/or the appearance of perceptual disturbance (e.g., ringing in ears, sensitivity to sounds, and dizziness). Whenever possible, doses should be adjusted to keep patients comfortable. Adjunctive medications can be used as described later in this chapter, in the section on adjunctive medication strategies. Close monitoring for the week after detoxification is prudent, because some symptoms may not be evident until then, as the desmethyldiazepam and other metabolite levels continue to fall.

Benzodiazepines in Mixed Substance Abuse

Sporadic use (e.g., for the induction of sleep after a psychostimulant binge) does not require specific detoxification. Sustained use can be treated as described in the previous sections on detoxification from therapeutic or high dosages but with added caution. In mixed opioid and benzodiazepine abuse, the patient should be stabilized with methadone (some clinicians use other oral preparations of opioids) and a benzodiazepine. Buprenorphine should not be administered with benzodiazepines, because a pharmacodynamic interaction is possible (Ibrahim et al. 2000; Kilicarslan and Sellers 2000) and fatalities have been reported with the combination (Reynaud et al. 1998). Sedative-hypnotic withdrawal is the more medically serious procedure, and we usually

taper the benzodiazepine first. If the dosages of the abused drugs are low, simultaneous tapering may be possible. For patients who are misusing several different anxiolytics and hypnotics, (e.g., benzodiazepines, barbiturates, ethanol, and propanediols), adequate coverage can most often be achieved by a single medication, and a benzodiazepine is probably the safest choice; however, some experienced clinicians prefer to administer a barbiturate in these cases.

Adjunctive Medication Strategies

Adjunctive medications that may be of value in the management of benzodiazepine withdrawal are listed in Table 3–2. The two major roles for adjunctive medication are to reduce acute withdrawal symptoms and to maintain long-term discontinuation. Although neither approach is well studied, clinical experience suggests that adjunctive medications are of value in acute withdrawal. Long-term discontinuation depends on many factors, such as psychiatric diagnosis, personality traits, and the efficacy of alternative agents in treating anxiety (e.g., antidepressants).

In acute withdrawal, blockade of β-adrenergic receptors by propranolol (60–120 mg/day) attenuates some withdrawal symptoms (Tyrer et al. 1981), and it (or another β blocker) is commonly used. The benzodiazepine should still be gradually tapered, however, because abrupt discontinuation even in the presence of propranolol will lead to severe withdrawal symptoms (Cantopher et al. 1990). Reduction of adrenergic transmission by use of clonidine (an α_2 agonist) has also been used with moderate success (Ashton 1984; Fyer et al. 1988). Clonidine can be started at 0.1 mg bid, and the dosage can be increased to 0.2 mg tid if an adequate blood pressure measurement is sustained. The use of a clonidine patch is now common. Some evidence suggested that clonidine is not an effective agent for reducing symptoms of benzodiazepine withdrawal (Goodman et al. 1986). It must be stressed that neither propranolol nor clonidine reduces the risk of seizures, and therefore neither agent alone is sufficient to treat benzodiazepine withdrawal. Buspirone is not cross-tolerant to benzodiazepines and is not helpful in relieving withdrawal symptoms (Lader and Olajide 1987).

Other medication strategies have been shown to be of benefit in assisting alprazolam tapering. Clonazepam can be substituted gradually over the course of a week at an alprazolam-to-clonazepam equivalency ratio of 2:1 (Herman et al. 1987), and the clonazepam may be tapered as described earlier in this

Table 3–2. Adjunctive medications used in the treatment of benzodiazepine withdrawal

Medication Class	Medication
α_2 Receptor agonists	Clonidine
Anticonvulsants	Carbamazepine, valproic acid, gabapentin, topiramate
Antidepressants[a]	Trazodone, mirtazapine, paroxetine, other selective serotonin reuptake inhibitors; venlafaxine
β Receptor antagonists	Propranolol, others
Serotonin$_{1A}$ receptor (5-HT$_{1A}$) agonists	Buspirone[b]

Note. Efficacy of these agents is not established.
[a]Sedative antidepressants are used in acute withdrawal; antidepressants with antianxiety actions are used for long-term discontinuation.
[b]Not cross-tolerant to benzodiazepines and should not be used for acute withdrawal; high doses may be used to treat anxiety disorders to help maintain long-term discontinuation after abstinence has been achieved.

chapter in the sections on detoxification. It is important to note that diazepam may not block alprazolam withdrawal symptoms in some patients, either because of insufficient doses of diazepam or because of different pharmacodynamic actions of alprazolam. Carbamazepine has also been used to facilitate alprazolam withdrawal (Klein et al. 1986). The optimal dose to help with withdrawal has yet to be experimentally verified. In practice, once the alprazolam has been tapered to the lowest level tolerable for the patient, 200 mg bid of carbamazepine can be added. The carbamazepine dose is adjusted to obtain a serum level found to be therapeutic in seizure disorders (4–10 μg/mL), and then the alprazolam is tapered over 1–2 weeks. Carbamazepine can then be rapidly tapered, but while it is being administered, the usual laboratory indices (liver function tests and complete blood count) should be monitored. The use of carbamazepine has been extended to withdrawal from all benzodiazepines.

The use of divalproex in benzodiazepine withdrawal has also become a common clinical strategy. It is usually started in doses of 500–1,000 mg in two or three divided doses daily and increased to achieve serum levels of 50–120 μg/mL. Some protocols recommend a loading dose of 20 mg/kg.

Other anticonvulsants, such as gabapentin and topiramate, are also being used by some clinicians, but controlled trials are lacking.

Antidepressants are commonly used to treat both acute withdrawal and persistent anxiety or insomnia. There is evidence to suggest that they are effective in relieving some acute abstinence symptoms, but it has been more difficult to establish their effectiveness in long-term discontinuation. Antidepressants with sedative and antianxiety effects are the preferred drugs.

Role of Psychosocial Therapy

In two studies in which benzodiazepines were gradually tapered, concurrent cognitive-behavioral therapy (CBT) did not increase the proportion of patients who were able to successfully discontinue their use of these agents (Oude Voshaar et al. 2003; Vorma et al. 2003). On the other hand, other studies of patients with panic disorder found that CBT facilitated the discontinuation of benzodiazepine use (Otto et al. 1993). Similarly, CBT may be superior to supportive medical management in preventing the reoccurrence of panic attacks in panic disorder patients in whom alprazolam has been tapered (Bruce et al. 1999).

Predictors of Long-Term Discontinuation

Factors that may predict the maintenance of abstinence from benzodiazepines include a low dosage before the discontinuation attempt (Oude Voshaar et al. 2003; Vorma et al. 2003) and high levels of life satisfaction (Vorma et al. 2003). In a 1-year follow-up study of patients with high-dose benzodiazepine dependence (mean of 51.8 mg/day of diazepam equivalents at baseline) and comorbidity (50% with anxiety disorder, 44% with depressive disorder, 64% with personality disorder, 31% with current and 64% with lifetime alcohol use disorder) who had received benzodiazepine withdrawal treatment with CBT or treatment as usual, 25% of the entire sample remained benzodiazepine free, independent of treatment (Vorma et al. 2002, 2003). Lower initial benzodiazepine dosage, lack of previous withdrawal attempts, and high levels of life satisfaction (which was inversely related to psychopathology) predicted discontinuation. Contrary to studies involving patients with less complex clinical characteristics (Bruce et al. 1999), these investigators found that the efficacy of CBT and treatment as usual was equivalent.

Using a standardized scale to assess benzodiazepine dependence in more than 1,000 patients in a primary care setting, investigators found that high dosage, long duration of use, and the concomitant use of antidepressants were associated with dependence (de las Cuevas et al. 2003). The last finding is of particular importance because it may imply that long-term users have more severe or treatment-resistant anxiety that requires combination drug therapy for successful long-term treatment.

In subjects with sedative-hypnotic dependence who underwent detoxification in an addictions treatment unit, a significant association was not found between abstinence rate and either gender or psychiatric status (Charney et al. 2000). Patients dependent on benzodiazepines reported decreased anxiety during follow-up, even though their use of these agents had decreased.

Summary of Benzodiazepine Dependence Issues

Anxiety is a normal part of mental life and plays a crucial role in human psychological development and other forms of learning. Although systematic studies are lacking, suppression of normal levels of anxiety could impair the development of adaptive coping mechanisms. On the other hand, disabling anxiety impairs adaptation as well and is associated with significant morbidity and mortality.

Patients with specifically diagnosed anxiety disorders often require psychopharmacologic treatment. There are inadequate data to provide absolute guidelines for the optimal length of treatment, but the prudent clinician should periodically assess the need for continued pharmacotherapy. It is well established that the longer the period of therapy and the higher the benzodiazepine dosage, the more severe the discontinuation syndrome. Most withdrawal symptoms are easily managed by slow taper or adjunctive therapy with anticonvulsants, such as carbamazepine, valproate, gabapentin, β blockers, α-adrenergic blockers, or antidepressants.

In clinical practice, patients are referred for assessment of benzodiazepine dependence in the context of both therapeutic use and drug misuse. For the group of patients taking legitimately prescribed medication, it is necessary to reevaluate the indications for the benzodiazepine, assess for the presence of adverse effects, and determine whether a trial at a lower dosage, with alternative agents (SSRI or buspirone), psychotherapy, and/or a medication-free period are appropriate. Patients who are using the drugs outside of the thera-

peutic context are rarely dependent on benzodiazepines alone, and these drugs are usually part of a picture of mixed substance dependence. When benzodiazepines are part of mixed substance dependence, the dosages tend to be higher and the patients younger than in "pure" benzodiazepine dependence (Busto et al. 1986a, 1986b). High-dose use may be correlated with high levels of caffeine use, male sex, and youth (Perera and Jenner 1987).

Benzodiazepines have a low risk for abuse in anxiety disorder patients without a history of alcohol or other substance abuse. Among the benzodiazepines there may be a spectrum of abuse liability, with drugs that serve as prodrugs for desmethyldiazepam (e.g., clorazepate), slow-onset agents (e.g., oxazepam), and partial agonists (e.g., abecarnil) having the least potential for abuse. However, there is no currently marketed benzodiazepine or related drug that is free of potential for abuse.

Barbiturates

Prevalence of Dependence

Dependence on barbiturates has declined in recent years as physicians have substituted benzodiazepines for the treatment of many of the conditions for which barbiturates were formerly used. Clinicians will still see cases of abuse and dependence among medical patients receiving barbiturates or barbiturate combination products (e.g., Fiorinal) and in substance abusers (Silberstein and McCrory 2001).

Pharmacology

Charney et al. (2001), Harvey (1985), Matthew (1971), and Wesson and Smith (1977) have discussed the pharmacology of barbiturates. Barbiturates are derived from barbituric acid, which is the product of the fusion of malonic acid and urea. Barbituric acid lacks CNS activity. The two main classes of barbiturates are the highly lipid-soluble thiobarbiturates, in which sulfur replaces oxygen at the second carbon atom of the barbituric acid ring, and the less soluble oxybarbiturates, with oxygen at the second carbon atom (Table 3–3). Highly lipid-soluble barbiturates have a more rapid onset, a short duration of action, and greater potency than those with lower lipid solubility.

Table 3–3. Barbiturates

Duration of action	Generic name	Brand name(s)
Ultra-short acting (15 minutes to 3 hours)	Thiopental	Pentothal
	Methohexital	Brevital
Short acting (3–6 hours)	Pentobarbital	Nembutal
	Secobarbital	Seconal, Tuinal (with amobarbital)
Intermediate acting (6–12 hours)	Amobarbital	Amytal, Tuinal (with secobarbital)
	Butabarbital	Butisol
	Butalbital	Many combination products (e.g., Esgic, Fioricet, Fipricet with Codeine, and Fiorinal with Codeine)
Long acting (12–24 hours)	Phenobarbital	Luminal and many combination products, such as antispasmodic drugs, Barbidonna, belladonna alkaloids plus phenobarbital, Bel-Phen-Ergot SR, and Hyosophen
	Mephobarbital	Mebaral

The ultra-short-acting barbiturates include methohexital sodium (Brevital) and thiopental sodium (Pentothal). These agents are used as anesthetics and are administered intravenously. Barbiturates with short-to-intermediate duration of action are used for their sedative-hypnotic effect in the treatment of anxiety. These medications include amobarbital (Amytal), butabarbital (Butisol), sodium pentobarbital (Nembutal), and secobarbital (Seconal).

Long-acting barbiturates used as sedative-hypnotics and also for their anticonvulsant effects include phenobarbital (Luminal) and mephobarbital (Mebaral).

Although these divisions are of historical interest, duration of action, especially with a single dose, depends more on distribution effects than on elimination half-life. Furthermore, as the dose increases, duration of action is prolonged. In addition, the availability of these drugs in the United States is limited.

Barbiturates produce CNS depression, which ranges from sedation to general anesthesia. Action is through suppression of the mesencephalic reticular activating system. Barbiturates enhance GABA-induced inhibition; the site of inhibition may be presynaptic in the spinal cord or postsynaptic in the cortical

and cerebellar pyramidal cells, substantia nigra, and thalamic relay neurons. Studies have shown that barbiturates potentiate GABA-induced increases in chloride ion conductance in spinal neurons while reducing glutamate-induced depolarization. Barbiturates may block the excitatory effects of glutamate by inhibiting the actions of AMPA receptors (Marszalec and Narahashi 1993); however, barbiturate inhibition of AMPA receptors may not play a role in either the hypnotic (Kamiya et al. 1999) or anesthetic actions (Joo et al. 1999) of these agents. In high concentrations, barbiturates depress the activity of voltage-dependent sodium channels (Frenkel et al. 1990). Although barbiturates decrease the frequency of chloride channel openings, this decrease is more than compensated for by their ability to increase the length of time the channels remain open. In addition to the CNS effect, barbiturates depress autonomic ganglia and nicotinic excitation. This effect may explain the drop in blood pressure in cases of barbiturate intoxication. The type of α subunit in $GABA_A$ receptors may determine the extent to which pentobarbital can potentiate the effects of GABA (Mehta and Ticku 1999). In contrast to benzodiazepines such as diazepam, pentobarbital can potentiate the action of GABA in receptors containing α_4 and α_6 subunits (Mehta and Ticku 1999).

Psychological Effects

Barbiturates create a sense of relaxation, reduce tensions, and induce euphoria as measured by standardized scales. Concentration is greatly reduced, as is judgment, and irritability often results. Chronic use slurs speech and leads to incoherence, staggered gait, and tremors.

CNS Effects

The administration of butabarbital to recreational drug users produces significant elevations in drug liking and abuse potential scale scores (Zawertailo et al. 2003). The abuse potential of butabarbital appears to be significantly greater than that of either triazolam or meprobamate (Zawertailo et al. 2003). As previously described, all barbiturates produce general CNS depression, and they have been used to treat anxiety. Barbiturates with a 5-phenyl substituent (phenobarbital and mephobarbital) have an anticonvulsant effect as well. The effects of barbiturates are largely nonselective, and general CNS depression is required to produce a particular effect, although pain sensitivity is unaffected by barbiturates until the subject loses consciousness.

Barbiturates alter characteristics of sleep, with body movement and the number of awakenings per night being reduced. Rapid eye movement (REM) activity is reduced, although in the last third of the night some REM compensation occurs. Slow-wave sleep (stages 3 and 4) is shortened, although phenobarbital may increase stage 4 sleep.

Effects on Other Organs

Respiratory drive and rhythm are depressed by barbiturates. Coughing, sneezing, hiccupping, and laryngospasm may occur during anesthesia with barbiturates. Sedative or hypnotic doses of barbiturates reduce heart rate and blood pressure to levels found in normal sleep. Anesthetic doses produce more pronounced effects. Barbiturates cross the placenta; when used in labor, they can cause respiratory depression in neonates. Anesthetic doses decrease force and frequency of uterine contractions among pregnant women.

Pharmacokinetics

The pharmacokinetics of barbiturates have been discussed by Charney et al. (2001) and Harvey (1985). When used as hypnotics or antianxiety agents, the barbiturates are administered orally. As anticonvulsants, they may be used either orally or intravenously, although the latter route of administration may be problematic because these drugs are very alkaline and necrosis and pain occur at the site of injection.

Barbiturates are primarily absorbed in the intestine and bind to plasma albumin in varying degrees on the basis of their lipid solubility (the more lipid soluble, the more highly bound). The most lipid-soluble barbiturates (e.g., thiopental) reach the gray matter of the brain in a flow-limited uptake within 30 seconds, inducing sleep shortly thereafter. Because they are highly vascular, the heart, liver, and kidney also quickly reach their equilibrium concentrations. In contrast, barbiturates with low lipid solubility such as phenobarbital take up to 20 minutes to induce sleep, because permeability, and not flow, is the limitation on uptake. In both cases, the drug then redistributes to the less vascular brain areas and to smooth muscle and skin within about 30 minutes and to fat after 60 minutes. With short-acting barbiturates, this redistribution reduces gray matter levels of the drug by up to 90% and is responsible for termination of the drug effect after a single dose.

Elimination of barbiturates depends on their lipid solubility. Lipid-soluble barbiturates are highly bound; these are poorly filtered by the kidneys and reabsorbed from the lumina and tubules. Appreciable amounts (e.g., 25%) of less lipid-soluble barbiturates, such as phenobarbital, may be excreted unchanged in the urine. Both urine alkalinization and osmotic diuresis increase renal excretion of phenobarbital or other less lipid-soluble barbiturates. Oxybarbiturates are metabolized exclusively in the liver; thiobarbiturates are also metabolized in the kidney and brain. Metabolites are more polar than the parent compounds and are easily excreted. Because of long elimination half-lives, oral doses of barbiturates will accumulate during chronic administration, requiring dosage adjustment to avoid toxicity. There is some evidence that enantiomers of barbiturates have different clinical effects and kinetic characteristics.

Clinical Uses

Although benzodiazepines have largely replaced the barbiturates in the treatment of anxiety and insomnia, the barbiturates still have many therapeutic uses (Cooper 1977; Harvey 1985). In psychiatry, they are used to treat agitated psychotic patients who are unresponsive to neuroleptics alone or to neuroleptics with benzodiazepines. Occasionally, patients withdrawing from alcohol will be resistant to benzodiazepines yet be responsive to barbiturates. The barbiturates are also used in catatonia ("Amytal interview") to temporarily relieve symptoms, permitting the patient to eat, bathe, and give historical information to the staff. Butalbutal is a component of a commonly used treatment for migraine and tension headaches (Silberstein and McCrory 2001). In other areas of medicine, barbiturates are sometimes used as sedatives for ill children, in seizure disorders, as preanesthetic agents, and to induce anesthesia.

Toxicity

The most common unwanted effects of the barbiturates are oversedation and psychomotor impairment, which may persist well into the next day following a hypnotic dose. Paradoxical excitement, hypersensitivity reactions, and muscle or joint pain may occur in rare cases. Drug-drug interactions occur with the CNS sedatives, and a number of drugs have enhanced metabolism when co-administered with barbiturates (Barnhill et al. 1989).

Death from overdose of barbiturates may occur and is more likely when more than 10 times the hypnotic dose is ingested. The barbiturates with high lipid solubility and short half-lives are the most toxic. Thus the lethal dose of phenobarbital is 6–10 g, whereas that of secobarbital, pentobarbital, or amobarbital is 2–3 g. Symptoms of barbiturate poisoning include CNS depression, coma, depressed reflex activity, a positive Babinski reflex, contracted pupils (with hypoxia there may be paralytic dilation), altered respiration, hypothermia, depressed cardiac function, hypotension, shock, pulmonary complications, and renal failure.

Tolerance and Withdrawal

Pharmacodynamic tolerance to barbiturates develops over weeks to months, whereas pharmacokinetic tolerance occurs in a period of days. At maximum tolerance, the dosage of a barbiturate may be six times the original dosage.

Pentobarbital withdrawal may involve a distal region of the chromosome 1 in the mouse (Buck et al. 1999), a site that may be identical to that associated with alcohol withdrawal. This finding suggests that common genes may be involved in both ethanol and pentobarbital dependence.

Detoxification

Tolerance to the clinical effects of barbiturates and an abstinence syndrome occurring on abrupt discontinuation of administration are well recognized. We have previously described the management of barbiturate withdrawal (Ciraulo and Ciraulo 1988). The oxybarbiturates, with short to intermediate elimination half-lives (such as butalbital, amobarbital, secobarbital, and pentobarbital), are most likely to produce a withdrawal syndrome. Figure 3–3 shows the periods of onset and duration of the signs and symptoms of the barbiturate abstinence syndrome occurring after the abrupt withdrawal of secobarbital or pentobarbital following chronic intoxication at oral doses of 0.8–2.2 g/day for 6 weeks or more. According to Wikler's (1968) classification, minor symptoms (apprehension, muscular weakness, tremors, postural hypotension, twitches, insomnia, diaphoresis, paroxysmal discharges in the electroencephalogram [EEG], and anorexia) appear within 24 hours of the last barbiturate dose and persist up to 2 weeks. Major abstinence phenomena include clonic-tonic seizures and delirium. Two-thirds of patients with seizures have more than one, and they may have as many as four. The interictal EEG

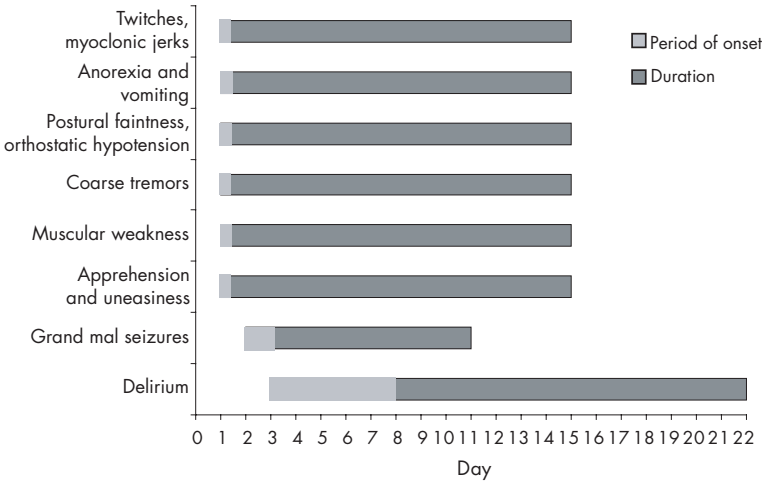

Figure 3–3. Signs and symptoms of barbiturate withdrawal.

shows recurrent 4-per-second spike-wave discharges. The delirium may be accompanied by hyperthermia, which can be fatal. Chronic intoxication with pentobarbital at a daily dosage of 0.6–0.8 g for periods of 35–57 days produces a clinically significant withdrawal syndrome; a daily dosage of 0.2–0.4 g for 90 days or more rarely leads to withdrawal symptoms.

There are three common protocols for barbiturate detoxification. In all approaches, the goal is to prevent the occurrence of major symptoms and to minimize the development of intolerable minor symptoms. The first procedure is based on protocols described by several authors (Ewing and Bakewell 1967; Isbell 1950; Wikler 1968) (see Table 3–4). The first step is to determine the severity of tolerance. If the patient is intoxicated, no additional barbiturate should be given until the symptoms of intoxication have resolved. If there is substantial evidence or strong suspicion of chronic barbiturate use, it is not necessary or desirable to wait until withdrawal symptoms appear. A 200-mg oral dose of pentobarbital may be given on an empty stomach to a

Table 3–4. Guidelines for barbiturate detoxification

Symptoms after test dose of 200 mg of oral pentobarbital	Estimated 24-hour oral pentobarbital dose (mg)	Estimated 24-hour oral phenobarbital dose (mg)
Asleep, but can be aroused	0	0
Sedated, drowsy, slurred speech, nystagmus, ataxia, positive Romberg test result	500–600	150–200
Few signs of intoxication, patient is comfortable, may have lateral nystagmus	800	250
No drug effect	1,000–1,200	300–400

Note. Maximum phenobarbital dose is 600 mg.
Source. Procedure modified from Ewing and Bakewell 1967.

sober patient (i.e., one who is not exhibiting signs of barbiturate intoxication), and the effects are observed at 1 hour. The patient's condition 1 hour after the test is used to determine the daily dose for stabilization.

If no physical changes are observed after 1 hour, the test is repeated 3 hours later with 300 mg. If there is no response to the 300-mg dose, the probable 24-hour requirement is above 1,600 mg/day. The daily dosage is given in divided doses every 4–6 hours for a stabilization period lasting 2–3 days. Withdrawal regimens must be individualized, but the initial reduction is usually 10% of the daily stabilization dose. Some clinicians recommend the use of phenobarbital for stabilization and withdrawal, because it is longer acting and may provide a smoother course of withdrawal. Phenobarbital doses are one-third those suggested for pentobarbital and may be adapted to the schedule described for pentobarbital. The barbiturate withdrawal protocol can also be used for other sedative-hypnotic abstinence syndromes (e.g., syndromes associated with chloral hydrate, glutethimide, and meprobamate).

The second protocol for barbiturate withdrawal has been proposed by Sellers (1988). Citing uncertainties regarding dosage, reinforcement of drug-taking behavior by repeated administration, and difficulties assessing the clinical state as shortcomings of the older protocol, he proposed a loading-dose strategy. With this protocol, 120-mg doses of phenobarbital are given every 1–2

Table 3–5. Sedative-hypnotic dose equivalency (equal to 30 mg of phenobarbital)

Generic name	Dose (mg)
Secobarbital	100
Pentobarbital	60
Chloral hydrate	250
Glutethimide	250
Meprobamate	200
Diazepam	5

hours until three of five signs—nystagmus, drowsiness, ataxia, dysarthria, and emotional lability—are present or, if the patient is symptomatic, withdrawal signs disappear. Patients are assessed for therapeutic or toxic effects before each dose. (It should be emphasized that some clinicians recommend lower individual phenobarbital doses, such as 40-mg doses.). Sellers reported that the total loading dose was 1,440 mg among the patients he tested. In some cases, hourly doses are required for 15–20 hours. In medically ill patients, phenobarbital may be infused intravenously (0.3 mg/kg/minute). For this protocol, medical supervision is necessary for 3 days. Patients who require less than 7 mg/kg (usually about 480 mg) are not sufficiently dependent to require further detoxification.

The third protocol is to determine the level of drug use and calculate equivalent doses of phenobarbital (Table 3–5). The patient is stabilized on this dose (divided into administration every 8 hours) for a few days, and then the dose is tapered by 10% daily. Although this method has its proponents, the determination of equivalency is an approximation, drug histories are unreliable, and mixed sedative-hypnotic dependence will complicate the procedure.

Glutethimide Dependence

Glutethimide (3-ethyl-3-phenyl-2,6-piperidinedione) is a sedative-hypnotic drug that is now rarely used therapeutically because of wide variation in gastrointestinal absorption, fast development of pharmacodynamic tolerance, a fairly severe discontinuation syndrome, and potential for abuse. Reports of

glutethimide dependence have declined pari passu with a decline in physician prescribing. The drug, when taken along with codeine orally, is reported to be euphorigenic in a manner resembling parenteral opioids (Khajawall et al. 1982; Sramek and Khajawall 1981).

Patients with glutethimide intoxication may present with CNS depression, widely dilated and fixed pupils, less respiratory depression than with barbiturates (although sudden apnea may occur), and a waxing and waning course that may persist for up to 120 hours (Maher et al. 1962). It has been suggested that such fluctuations may actually represent superimposed withdrawal phenomena (Bauer et al. 1988). The abstinence syndrome may include tremulousness, nausea, tachycardia, fever, tonic muscle spasms, and generalized convulsions (Harvey 1985). Catatonia-like symptoms and dyskinesias have been associated with glutethimide withdrawal (Campbell et al. 1983; Good 1975).

Detoxification may be accomplished with phenobarbital (60 mg of phenobarbital for 500 mg of glutethimide). If concomitant codeine dependence is present (and this codependence should be strongly suspected), then methadone can be used adjunctively (10 mg of methadone for 120 mg of codeine) (Khajawall et al. 1982). Approximate sedative-hypnotic dosage equivalencies are listed in Table 3–5.

Conclusion

The benzodiazepines and selective $GABA_{A1}$ agonists, which are in common clinical use, are associated with lower abuse liability and toxicity than older sedative-hypnotics, including the barbiturates. Their mechanisms of action are similar but not identical, which may influence their efficacy, abuse liability, and abstinence syndrome. There are clinically significant differences in abuse liability between and within the drug classes, although patients' characteristics strongly influence the potential for misuse. The mechanisms by which tolerance develops to these agents also differ, as does the specific pattern of pharmacologic actions that are most affected by tolerance. However, the therapeutic principles of prescribing are similar, requiring accurate diagnosis, appropriate dosage and length of treatment, close medical management of the abstinence syndrome, and vigilance concerning misuse, especially in high-risk populations.

References

Allison C, Pratt JA: Neuroadaptive processes in GABAergic and glutamatergic systems in benzodiazepine dependence. Pharmacol Ther 98:171–195, 2003

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000

Anzini M, Canullo L, Braile C, et al: Synthesis, biological evaluation, and receptor docking simulations of 2-[(acylamino)ethyl]-1,4-benzodiazepines as kappa-opioid receptor agonists endowed with antinociceptive and antiamnesic activity. J Med Chem 46:3853–3864, 2003

Apsler R, Rothman E: Correlates of compliance with psychoactive prescriptions. J Psychoactive Drugs 16:193–199, 1984

Arendt RM, Greenblatt DJ, deJong RH, et al: In vitro correlates of benzodiazepine cerebrospinal fluid uptake, pharmacodynamic action and peripheral distribution. J Pharmacol Exp Ther 227:98–106, 1983

Ashley MJ, le Riche WH, Hatcher J, et al: 'Mixed' (drug abusing) and 'pure' alcoholics: a socio-medical comparison. Br J Addict Alcohol Other Drugs 73:19–34, 1978

Ashton H: Benzodiazepine withdrawal: an unfinished story. Br Med J (Clin Res Ed) 288:1135–1140, 1984

Atack JR: Anxioselective compounds acting at the GABA(A) receptor benzodiazepine binding site. Curr Drug Target CNS Neurol Disord 2:213–232, 2003

Ator NA: Relation between discriminative and reinforcing effects of midazolam, pentobarbital, chlordiazepoxide, zolpidem, and imidazenil in baboons. Psychopharmacology (Berl) 163:477–487, 2002

Ator NA: Selectivity in generalization to GABAergic drugs in midazolam-trained baboons. Pharmacol Biochem Behav 75:435–445, 2003

Ator NA, Weerts EM, Kaminski BJ, et al: Zaleplon and triazolam physical dependence assessed across increasing doses under a once-daily dosing regimen in baboons. Drug Alcohol Depend 61:69–84, 2000

Balter MB, Manheimer DI, Mellinger GD, et al: A cross-national comparison of anti-anxiety/sedative drug use. Curr Med Res Opin 8(suppl 4):5–20, 1984

Barker MJ, Greenwood KM, Jackson M, et al: Cognitive effects of long-term benzodiazepine use: a meta-analysis. CNS Drugs 18:37–48, 2004

Barnard EA, Skolnick P, Olsen RW, et al: International Union of Pharmacology. XV. Subtypes of gamma-aminobutyric acidA receptors: classification on the basis of subunit structure and receptor function. Pharmacol Rev 50:291–313, 1998

Barnhill JG, Ciraulo AM, Ciraulo DA: Interactions of importance in chemical dependence, in Drug Interactions in Psychiatry, 1st Edition. Edited by Ciraulo DA, Shader RI, Greenblatt DJ, et al. Baltimore, MD, Williams & Wilkins, 1989, pp 234–237

Bauer MS, Fus AF, Hanich RF, et al: Glutethimide intoxication and withdrawal. Am J Psychiatry 145:530–531, 1988

Bell R, Havlicek PL, Roncek DW: Sex differences in the use of alcohol and tranquilizers: testing a role convergence hypothesis. Am J Drug Alcohol Abuse 10:551–561, 1984

Bossert JM, Franklin KB: Pentobarbital-induced place preference in rats is blocked by GABA, dopamine, and opioid antagonists. Psychopharmacology (Berl) 157:115–122, 2001

Bowden CL, Fisher JG: Safety and efficacy of long-term diazepam therapy. South Med J 73:1581–1584, 1980

Braestrup C, Nielsen M, Honore T, et al: Benzodiazepine receptor ligands with positive and negative efficacy. Neuropharmacology 22:1451–1457, 1983

Brogden RN, Goa KL: Flumazenil: a preliminary review of its benzodiazepine antagonist properties, intrinsic activity and therapeutic use. Drugs 35:448–467, 1988

Bruce TJ, Spiegel DA, Hegel MT: Cognitive-behavioral therapy helps prevent relapse and recurrence of panic disorder following alprazolam discontinuation: a long-term follow-up of the Peoria and Dartmouth studies. J Consult Clin Psychol 67: 151–156, 1999

Buck K, Metten P, Belknap J, et al: Quantitative trait loci affecting risk for pentobarbital withdrawal map near alcohol withdrawal loci on mouse chromosomes 1, 4, and 11. Mamm Genome 10:431–437, 1999

Buldakova S, Weiss M: Electrophysiological evidence for agonist properties of flumazenil, a benzodiazepine receptor antagonist, in rat hippocampus slices. J Neurol Sci 149:121–126, 1997

Busto U, Simpkins J, Sellers EM, et al: Objective determination of benzodiazepine use and abuse in alcoholics. Br J Addict 78:429–435, 1983

Busto U, Sellers EM, Naranjo CA, et al: Withdrawal reaction after long-term therapeutic use of benzodiazepines. N Engl J Med 315:854–859, 1986a

Busto U, Sellers EM, Naranjo CA, et al: Patterns of benzodiazepine abuse and dependence. Br J Addict 81:87–94, 1986b

Busto UE, Romach MK, Sellers EM: Multiple drug use and psychiatric comorbidity in patients admitted to the hospital with severe benzodiazepine dependence. J Clin Psychopharmacol 16:51–57, 1996

Caille G, Spenard J, Lacasse Y, et al: Pharmacokinetics of two lorazepam formulations, oral and sublingual, after multiple doses. Biopharm Drug Dispos 4:31–42, 1983

Campbell R, Schaffer CB, Tupin J: Catatonia associated with glutethimide withdrawal. J Clin Psychiatry 44:32–33, 1983

Cantopher T, Olivieri S, Cleave N, et al: Chronic benzodiazepine dependence: a comparative study of abrupt withdrawal under propranolol cover versus gradual withdrawal. Br J Psychiatry 156:406–411, 1990

Caplan RD, Andrews FM, Conway TL, et al: Social effects of diazepam use: a longitudinal field study. Soc Sci Med 21:887–898, 1985

Charney DA, Paraherakis AM, Gill KJ: The treatment of sedative-hypnotic dependence: evaluating clinical predictors of outcome. J Clin Psychiatry 61:190–195, 2000

Charney DA, Paraherakis AM, Gill KJ: Integrated treatment of comorbid depression and substance use disorders. J Clin Psychiatry 62:672–677, 2001

Chen S, Huang X, Zeng XJ, et al: Benzodiazepine-mediated regulation of $alpha_1$, $alpha_2$, $beta_{1-3}$ and $gamma_2$ GABA(A) receptor subunit proteins in the rat brain hippocampus and cortex. Neuroscience 93:33–44, 1999

Ciraulo DA, Ciraulo AM: Substance abuse, in Handbook of Clinical Psychopharmacology, 2nd Edition. Edited by Tupin JP, Shader RI, Harnett DS. Northvale, NJ, Jason Aronson, 1988, pp 121–158

Ciraulo DA, Nace EP: Benzodiazepine treatment of anxiety or insomnia in substance abuse patients. Am J Addict 9:276–284, 2000

Ciraulo DA, Barnhill JG, Greenblatt DJ, et al: Abuse liability and clinical pharmacokinetics of alprazolam in alcoholic men. J Clin Psychiatry 49:333–337, 1988a

Ciraulo DA, Sands BF, Shader RI: Critical review of liability for benzodiazepine abuse among alcoholics. Am J Psychiatry 145:1501–1506, 1988b

Ciraulo DA, Barnhill JG, Ciraulo AM, et al: Parental alcoholism as a risk factor in benzodiazepine abuse: a pilot study. Am J Psychiatry 146:1333–1335, 1989

Ciraulo DA, Antal EJ, Smith RB, et al: The relationship of alprazolam dose to steady-state plasma concentrations. J Clin Psychopharmacol 10:27–32, 1990

Ciraulo DA, Sarid-Segal O, Knapp C, et al: Liability to alprazolam abuse in daughters of alcoholics. Am J Psychiatry 153:956–958, 1996

Ciraulo DA, Barnhill JG, Ciraulo AM, et al: Alterations in pharmacodynamics of anxiolytics in abstinent alcoholic men: subjective responses, abuse liability, and electroencephalographic effects of alprazolam, diazepam, and buspirone. J Clin Pharmacol 37:64–73, 1997

Ciraulo DA, Knapp CM, LoCastro JS, et al: A benzodiazepine mood effect scale: reliability and validity determined for alcohol-dependent subjects and adults with a parental history of alcoholism. Am J Drug Alcohol Abuse 27:339–347, 2001

Ciraulo DA, Sarid-Segal O, Ciraulo JA: Sedative-, hypnotic-, or anxiolytic-related disorders, in Comprehensive Textbook of Psychiatry, 8th Edition, Vol. 1. Edited by Sadock BJ, Sadock BA. New York, Lippincott Williams & Wilkins, 2004, pp 1300–1318

Conell LJ, Berlin RM: Withdrawal after substitution of a short-acting for a long-acting benzodiazepine. JAMA 250:2838–2840, 1983

Cooper JR: Sedative-Hypnotic Drugs: Risks and Benefits (DHEW Publ No ADM-78–592). Rockville, MD, National Institute on Drug Abuse, 1977

Covi L, Lipman RS, Pattison JH, et al: Length of treatment with anxiolytic sedatives and response to their sudden withdrawal. Acta Psychiatr Scand 49:51–64, 1973

Cumming RG, Miller JP, Kelsey JL, et al: Medications and multiple falls in elderly people: the St Louis OASIS study. Age Ageing 20:455–461, 1991

Cumming RG, Le Couteur DG: Benzodiazepines and risk of hip fractures in older people: a review of the evidence. CNS Drugs 17:825–837, 2003

Curran HV: Tranquillising memories: a review of the effects of benzodiazepines on human memory. Biol Psychol 23:179–213, 1986

Cushman P, Benzer D: Benzodiazepines and drug abuse: clinical observations in chemically dependent persons before and during abstinence. Drug Alcohol Depend 6:365–371, 1980

Darke S, Ross J, Teesson M, et al: Health service utilization and benzodiazepine use among heroin users: findings from the Australian Treatment Outcome Study (ATOS). Addiction 98:1129–1135, 2003

Darragh A, Lambe R, Kenny M, et al: Tolerance of healthy volunteers to intravenous administration of the benzodiazepine antagonist Ro 15-1788. Eur J Clin Pharmacol 24:569–370, 1983

de las Cuevas C, Sanz E, de la Fuente J: Benzodiazepines: more "behavioural" addiction than dependence. Psychopharmacology (Berl) 167:297–303, 2003

de Wit H, Johanson CE, Uhlenhuth EH: Reinforcing properties of lorazepam in normal volunteers. Drug Alcohol Depend 13:31–41, 1984

de Wit H, Pierri J, Johanson CE: Reinforcing and subjective effects of diazepam in nondrug-abusing volunteers. Pharmacol Biochem Behav 33:205–213, 1989

Dealberto MJ, McAvay GJ, Seeman T, et al: Psychotropic drug use and cognitive decline among older men and women. Int J Geriatr Psychiatry 12:567–574, 1997

Dennis T, Dubois A, Benavides J, et al: Distribution of central omega$_1$ (benzodiazepine$_1$) and omega$_2$ (benzodiazepine$_2$) receptor subtypes in the monkey and human brain: an autoradiographic study with [^{3}H]flunitrazepam and the omega$_1$ selective ligand [^{3}H]zolpidem. J Pharmacol Exp Ther 247:309–322, 1988

DiChiara G, Imperato A: Preferential stimulation of dopamine release in the nucleus accumbens by opiates, alcohol, and barbiturates: studies with transcerebral dialysis in freely moving rats. Ann N Y Acad Sci 473:367–381, 1986

DiChiara G, Imperato A: Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc Natl Acad Sci U S A 85:5274–5278, 1988

Dinwiddie SH, Cottler L, Compton W, et al: Psychopathology and HIV risk behaviors among injection drug users in and out of treatment. Drug Alcohol Depend 43:1–11, 1996

Dunbar GC, Perera MH, Jenner FA: Patterns of benzodiazepine use in Great Britain as measured by a general population survey. Br J Psychiatry 155:836–841, 1989

Elie R, Ruther E, Farr I, et al: Sleep latency is shortened during 4 weeks of treatment with zaleplon, a novel nonbenzodiazepine hypnotic. Zaleplon Clinical Study Group. J Clin Psychiatry 60:536–544, 1999

Ensrud KE, Blackwell T, Mangione CM, et al: Central nervous system active medications and risk for fractures in older women. Arch Intern Med 163:949–957, 2003

Evans SM, Griffiths RR, de Wit H: Preference for diazepam, but not buspirone, in moderate drinkers. Psychopharmacology (Berl) 123:154–163, 1996

Ewing JA, Bakewell WE: Diagnosis and management of depressant drug dependence. Am J Psychiatry 123:909–917, 1967

Fahey JM, Pritchard GA, Grassi JM, et al: Pharmacodynamic and receptor binding changes during chronic lorazepam administration. Pharmacol Biochem Behav 69:1–8, 2001

File SE: Tolerance to the behavioral actions of benzodiazepines. Neurosci Biobehav Rev 9:113–121, 1985

Finlay JM, Damsma G, Fibiger HC: Benzodiazepine-induced decreases in extracellular concentrations of dopamine in the nucleus accumbens after acute and repeated administration. Psychopharmacology (Berl) 106:202–208, 1992

Fishbain DA, Rosomoff HL, Rosomoff RS: Drug abuse, dependence, and addiction in chronic pain patients. Clin J Pain 8:77–85, 1992

Fleischhacker WW, Barnas C, Hackenberg B: Epidemiology of benzodiazepine dependence. Acta Psychiatr Scand 74:80–83, 1986

Frenkel C, Duch DS, Urban BW: Molecular actions of pentobarbital isomers on sodium channels from human brain cortex. Anesthesiology 72:640–649, 1990

Fry J, Scharf M, Mangano R, et al: Zaleplon improves sleep without producing rebound effects in outpatients with insomnia. Zaleplon Clinical Study Group. Int Clin Psychopharmacol 15:141–152, 2000

Fyer AJ, Liebowitz MR, Gorman JM, et al: Effects of clonidine on alprazolam discontinuation in panic patients: a pilot study. J Clin Psychopharmacol 8:270–274, 1988

Garvey MJ, Tollefson GD: Prevalence of misuse of prescribed benzodiazepines in patients with primary anxiety disorder or major depression. Am J Psychiatry 143: 1601–1603, 1986

Gerra G, Zaimovic A, Giusti F, et al: Intravenous flumazenil versus oxazepam tapering in the treatment of benzodiazepine withdrawal: a randomized, placebo-controlled study. Addict Biol 7:385–395, 2002

Good MI: Catatonia-like symptomatology and withdrawal dyskinesias. Am J Psychiatry 133:1454–1456, 1975

Goodman WK, Charney DS, Price LH, et al: Ineffectiveness of clonidine in the treatment of the benzodiazepine withdrawal syndrome: report of three cases. Am J Psychiatry 143:900–903, 1986

Gottschalk LA, Bates DE, Fox RA, et al: Psychoactive drug use: patterns found in samples from a mental health clinic and a general medical clinic. Arch Gen Psychiatry 25:395–397, 1971

Gray A, Allison C, Pratt JA: A role for AMPA/kainate receptors in conditioned place preference induced by diazepam in the rat. Neurosci Lett 268:127–130, 1999

Greenblatt DJ, Shader RI: Dependence, tolerance, and addiction to benzodiazepines: clinical and pharmacokinetic considerations. Drug Metab Rev 8:13–28, 1978

Greenblatt DJ, Shader RI: Long-term administration of benzodiazepines: pharmacokinetic versus pharmacodynamic tolerance. Psychopharmacol Bull 22:416–423, 1986

Greenblatt DJ, Shader RI, Koch-Weser J: Psychotropic drug use in the Boston area: a report from the Boston Collaborative Drug Surveillance Program. Arch Gen Psychiatry 32:518–521, 1975

Greenblatt DJ, Shader RI, Harmatz JS, et al: Self-rated sedation and plasma concentrations of desmethyldiazepam following single doses of clorazepate. Psychopharmacology (Berl) 66:289–290, 1979

Greenblatt DJ, Divoll M, Harmatz JS, et al: Pharmacokinetic comparison of sublingual lorazepam with intravenous, intramuscular, and oral lorazepam. J Pharm Sci 71: 248–252, 1982

Greenblatt DJ, Shader RI, Abernethy DR: Drug therapy. Current status of benzodiazepines. N Engl J Med 309:354–358, 1983a

Greenblatt DJ, Shader RI, Abernethy DR: Drug therapy. Current status of benzodiazepines. N Engl J Med 309:410–416, 1983b

Greenblatt DJ, Harmatz JS, Zinny MA, et al: Effect of gradual withdrawal on the rebound sleep disorder after discontinuation of triazolam. N Engl J Med 317:722–728, 1987

Greenblatt DJ, Harmatz JS, von Moltke LL, et al: Comparative kinetics and dynamics of zaleplon, zolpidem, and placebo. Clin Pharmacol Ther 64:553–561, 1998

Greenblatt DJ, von Moltke LL, Harmatz JS, et al: Differential impairment of triazolam and zolpidem clearance by ritonavir. J Acquir Immune Defic Syndr 24:129–136, 2000

Griffiths RR, Wolf B: Relative abuse liability of different benzodiazepines in drug abusers. J Clin Psychopharmacol 10:237–243, 1990

Griffiths RR, Weerts EM: Benzodiazepine self-administration in humans and laboratory animals—implications for problems of long-term use and abuse. Psychopharmacology (Berl) 134:1–37, 1997

Griffiths RR, Bigelow GE, Liebson I, et al: Drug preference in humans: double-blind choice comparison of pentobarbital, diazepam and placebo. J Pharmacol Exp Ther 215:649–661, 1980

Griffiths RR, McLeod DR, Bigelow GE, et al: Comparison of diazepam and oxazepam: preference, liking and extent of abuse. J Pharmacol Exp Ther 229:501–508, 1984

Griffiths RR, Evans SM, Guarino JJ, et al: Intravenous flumazenil following acute and repeated exposure to lorazepam in healthy volunteers: antagonism and precipitated withdrawal. J Pharmacol Exp Ther 265:1163–1174, 1993

Hadingham KL, Wingrove P, Le Bourdelles B, et al: Cloning of cDNA sequences encoding human alpha 2 and alpha 3 gamma-aminobutyric acidA receptor subunits and characterization of the benzodiazepine pharmacology of recombinant alpha 1-, alpha 2-, alpha 3-, and alpha 5-containing human gamma-aminobutyric acidA receptors. Mol Pharmacol 43:970–975, 1993

Hajak G, Muller WE, Wittchen HU, et al: Abuse and dependence potential for the non-benzodiazepine hypnotics zolpidem and zopiclone: a review of case reports and epidemiological data. Addiction 98:1371–1378, 2003

Hallstrom C, Lader MH: The incidence of benzodiazepine dependence in long-term users. J Psychiatr Treat Eval 1982:293–296, 1982

Hanlon JT, Horner RD, Schmader KE, et al: Benzodiazepine use and cognitive function among community-dwelling elderly. Clin Pharmacol Ther 64:684–692, 1998

Hardo PG, Kennedy TD: Night sedation and arthritic pain. J R Soc Med 84:73–75, 1991

Harvey SC: Hypnotics and sedatives, in Goodman and Gilman's The Pharmacologic Basis of Therapeutics, 7th Edition. Edited by Gilman AG, Goodman LS, Rall TW, et al. New York, Macmillan, 1985, pp 339–371

Hendler N, Cimini C, Ma T, et al: A comparison of cognitive impairment due to benzodiazepines and to narcotics. Am J Psychiatry 137:828–830, 1980

Herman JB, Rosenbaum JF, Brotman AW: The alprazolam to clonazepam switch for the treatment of panic disorder. J Clin Psychopharmacol 7:175–178, 1987

Higgitt A, Lader M, Fonagy P: The effects of the benzodiazepine antagonist Ro 15–1788 on psychophysiological performance and subjective measures in normal subjects. Psychopharmacology (Berl) 89:395–403, 1986

Hollister LE, Motzenbecker FP, Degan RO: Withdrawal reactions from chlordiazepoxide ("Librium"). Psychopharmacologia 2:63–68, 1961

Hollister LE, Bennett JL, Kimbell I Jr, et al: Diazepam in newly admitted schizophrenics. Dis Nerv Syst 24:746–750, 1963

Ibrahim RB, Wilson JG, Thorsby ME, et al: Effect of buprenorphine on CYP3A activity in rat and human liver microsomes. Life Sci 66:1293–1298, 2000

Iguchi MY, Handelsman L, Bickel WK, et al: Benzodiazepine and sedative use/abuse by methadone maintenance clients. Drug Alcohol Depend 32:257–266, 1993

Isbell H: Manifestations and treatment of addiction to narcotic drugs and barbiturates. Med Clin North Am 34:425–438, 1950

Jaffe JH, Ciraulo DA, Nies A, et al: Abuse potential of halazepam and of diazepam in patients recently treated for acute alcohol withdrawal. Clin Pharmacol Ther 34: 623–630, 1983

Johanson CE, de Wit H: Lack of effect of social context on the reinforcing effects of diazepam in humans. Pharmacol Biochem Behav 43:463–469, 1992

Johansson BA, Berglund M, Hanson M, et al: Dependence on legal psychotropic drugs among alcoholics. Alcohol Alcohol 38:613–618, 2003

Joo DT, Xiong Z, MacDonald JF, et al: Blockade of glutamate receptors and barbiturate anesthesia: increased sensitivity to pentobarbital-induced anesthesia despite reduced inhibition of AMPA receptors in GluR2 null mutant mice. Anesthesiology 91:1329–1341, 1999

Kamiya Y, Andoh T, Furuya R, et al: Comparison of the effects of convulsant and depressant barbiturate stereoisomers on AMPA-type glutamate receptors. Anesthesiology 90:1704–1713, 1999

Kania J, Kofoed L: Drug use by alcoholics in outpatient treatment. Am J Drug Alcohol Abuse 10:529–534, 1984

Khajawall AM, Sramek JJ, Jr., Simpson GM: 'Loads' alert. West J Med 137:166–168, 1982

Kilicarslan T, Sellers EM: Lack of interaction of buprenorphine with flunitrazepam metabolism. Am J Psychiatry 157:1164–1166, 2000

King SA, Strain JJ: Benzodiazepines and chronic pain. Pain 41:3–4, 1990a

King SA, Strain JJ: Benzodiazepine use by chronic pain patients. Clin J Pain 6:143–147, 1990b

Klein E, Uhde TW, Post RM: Preliminary evidence for the utility of carbamazepine in alprazolam withdrawal. Am J Psychiatry 143:235–236, 1986

Kouyanou K, Pither CE, Wessely S: Medication misuse, abuse and dependence in chronic pain patients. J Psychosom Res 43:497–504, 1997

Kryspin-Exner K: [Misuse of bezodiazepine derivatives in alcoholics] (German). Br J Addict Alcohol Other Drugs 61:283–290, 1966

Kryspin-Exner K, Demel I: The use of tranquilizers in the treatment of mixed drug abuse. Int J Clin Pharmacol Biopharm 12:13–18, 1975

Kushner MG, Sher KJ, Beitman BD: The relation between alcohol problems and the anxiety disorders. Am J Psychiatry 147:685–695, 1990

Lader M, Olajide D: A comparison of buspirone and placebo in relieving benzodiazepine withdrawal symptoms. J Clin Psychopharmacol 7:11–15, 1987

Lejoyeux M, Solomon J, Ades J: Benzodiazepine treatment for alcohol-dependent patients. Alcohol Alcohol 33:563–575, 1998

Lingford-Hughes A, Hume SP, Feeney A, et al: Imaging the GABA-benzodiazepine receptor subtype containing the alpha5-subunit in vivo with [11C]Ro15 4513 positron emission tomography. J Cereb Blood Flow Metab 22:878–889, 2002

Lister RG: The amnesic action of benzodiazepines in man. Neurosci Biobehav Rev 9:87–94, 1985

Low K, Crestani F, Keist R, et al: Molecular and neuronal substrate for the selective attenuation of anxiety. Science 290:131–134, 2000

Luddens H, Pritchett DB, Kohler M, et al: Cerebellar GABAA receptor selective for a behavioural alcohol antagonist. Nature 346:648–651, 1990

Lupolover Y, Safran AB, Desangles D, et al: Evaluation of visual function in healthy subjects after administration of Ro 15–1788. Eur J Clin Pharmacol 27:505–507, 1984

Maher JF, Schreiner GE, Westervelt FB Jr: Acute glutethimide intoxication: I. clinical experience (twenty-two patients) compared to acute barbiturate intoxication (sixty-three patients). Am J Med 33:70–82, 1962

Marks J: The Benzodiazepines: Use, Overuse, Misuse, Abuse. Baltimore, MD, University Park Press, 1978

Marszalec W, Narahashi T: Use-dependent pentobarbital block of kainate and quisqualate currents. Brain Res 608:7–15, 1993

Matthew H: Acute Barbiturate Poisoning. Amsterdam, Excerpta Medica, 1971

Mattila-Evenden M, Bergman U, Franck J: A study of benzodiazepine users claiming drug-induced psychiatric morbidity. Nord J Psychiatry 55:271–278, 2001

Maubach K: GABA(A) receptor subtype selective cognition enhancers. Curr Drug Target CNS Neurol Disord 2:233–239, 2003

McAndrews PM, Weiss RT, Sandor P, et al: Cognitive effects of long-term benzodiazepine use in older adults. Hum Psychopharmacol 18:51–57, 2003

McKernan RM, Rosahl TW, Reynolds DS, et al: Sedative but not anxiolytic properties of benzodiazepines are mediated by the GABA(A) receptor alpha1 subtype. Nat Neurosci 3:587–592, 2000

Mehta AK, Ticku MK: An update on GABAA receptors. Brain Res Brain Res Rev 29: 196–217, 1999

Mellinger GD, Balter MB: Prevalence and patterns of use of psychotropic drugs: results from a 1979 national survey of American adults, in Epidemiological Impact of Psychotropic Drugs: Proceedings of International Seminar on Psychotropic Drugs. Edited by Tognomi G, Bellantuono C, Lader M. Amsterdam, North Holland, 1981, pp 117–135

Mellinger GD, Balter MB, Uhlenhuth EH: Prevalence and correlates of the long-term regular use of anxiolytics. JAMA 251:375–379, 1984

Miller LG, Greenblatt DJ, Barnhill JG, et al: Benzodiazepine receptor binding of triazolobenzodiazepines in vivo: increased receptor number with low-dose alprazolam. J Neurochem 49:1595–1601, 1987

Miller LG, Greenblatt DJ, Barnhill JG, et al: Chronic benzodiazepine administration, I: tolerance is associated with benzodiazepine receptor downregulation and decreased gamma-aminobutyric acidA receptor function. J Pharmacol Exp Ther 246:170–176, 1988a

Miller LG, Greenblatt DJ, Roy RB, et al: Chronic benzodiazepine administration, II: discontinuation syndrome is associated with upregulation of gamma-aminobutyric acid$_A$ receptor complex binding and function. J Pharmacol Exp Ther 246: 177–182, 1988b

Mintzer MZ, Stoller KB, Griffiths RR: A controlled study of flumazenil-precipitated withdrawal in chronic low-dose benzodiazepine users. Psychopharmacology (Berl) 147:200–209, 1999

Mueller TI, Goldenberg IM, Gordon AL, et al: Benzodiazepine use in anxiety disordered patients with and without a history of alcoholism. J Clin Psychiatry 57:83–89, 1996

Mumford GK, Evans SM, Fleishaker JC, et al: Alprazolam absorption kinetics affects abuse liability. Clin Pharmacol Ther 57:356–365, 1995a

Mumford GK, Rush CR, Griffiths RR: Abecarnil and alprazolam in humans: behavioral, subjective and reinforcing effects. J Pharmacol Exp Ther 272:570–580, 1995b

Nutt DJ, Linnoila M: Neuroreceptor science: a clarification of terms. J Clin Psychopharmacol 8:387–389, 1988

Nutt DJ, Glue P, Lawson C, et al: Flumazenil provocation of panic attacks: evidence for altered benzodiazepine receptor sensitivity in panic disorder. Arch Gen Psychiatry 47:917–925, 1990

Orzack MH, Cole JO, Ionescu-Pioggia M, et al: A comparison of some subjective effects of prazepam, diazepam, and placebo. NIDA Res Monogr 41:309–317, 1982

Otto MW, Pollack MH, Sachs GS, et al: Alcohol dependence in panic disorder patients. J Psychiatr Res 26:29–38, 1992

Otto MW, Pollack MH, Sachs GS, et al: Discontinuation of benzodiazepine treatment: efficacy of cognitive-behavioral therapy for patients with panic disorder. Am J Psychiatry 150:1485–1490, 1993

Oude Voshaar RC, Gorgels WJ, Mol AJ, et al: Tapering off long-term benzodiazepine use with or without group cognitive-behavioural therapy: three-condition, randomised controlled trial. Br J Psychiatry 182:498–504, 2003

Parry HJ, Balter MB, Mellinger GD, et al: National patterns of psychotherapeutic drug use. Arch Gen Psychiatry 28:18–74, 1973

Perera KM, Jenner FA: Some characteristics distinguishing high and low dose users of benzodiazepines. Br J Addict 82:1329–1334, 1987

Perez MF, Salmiron R, Ramirez OA: NMDA-NR1 and -NR2B subunits mRNA expression in the hippocampus of rats tolerant to diazepam. Behav Brain Res 144: 119–124, 2003

Petrovic M, Vandierendonck A, Mariman A, et al: Personality traits and socioepidemiological status of hospitalised elderly benzodiazepine users. Int J Geriatr Psychiatry 17:733–738, 2002

Petursson H, Lader MH: Benzodiazepine dependence. Br J Addict 76:133–145, 1981a

Petursson H, Lader MH: Withdrawal from long-term benzodiazepine treatment. Br Med J (Clin Res Ed) 283:643–645, 1981b

Pichard L, Gillet G, Bonfils C, et al: Oxidative metabolism of zolpidem by human liver cytochrome P450S. Drug Metab Dispos 23:1253–1262, 1995

Piesiur-Strehlow B, Strehlow U, Poser W: Mortality of patients dependent on benzodiazepines. Acta Psychiatr Scand 73:330–335, 1986

Piper A Jr: Addiction to benzodiazepines—how common? Arch Fam Med 4:964–970, 1995

Pontieri FE, Tanda G, DiChiara G: Intravenous cocaine, morphine, and amphetamine preferentially increase extracellular dopamine in the "shell" as compared with the "core" of the rat nucleus accumbens. Proc Natl Acad Sci U S A 92:12304–12308, 1995

Posternak MA, Mueller TI: Assessing the risks and benefits of benzodiazepines for anxiety disorders in patients with a history of substance abuse or dependence. Am J Addict 10:48–68, 2001

Pritchett DB, Seeburg PH: Gamma-aminobutyric acidA receptor alpha5-subunit creates novel type II benzodiazepine receptor pharmacology. J Neurochem 54:1802–1804, 1990

Reynaud M, Petit G, Potard D, et al: Six deaths linked to concomitant use of buprenorphine and benzodiazepines. Addiction 93:1385–1392, 1998

Richards JG, Martin JR: Binding profiles and physical dependence liabilities of selected benzodiazepine receptor ligands. Brain Res Bull 45:381–387, 1998

Rickels K, Case WG, Downing RW, et al: Long-term diazepam therapy and clinical outcome. JAMA 250:767–771, 1983

Rickels K, Case WG, Schweizer E, et al: Long-term benzodiazepine users 3 years after participation in a discontinuation program. Am J Psychiatry 148:757–761, 1991

Rickels K, Schweizer E: Anxiolytics: indications, benefits, and risks of short- and long-term benzodiazepine therapy: current research data. NIDA Res Monogr 131:51–67, 1993

Roache JD, Griffiths RR: Diazepam and triazolam self-administration in sedative abusers: concordance of subject ratings, performance and drug self-administration. Psychopharmacology (Berl) 99:309–315, 1989

Roache JD, Stanley MA, Creson DR, et al: Diazepam reinforcement in anxious patients. Exp Clin Psychopharmacol 4:308–314, 1996

Roache JD, Stanley MA, Creson DR, et al: Alprazolam-reinforced medication use in outpatients with anxiety. Drug Alcohol Depend 45:143–155, 1997

Roehrs T, Merlotti L, Zorick F, et al: Rebound insomnia and hypnotic self administration. Psychopharmacology (Berl) 107:480–484, 1992

Romach MK, Somer GR, Sobell LC, et al: Characteristics of long-term alprazolam users in the community. J Clin Psychopharmacol 12:316–321, 1992

Romach M, Busto U, Somer G, et al: Clinical aspects of chronic use of alprazolam and lorazepam. Am J Psychiatry 152:1161–1167, 1995

Rosenberg HC, Chiu TH: Time course for development of benzodiazepine tolerance and physical dependence. Neurosci Biobehav Rev 9:123–131, 1985

Ross J, Darke S: The nature of benzodiazepine dependence among heroin users in Sydney, Australia. Addiction 95:1785–1793, 2000

Rothstein E, Cobble JC, Sampson N: Chlordiazepoxide: long-term use in alcoholism. Ann N Y Acad Sci 273:381–384, 1976

Rush CR, Baker RW, Wright K: Acute behavioral effects and abuse potential of trazodone, zolpidem and triazolam in humans. Psychopharmacology (Berl) 144:220–233, 1999a

Rush CR, Frey JM, Griffiths RR: Zaleplon and triazolam in humans: acute behavioral effects and abuse potential. Psychopharmacology (Berl) 145:39–51, 1999b

Salinsky JV, Dore CJ: Characteristics of long term benzodiazepine users in general practice. J R Coll Gen Pract 37:202–204, 1987

Salva P, Costa J: Clinical pharmacokinetics and pharmacodynamics of zolpidem: therapeutic implications. Clin Pharmacokinet 29:142–153, 1995

Samarasinghe DS, Tilley S, Marks IM: Alcohol and sedative drug use in neurotic outpatients. Br J Psychiatry 145:45–48, 1984

Sanna E, Busonero F, Talani G, et al: Comparison of the effects of zaleplom, zolpidem, and triazolam at various $GABA_A$ receptor subtypes. Eur J Pharmacol 451:103–110, 2002

Saunders PA, Ho IK: Barbiturates and the $GABA_A$ receptor complex. Prog Drug Res 34:261–286, 1990

Saxon L, Hjemdahl P, Hiltunen AJ, et al: Effects of flumazenil in the treatment of benzodiazepine withdrawal—a double-blind pilot study. Psychopharmacology (Berl) 131:153–160, 1997

Schmidt LG, Grohmann R, Muller-Oerlinghausen B, et al: Prevalence of benzodiazepine abuse and dependence in psychiatric in-patients with different nosology: an assessment of hospital-based drug surveillance data. Br J Psychiatry 154:839–843, 1989

Schuckit MA, Morrissey ER: Drug abuse among alcoholic women. Am J Psychiatry 136:607–611, 1979

Schweizer E, Patterson W, Rickels K, et al: Double-blind, placebo-controlled study of a once-a-day, sustained-release preparation of alprazolam for the treatment of panic disorder. Am J Psychiatry 150:1210–1215, 1993

Seivewright N: Benzodiazepine misuse by illicit drug misusers. Addiction 96:333–334, 2001

Sellers EM: Alcohol, barbiturate and benzodiazepine withdrawal syndromes: clinical management. CMAJ 139:113–120, 1988

Silberstein SD, McCrory DC: Butalbital in the treatment of headache: history, pharmacology, and efficacy. Headache 41:953–967, 2001

Smith DE, Wesson DR: Benzodiazepine dependency syndromes. J Psychoactive Drugs 15:85–95, 1983

Sokolow L, Welte J, Hynes G, et al: Multiple substance use by alcoholics. Br J Addict 76:147–158, 1981

Spyraki C, Fibiger HC: A role for the mesolimbic dopamine system in the reinforcing properties of diazepam. Psychopharmacology (Berl) 94:133–137, 1988

Sramek JJ, Khajawall A: "Loads." N Engl J Med 305:231, 1981

Stahl SM: Don't ask, don't tell, but benzodiazepines are still the leading treatments for anxiety disorder. J Clin Psychiatry 63:756–757, 2002

Stephenson FA, Duggan MJ, Pollard S: The gamma 2 subunit is an integral component of the gamma-aminobutyric acidA receptor but the alpha 1 polypeptide is the principal site of the agonist benzodiazepine photoaffinity labeling reaction. J Biol Chem 265:21160–21165, 1990

Stitzer ML, Griffiths RR, McLellan AT, et al: Diazepam use among methadone maintenance patients: patterns and dosages. Drug Alcohol Depend 8:189–199, 1981

Stoops WW, Rush CR: Differential effects in humans after repeated administrations of zolpidem and triazolam. Am J Drug Alcohol Abuse 29:281–299, 2003

Strain EC, Brooner RK, Bigelow GE: Clustering of multiple substance use and psychiatric diagnoses in opiate addicts. Drug Alcohol Depend 27:127–134, 1991

Substance Abuse and Mental Health Services Administration: Treatment episode data set (TEDS), 1999. Available at http://www.icpsr.umich.edu/cocoon/ICPSR STUDY/03314.xml. Accessed Feburary 13, 2004

Substance Abuse and Mental Health Services Administration: Overview of Findings from 2002 National Survey on Drug Use and Health (DHHS Publ No SMA 03–3774). Rockville, MD, Substance Abuse and Mental Health Services Administration, 2003

Szabo ST, Gould TD, Manji HK: Neurotransmitters, receptors, signal transduction, and second messengers in psychiatric disorders, in American Psychiatric Publishing Textbook of Psychopharamcology, Third Edition. Edited by Schatzberg AF, Nemeroff CB. Washington, DC, American Psychiatric Publishing, 2004, pp 3–52

Tyrer P, Rutherford D, Huggett T: Benzodiazepine withdrawal symptoms and propranolol. Lancet 1:520–522, 1981

Van Sickle BJ, Tietz EI: Selective enhancement of AMPA receptor-mediated function in hippocampal CA1 neurons from chronic benzodiazepine-treated rats. Neuropharmacology 43:11–27, 2002

Vartzopoulos D, Bozikas V, Phocas C, et al: Dependence on zolpidem in high dose. Int Clin Psychopharmacol 15:181–182, 2000

Venault P, Chapouthier G, de Carvalho LP, et al: Benzodiazepine impairs and beta-carboline enhances performance in learning and memory tasks. Nature 321:864–866, 1986

Vermeeren A, Jackson JL, Muntjewerff ND, et al: Comparison of acute alprazolam (0.25, 0.50 and 1.0 mg) effects versus those of lorazepam 2 mg and placebo on memory in healthy volunteers using laboratory and telephone tests. Psychopharmacology (Berl) 118:1–9, 1995

Voderholzer U, Riemann D, Hornyak M, et al: A double-blind, randomized and placebo-controlled study on the polysomnographic withdrawal effects of zopiclone, zolpidem and triazolam in healthy subjects. Eur Arch Psychiatry Clin Neurosci 251:117–123, 2001

von Moltke LL, Greenblatt DJ, Granda BW, et al: Zolpidem metabolism in vitro: responsible cytochromes, chemical inhibitors, and in vivo correlations. Br J Clin Pharmacol 48:89–97, 1999

Vorma H, Naukkarinen H, Sarna S, et al: Treatment of out-patients with complicated benzodiazepine dependence: comparison of two approaches. Addiction 97:851–859, 2002

Vorma H, Naukkarinen H, Sarna S, et al: Long-term outcome after benzodiazepine withdrawal treatment in subjects with complicated dependence. Drug Alcohol Depend 70:309–314, 2003

Wafford KA, Thompson SA, Thomas D, et al: Functional characterization of human gamma-aminobutyric acidA receptors containing the alpha 4 subunit. Mol Pharmacol 50:670–678, 1996

Walker BM, Ettenberg A: The effects of alprazolam on conditioned place preferences produced by intravenous heroin. Pharmacol Biochem Behav 75:75–80, 2003

Weerts EM, Griffiths RR: Zolpidem self-injection with concurrent physical dependence under conditions of long-term continuous availability in baboons. Behav Pharmacol 9:285–297, 1998

Wesson DR, Smith DE: Barbiturates: Their Use, Misuse, and Abuse. New York, Human Sciences Press, 1977

Wikler A: Diagnosis and treatment of drug dependence of the barbiturate type. Am J Psychiatry 125:758–765, 1968

Williams H, Oyefeso A, Ghodse AH: Benzodiazepine misuse and dependence among opiate addicts in treatment. Ir J Psychol Med 13:62–64, 1996

Wiseman SM, Spencer-Peet J: Prescribing for alcoholics: a survey of drugs taken prior to admission to an alcoholism unit. Practitioner 229:88–89, 1985

Wolf B, Grohmann R, Biber D, et al: Benzodiazepine abuse and dependence in psychiatric inpatients. Pharmacopsychiatry 22:54–60, 1989

Wood MR, Kim JJ, Han W, et al: Benzodiazepines as potent and selective bradykinin B1 antagonists. J Med Chem 46:1803–1806, 2003

Zawertailo LA, Busto UE, Kaplan HL, et al: Comparative abuse liability and pharmacological effects of meprobamate, triazolam, and butabarbital. J Clin Psychopharmacol 23:269–280, 2003

4

Cannabis

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Plant extracts from *Cannabis sativa* have been used recreationally and therapeutically for thousands of years (Mechoulam 1986). However, it was not until 1964 that the principal psychoactive ingredient of cannabis was identified as Δ9–tetrahydrocannabinol (THC) (Gaoni and Mechoulam 1964).

It was also during the 1960s that recreational use of cannabis—or marijuana—became widespread in the United States and many other countries. In the United States, the rate of lifetime cannabis use rose steadily during the 1970s, reaching a peak around 1979, when an estimated 60% of high school seniors reported having used cannabis on at least one occasion (Johnston et al. 2004). During the 1980s, the lifetime prevalence of cannabis use declined among adolescents and young people, but during the 1990s it rose again

(Johnston et al. 2004). Within the past 5 years, there has been some suggestion that the lifetime prevalence of cannabis use may again be declining among high school students. Nonetheless, cannabis use remains widespread. Specifically, the Monitoring the Future Project, which conducts annual surveys of large (N=50,000) and representative samples of adolescents and young adults, reported that in 2003 (the latest year for which data are available), 46.1% of twelfth-grade students had ever used cannabis, 34.9% had used it in the last year, and 21.2% had used it in the past month (Johnston et al. 2004). Widespread cannabis use among youths is not limited to the United States; numerous studies have reported a similar lifetime prevalence of cannabis use among youths in most industrialized nations (Dennis et al. 2003; Hall and Babor 2000).

Longitudinal studies have demonstrated that peak rates of initiation and heavy use of cannabis typically occur among teenagers and individuals in their early 20s, respectively (Chen and Kandel 1995). However, some use of cannabis is also relatively common among the adult population: recent U.S. national household survey findings indicated that 36.9% of adults report lifetime cannabis use (41.1% of men, 33.0% of women), although there are also clear cohort differences in the prevalence of cannabis use in the United States (Johnston et al. 2003a, 2003b), as well as in Australia (Degenhardt et al. 2000).

As noted earlier, although some lifetime experience with cannabis is common—to the point of being normative—a substantial number of people use cannabis heavily and experience a range of adverse consequences as a result of their cannabis use. Perhaps the clearest evidence of this phenomenon comes from treatment episode data. The U.S. Treatment Episode Data System (TEDS) indicated cannabis as the primary drug problem for 236,400 admissions to public substance abuse treatment services in 2000 (Substance Abuse and Mental Health Services Administration 2003). This number represented 15% of all substance abuse treatment admissions that year, more than twice as high (as a proportion of all admissions) as the rate of cannabis-related admissions reported in 1993 (7%) (Substance Abuse and Mental Health Services Administration 2002a). Also in 2000, cannabis was reported as a secondary problem in an additional 22% of all admissions. Those entering treatment primarily for cannabis-related problems were predominantly male (76%) and adolescents or young adults (67% were less than 25 years old). Finally, in

2000, people with cannabis abuse or dependence accounted for an estimated 62% of all people who abuse or are dependent on an illicit drug in the United States. (Substance Abuse and Mental Health Services Administration 2002b).

Although it is difficult to determine whether these higher rates of treatment-seeking associated with cannabis use represent actual cannabis-related problems or are an artifact of coerced treatment, the potential for cannabis to be associated with both abuse and dependence syndromes is recognized in both the DSM-IV-TR (American Psychiatric Association 2000) and ICD-10 (World Health Organization 1992) systems of nomenclature. In both systems the diagnostic criteria for cannabis use disorders are based largely on the criteria developed for alcohol and other substance use disorders, with some important differences, which are discussed in the following section.

Prevalence of Cannabis Dependence

The prevalence of cannabis dependence has been estimated by a number of studies employing large samples, representative sampling frames, and rigorous assessment of symptoms. The estimated prevalence of cannabis dependence has varied widely, with lifetime prevalence estimated to be 0.9%–2.2% of the adult population, although, seemingly paradoxically, the 12-month prevalence of cannabis dependence has been estimated to be as high as 9%. This discrepancy is likely a function of the younger age of samples examined in studies reporting a higher prevalence and may reflect both cohort differences in rates of cannabis use and the "natural history" of cannabis use, with rates of use typically peaking among people in their early 20s and declining thereafter (Chen and Kandel 1995). It is interesting to note that a 2002 U.S. study showed that among youths ages 17–18 years, the prevalence of cannabis dependence was higher than the prevalence of alcohol dependence (Young et al. 2002), and there is evidence of a recent increase in the 12-month prevalence of cannabis abuse and dependence (Compton et al. 2004). It has been estimated that 10%–20% of all people who use cannabis will develop cannabis dependence (Anthony et al. 1994; Lynskey et al. 2002).

These prevalence estimates, however, obscure an ongoing controversy surrounding the nature of the cannabis dependence syndrome. Specifically, the studies cited earlier, which were designed to examine the prevalence of abuse

of or dependence on multiple drug classes, simply applied standard diagnostic criteria, many of which were initially developed for alcohol abuse and dependence. Writing in 1994, the authors of DSM-IV (American Psychiatric Association 1994) did not have at their disposal more recent data demonstrating that cessation of cannabis use in heavy or dependent users is associated with a distinct withdrawal syndrome. Ator and Griffiths (2003), for example, highlighted the central importance that a withdrawal syndrome occurring after chronic administration plays in determining the physical dependence potential of a drug. Thus, given the controversy surrounding the potential of cannabis cessation to induce withdrawal, we review the literature in this area in detail in the next section.

Cannabis Dependence and Withdrawal

Research With Human Subjects

In addition to anecdotal and case series reports of cannabis withdrawal, several large-scale epidemiological surveys, including those cited earlier, reported that symptoms of cannabis withdrawal are among the most frequently reported symptoms of cannabis dependence. For example, in a large-scale epidemiological survey of Australian households (Teesson et al. 2002), among those using cannabis at least five times in the preceding year, 29.7% reported withdrawal, making it the second most commonly reported symptom of dependence.

In one of the first detailed examinations of possible components of a cannabis withdrawal syndrome, Wiesbeck et al. (1996) evaluated reports of specific withdrawal symptoms in a sample of 270 frequent cannabis users. These individuals were selected from among participants in the Collaborative Study on the Genetics of Alcoholism on the basis of having reported some cannabis withdrawal symptoms. Typical symptoms, reported by more than 50% of this group, included feeling "nervous, tense, restless" (reported by 94.4% of subjects), sleep disturbance (75.6%), and changes in appetite (62.9%).

In two linked papers, Haney et al. (1999a , 1999b) reported on intensive laboratory studies of the effects of oral and smoked THC administration on mood and behavior. In both instances, they reported that abstinence from THC was associated with increases in anxiety and irritability coupled with re-

ductions in food intake. Abstinence from oral THC was also associated with sleep disturbance, and abstinence from smoked marijuana was associated with reports of stomach pain. The most compelling demonstration of the withdrawal effects of abstinence from smoked marijuana was reported by Budney et al. (2001), in an intensive study of the effects of abstinence from marijuana in a group of heavy (daily) cannabis smokers maintained in their home environment. The 16-day experimental study involved intensive observation over 5 days of cannabis use, followed by 3 days of abstinence, 5 days of resumed cannabis use, and 3 final days of abstinence. Strong evidence was found for an increase in withdrawal discomfort, craving for marijuana, and sleep difficulties and a decrease in appetite, and there was also moderate evidence that abstinence was associated with increased aggression, anger, irritability, restlessness, and sleep disturbances (i.e., strange dreams). Participant reports of these effects were confirmed by collateral observers. The authors concluded that

> the behavioral and emotional withdrawal symptoms associated with marijuana withdrawal…syndromes may be as, if not more, important than physical symptoms in contributing to the development of dependence and the undermining of abstinence attempts. (p. 923)

Using a similar research design in which a small group of heavy cannabis users was studied intensively over a 28-day period of abstinence from cannabis, Kouri and Pope (2000) found that abstinence was associated with increased anxiety, irritability, physical tension, deteriorating mood, and reduced appetite. In addition, Kouri et al. (1999) reported that cessation of cannabis use was associated with a significant increase in aggressive behavior, assessed with an experimental paradigm that included provocation. Aggressive responding increased during the first week of abstinence and then returned to prewithdrawal baseline levels. Noting the parallels between these findings and numerous reports that irritability is one of the most frequently reported features of cannabis withdrawal, the authors suggested that increased aggression may be an additional component of the cannabis withdrawal syndrome.

Animal Studies

Although it has been nearly 40 years since THC, the main active psychotropic constituent of the plant *Cannabis sativa*, was isolated (Gaoni and Mechoulam

1964), it was not until the late 1980s that the cannabinoid receptor CB1 was identified (Devane et al. 1988) and subsequently cloned (Matsuda et al. 1990). A second cannabinoid receptor, CB2, was subsequently identified (Jorda et al. 2003; Nowell et al. 1998), and more recently evidence of a third cannabinoid receptor, CB3, has emerged (Fride et al. 2003). The major cardiovascular, analgesic, psychomotor, and cognitive effects of THC are mediated through its actions on CB1 receptors, which are linked to guanine nucleotide–binding proteins (G proteins) and are located primarily in the central and peripheral nervous systems and, in particular, the substantia nigra, cerebellum, hippocampus, and striatum (Ledent et al. 1999; Matsuda et al. 1990).

Research on the pharmacological properties of THC has been greatly enhanced by the development both of the cannabinoid receptor antagonist SR141716A and of knockout mice deficient in the CB1 receptor (Ledent et al. 1999). These developments have led to an explosion of interest in the endocannabinoids as targets for potential therapeutic and medicinal uses across a wide range of domains, including appetite suppression, pain relief, anxiolysis, memory enhancement, and treatment of movement disorders. Consideration of the therapeutic potential of endocannabinoids is beyond the scope of this chapter, but several excellent reviews have been published (Baker et al. 2003; Goutopoulos and Makriyannis 2002; Robson 2001; Russo 2004; Wall et al. 2001). A brief description of evidence derived from animal models concerning the phenomenology and basis of cannabis withdrawal and dependence follows.

Withdrawal

Animal research has provided strong evidence for withdrawal symptoms following cessation of access to cannabinoids. These effects have been most readily apparent in studies that have used the selective CB1 receptor antagonist SR141716A to precipitate withdrawal. Withdrawal symptoms displayed by rats treated with SR141716A after chronic exposure to cannabinoids have included wet-dog shakes, facial rubs, horizontal and vertical activity, forepaw fluttering, chewing, tongue rolling, paw shakes, head shakes, retropulsion, myoclonic spasms, front paw treading, and eyelid ptosis (Aceto et al. 1995; Tsou et al. 1995). Similar symptoms have been reported in mice treated with SR141716A, although there appears to be some variability in symptoms across mice strains (Cook et al. 1998; Hutcheson et al. 1998; Ledent et al.

1999; Lichtman et al. 2001; Tzavara et al. 2000). A dog model of precipitated cannabinoid withdrawal, which includes increased salivation, vomiting, diarrhea, restless behavior, and trembling, has also been described (Lichtman et al. 1998).

Research on CB1 knockout mice demonstrated the pivotal role of CB1 receptors in cannabis dependence: knockout mice have been shown *not* to self-administer cannabinoids (Ledent et al. 1999) and also to fail to exhibit symptoms of SR141716A-precipitated withdrawal (Ledent et al. 1999; Lichtman et al. 2001). Although the research summarized earlier is consistent in reporting the occurrence of a variety of withdrawal symptoms following cessation of exposure to cannabinoids (which were injected), precipitated withdrawal in mice following chronic exposure to marijuana smoke was more recently reported (Lichtman and Martin 2002).

Cannabinoid Self-Administration

Although many earlier studies suggested that animals would not self-administer cannabinoids (see Gardner 2002 for a discussion of this literature), more recent research has established that many species can be trained to self-administer cannabinoids. Drug-naive mice have been shown to self-administer the synthetic cannabinoid agonist WIN 55,212–2 (Ledent et al. 1999; Martellotta et al. 1998), and rats have been reported to self-administer both WIN 55,212–2 (Fattore et al. 2001) and CP 55,940, another synthetic cannabinoid (Braida et al. 2001). It is important to note that cannabinoid self-administration has been shown to be blocked by the CB1 antagonist S141716A (Martelotta et al. 1998), although Ledent et al. (1999) reported that CB1 receptor knockout mice could not be trained to self-administer cannabinoids. Finally, Tanda et al. (2000) demonstrated that squirrel monkeys can be trained to self-administer low doses of THC by injection (but only after they had been trained to self-administer cocaine). The study by Tanda et al. (2000) is of particular importance, as it demonstrated that self-administration will occur at a dosage of THC that is equivalent to the dosage typically used by humans.

Conditioned Place Preference

Another important animal model of the addictive potential of drugs is the conditioned place paradigm. When administered a drug that has rewarding/pleasurable effects, animals will spend more time in the place associated with

the drug administration than in a comparable location that has not been paired with the drug. This paradigm has yielded mixed results when used to study the effects of cannabinoid administration. Although several groups have reported that cannabinoid administration induces conditioned place preference (Lepore et al. 1995), others have, in fact, reported that cannabinoid administration is aversive and that animals will avoid the place in which cannabinoids have previously been administered (e.g., Cheer et al. 2000; Parker and Gillies 1995). Gardner (2002) suggested that this apparent discrepancy can be resolved by considering variations in the dosage and potency of the cannabinoids tested and in the time between administration and testing. If one accepts these arguments, it is apparent that cannabinoid administration does induce conditioned place preference, signifying that the effects of cannabinoids are perceived as pleasurable and, therefore, that cannabinoids fulfill another criterion of abuse liability.

Summary

There is compelling evidence for the existence of a cannabis withdrawal syndrome. Research with animals has demonstrated that withdrawal from cannabinoids precipitated by the CB1 antagonist SR141716A is associated with a distinct behavioral syndrome analogous to that observed after withdrawal from other drugs. Similarly, recent well-controlled human experimental research has documented significant behavioral disturbances in chronic cannabis users following abstinence from smoked cannabis. In epidemiological surveys, withdrawal symptoms are among the most commonly reported symptoms of dependence, and controlled studies have identified restlessness, irritability, sleep disturbance, and decreased appetite as being among the core features of this syndrome. Relative to withdrawal associated with other substances, such as alcohol, the cannabis withdrawal syndrome is mild but may nonetheless contribute to continued cannabis use and difficulties experienced following cessation. In addition to research on the phenomena and mechanisms of withdrawal from cannabis, there has also been considerable research on the extent to which cannabis may induce other symptoms of dependence. Specifically, sound empirical evidence exists that continued cannabis use induces tolerance to its effects, which is one of the key defining features of drugs of dependence.

Treatments for Cannabis Dependence

Behavioral Treatments

Reports by several researchers have indicated that there is a substantial demand for treatment of cannabis dependence (Budney et al. 1998; Roffman and Barnhart 1987; Stephens et al. 1993). In addition, as long-term marijuana use has detrimental consequences for both the individual and society (Budney et al. 1998; Kandel 1984; Pope and Yurgelun-Todd 1996) and a cannabis withdrawal syndrome exists (see earlier section on cannabis withdrawal), treatments that are specific for cannabis dependence are now being studied. In a series of studies, Stephens et al. (1994, 2000) compared a cognitive-behavioral therapy (CBT) approach with social support and a brief two-session motivational enhancement intervention. All three approaches proved successful in producing abstinence rates of about 25% at 1-year follow-up. Other studies have confirmed the effectiveness of the CBT approach and motivational treatments. In a large study comparing five short-term outpatient interventions for youths, Dennis et al. (2004) showed that more than 30% of the adolescents in the study remained abstinent at 1-year follow-up, regardless of the specific treatment procedure. Adding a contingency management procedure (i.e., voucher-based incentives) to motivational enhancement plus behavioral coping skills training significantly improved abstinence rates and longevity of abstinence in adults seeking treatment (Budney et al. 2000). The voucher-based incentive group had a greater number of weeks of continuous abstinence and was the only group in which some subjects remained abstinent for the duration of the 14-week study.

Although their results were encouraging, these studies demonstrated how difficult it is to treat cannabis dependence. Experience with treating tobacco dependence has revealed that a *combination* of various psychotherapeutic techniques and pharmacotherapies is more effective than either approach alone in producing and maintaining cessation. Thus, the use of medication during the cessation period may significantly improve quit rates and maintenance of abstinence.

Pharmacological Aids in Cannabis Cessation

Given robust experimental evidence of cannabis withdrawal, recent interest has focused on the extent to which medications may assist in the amelioration

of withdrawal after cessation of cannabis use and hence may enhance abstinence rates. Interest has focused on a range of pharmacological agents, including antidepressants and anxiolytics. Evidence for the efficacy of these agents in ameliorating symptoms of cannabis withdrawal is reviewed in the following sections.

Antidepressants

Within the alcohol and other substance abuse literature there has been substantial interest in the extent to which antidepressants may be an effective adjunctive treatment for dependence. An initial exploration of the extent to which antidepressant medication may reduce cannabis use was reported by Cornelius et al. (1999), who compared rates of marijuana use in a subsample of marijuana users (n =22) enrolled in a larger, double-blind, placebo-controlled study of the efficacy of fluoxetine, a selective sertonin reuptake inhibitor (SSRI), in the treatment of alcohol dependence and comorbid depression (Cornelius et al. 1997). Despite the relatively small sample size, the authors reported a significant difference in the number of marijuana joints smoked during the course of the study, with the placebo group smoking 20 times as many joints as the group receiving fluoxetine. Although the results were promising, the extent to which such findings generalize to individuals who are not alcohol dependent or to those who are not depressed remains questionable. (The larger trial showed a large reduction in alcohol consumption among participants who received fluoxetine.) In addition, inclusion in the study that examined patterns of cannabis use was conditional on subjects' meeting the criteria for cannabis abuse, and it is unclear how many of these subjects also met the criteria for cannabis dependence or experienced withdrawal symptoms after cessation of cannabis use.

An initial examination of the extent to which lithium may prevent cannabis withdrawal in rats was conducted by Cui et al. (2001), who reported that, at clinically relevant serum levels, lithium prevented the appearance of the cannabis withdrawal syndrome. The authors also noted that these effects were accompanied by a release of oxytocin, which they conclude is responsible for suppression of the withdrawal signs.

Using a within-subject, placebo-controlled design, Haney et al. (2003) recently reported that nefazodone, an antidepressant that also has some sedative properties, decreased reports of anxiety and muscle pain during closely mon-

itored withdrawal from cannabis use in long-term frequent users of cannabis who were undergoing laboratory-induced cannabis withdrawal. Administration of nefazodone did not, however, alter ratings of irritability, feelings of being miserable, or sleep disturbances during cannabis withdrawal.

Although these results suggest potential utility for antidepressants in the relief of some symptoms of cannabis withdrawal in humans, the same group obtained less promising results using a similar design to study the effects of bupropion (Haney et al. 2001). Bupropion is an antidepressant that has been shown to be effective in reducing symptoms of nicotine withdrawal, thereby aiding in smoking cessation (Hughes et al. 1999; Jorenby et al. 1999). With respect to cannabis cessation, Haney et al. (2001) observed a worsening of mood with bupropion treatment at various timepoints during a repeated-measures, 12-day abrupt cessation paradigm. Irritability, feelings of being miserable, restlessness, lack of motivation, and depression were greater in the bupropion phase than in the placebo phase. These authors concluded that bupropion may not be an effective medication for treatment of cannabis dependence. However, subjects in this inpatient study underwent a regimen of enforced intake (smoking cannabis five times per day for 4 days) followed by continued smoking (of 0% THC content cigarettes) during the withdrawal period. Similarly, Haney et al. (2004) recently reported disappointing results in a trial of divalproex, a mood-stabilizing drug. Although administration of divalproex during cannabis abstinence reduced marijuana craving, its use was associated with worsened symptoms of withdrawal, relative to placebo.

Despite these disappointing results, given that bupropion has been effective in the treatment of tobacco dependence (Hughes et al. 1999; Jorenby et al. 1999), studies of cannabis dependence employing an outpatient design similar to that used in treatment programs for nicotine cessation should be conducted before it is concluded that this medication is inefficacious. Another reason to conduct treatment studies with antidepressants for cannabis dependence is the increased risk for major depressive disorder observed among cannabis-dependent individuals (Bovasso 2001; Chen et al. 2002; Degenhardt et al. 2001; Grant 1995). Treatment with antidepressants may be particularly effective in reducing cannabis use by ameliorating depressive symptoms among individuals with comorbid cannabis dependence and major depressive disorder. There have, however, been a number of case reports of adverse interactive effects of tricyclic antidepressants and smoked marijuana (Mannion

1999; Wilens et al. 1997), suggesting that the use of SSRIs may be preferable for this indication.

In summary, research on the use of antidepressants to treat cannabis dependence, particularly among individuals with comorbid major depressive disorder, although limited, offers a promising avenue for the development of pharmacological aids to assist in the treatment of cannabis withdrawal. There are clear parallels between this literature and the existing research on the use of antidepressants in the treatment of alcohol dependence comorbid with major depressive disorder (see Chapter 1, Medications to Treat Co-occurring Psychiatric Symptoms or Disorders in Alcoholic Patients).

Maintenance THC Therapy

The extent to which maintenance with oral THC may ameliorate cannabis withdrawal and potentially reduce use of smoked marijuana use has been rarely studied and remains controversial. Nonetheless, the rationale for such treatment seems clear and closely mimics the rationale for the use of methadone and other agonist maintenance therapies for the treatment of heroin or nicotine dependence. Specifically, the use of a shorter-acting substance administered through a potentially risky route (e.g., injection, smoking) is substituted with the use of a longer-acting drug administered through a safer route (e.g., oral or transdermal administration). Maintenance treatments have consistently been shown to be effective in the treatment of heroin dependence and nicotine dependence. The use of such interventions for cannabis dependence is further supported by recent findings that, compared with placebo, oral THC reduces symptoms of withdrawal, including anxiety, sleeping problems, craving, and changes in appetite while producing no subjective intoxication (Haney et al. 2004). Although such findings suggest that administration of oral THC may provide a useful treatment option for reducing cannabis use, Hart et al. (2002) reported that oral THC administration did not alter rates of (smoked) cannabis self-administration, despite previous findings that the subjective effects of smoked cannabis and oral THC are similar (Wachtel et al. 2002).

Cannabinoid Antagonists

As discussed earlier, SR171614A, a selective cannabinoid antagonist that is highly competitive at CB1 binding sites, has been identified and synthesized.

This drug has been shown to precipitate withdrawal in animal models (Aceto et al. 1995; Cook et al. 1998; Hutcheson et al. 1998; Ledent et al. 1999; Lichtman et al. 1998, 2001; Tsou et al. 1995; Tzavara et al. 2000) and has also been shown to block the euphoric effects of smoked marijuana (Huestis et al. 2001). These findings are important, as they confirm that CB1 receptor sites play a central role in mediating the effects of recreational cannabis use. They also suggest a potential role for cannabinoid antagonists both in the treatment of acute dysphoric effects of cannabis intoxication and in the treatment of cannabis use disorders (D'Souza and Kosten 2001), analogous to the use of naltrexone in the treatment of acute opioid overdose and opioid dependence (see Chapter 2, "Opioids"). However, the use of such an approach in the treatment of cannabis dependence is likely to face many of the same challenges raised about the use of naltrexone and thus may be of only limited utility for those seeking to reduce or abstain from cannabis use. As D'Souza and Kosten (2001) noted, the greater importance of this finding may be in the potential use of cannabinoid antagonists for a variety of conditions, including opioid addiction and psychotic disorders.

Conclusion

Cannabis use is common, as is cannabis dependence. Despite ongoing controversy, recent empirical evidence supports the conclusion that cessation of cannabis use is associated with a withdrawal syndrome similar to, but less intense than, that experienced upon cessation of other drugs that have been chronically administered. Given recent increases in the number of people seeking treatment for cannabis dependence, a trend that may continue as increasing numbers of people reach an age at which they have a long history of cannabis (e.g., a 20-year history), interest in developing and testing pharmacotherapies to reduce withdrawal symptoms and assist cessation is likely to increase. A number of promising avenues for treatment may be considered, including the use of antidepressants (particularly for patients with comorbid major depressive disorder) and the use of cannabinoid antagonists. Although promising, the research literature is distinguished by scarce and often contradictory findings concerning both the efficacy and safety of such agents as aids to cannabis cessation. It is clear that more research is needed before such interventions can routinely be recommended for use as treatment for cannabis withdrawal and dependence.

References

Aceto MD, Scates SM, Lowe JA, et al: Cannabinoid precipitated withdrawal by the selective cannabinoid receptor antagonist, SR 141716A. Eur J Pharmacol 282: R1–R2, 1995

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Washington, DC, American Psychiatric Association, 1994

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000

Anthony JC, Warner LA, Kessler RC: Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: basic findings from the National Comorbidity Survey. Exp Clin Psychopharmacol 2: 244–268, 1994

Ator NA, Griffiths RR: Principles of drug abuse liability assessment in laboratory animals. Drug Alcohol Depend 70(suppl):55–72, 2003

Baker D, Pryce G, Giovannoni G, et al: The therapeutic potential of cannabis. Lancet Neurol 2:291–298, 2003

Bovasso GB: Cannabis abuse as a risk factor for depressive symptoms. Am J Psychiatry 158:2033–2037, 2001

Braida D, Pozzi M, Cavallini R, et al: Intracerebral self-administration of the cannabinoid receptor agonist CP 55,940 in the rat: interaction with the opioid system. Eur J Pharmacol 413:227–234, 2001

Budney AJ, Radonovich KJ, Higgins ST, et al: Adults seeking treatment for marijuana dependence: a comparison with cocaine-dependent treatment seekers. Exp Clin Psychopharmacol 6:419–426, 1998

Budney AJ, Higgins ST, Radonivich KJ, et al: Adding voucher-based incentives to coping skills and motivational enhancement improves outcomes during treatment for marijuana dependence. J Consult Clin Psychol 68:1051–1061, 2000

Budney AJ, Hughes JR, Moore BA, et al: Marijuana abstinence effects in marijuana smokers maintained in their home environment. Arch Gen Psychiatry 58:917–924, 2001

Cheer JF, Kendall DA, Marsden CA: Cannabinoid receptors and reward in the rat: a conditioned place preference study. Psychopharmacology (Berl) 151:25–30, 2000

Chen K, Kandel DB: The natural history of drug use from adolescence to the mid-thirties in a general population sample. Am J Public Health 85:41–47, 1995

Chen CY, Wagner FA, Anthony JC: Marijuana use and the risk of major depressive episode: epidemiological evidence from the United States National Comorbidity Survey. Soc Psychiatry Psychiatr Epidemiol 37:199–206, 2002

Compton WM, Grant BF, Colliver JD, et al: Prevalence of marijuana use disorders in the United States: 1991–1992 and 2001–2002. JAMA 291:2114–2121, 2004

Cook SA, Lowe JA, Martin BR: CB1 receptor antagonist precipitates withdrawal in mice exposed to delta9-tetrahydrocannabinol. J Pharmacol Exp Ther 285:1150–1156, 1998

Cornelius JR, Salloum IM, Ehler JG, et al: Fluoxetine in depressed alcoholics: a double-blind, placebo-controlled trial. Arch Gen Psychiatry 54:700–705, 1997

Cornelius JR, Salloum IM, Haskett RF, et al: Fluoxetine versus placebo for the marijuana use of depressed alcoholics. Addict Behav 24:111–114, 1999

Cui S-S, Bowen RC, Gu G-B, et al: Prevention of cannabinoid withdrawal syndrome by lithium: involvement of oxytocinergic neuronal activation. J Neurosci 21:9867–9876, 2001

Degenhardt L, Lynskey MT, Hall W: Cohort trends in the age of initiation of drug use in Australia. Aust N Z J Public Health 24:421–426, 2000

Degenhardt L, Hall W, Lynskey MT: The relationship between cannabis use, depression and anxiety among Australian adults: findings from the National Survey of Mental Health and Well-Being. Soc Psychiatry Psychiatr Epidemiol 36:219–227, 2001

Dennis M, Babor TF, Roebuck C, et al: Changing the focus: the case for recognizing and treating cannabis use disorders. Addiction 97(suppl 1):4–15, 2003

Dennis M, Godley SH, Diamond G, et al: The Cannabis Youth Treatment (CYT) Study: main findings from two randomized trials. J Subst Abuse Treat 27:197–213, 2004

Devane WA, Dysarz FA, Johnson MR, et al: Determination and characterization of a cannabinoid receptor in rat brain. Mol Pharmacol 34:605–613, 1988

D'Souza DC, Kosten TR: Cannabinoid antagonists: a treatment in search of an illness. Arch Gen Psychiatry 58:330–331, 2001

Fattore L, Cossu G, Martellotta CM, et al: Intravenous self-administration of the Cb1 receptor agonist WIN 55,212–2 in rats. Psychopharmacology (Berl) 156:410–416, 2001

Fride E, Foox A, Rosenberg E, et al: Milk intake and survival in newborn cannabinoid CB1 receptor knockout mice: evidence for a "CB3" receptor. Eur J Pharmacol 461: 27–34, 2003

Gaoni Y, Mechoulam R: Isolation, structure, and partial synthesis of an active constituent of hashish. J Am Chem Soc 86:1646–1647, 1964

Gardner EL: Addictive potential of cannabinoids: the underlying neurobiology. Chem Phys Lipids 121:267–290, 2002

Goutopoulos A, Makriyannis A: From cannabis to cannabinergics: new therapeutic opportunities. Pharmacol Ther 95:103–17, 2002

Grant BF: Comorbidity between DSM-IV drug use disorders and major depression: results of a national survey of adults. J Subst Abuse 7:481–497, 1995

Hall W, Babor TF: Cannabis use and public health: assessing the burden. Addiction 95:485–490, 2000

Haney M, Ward AS, Comer SD, et al: Abstinence symptoms following oral THC administration in humans. Psychopharmacology (Berl) 141:385–394, 1999a

Haney M, Ward AS, Comer SD, et al: Abstinence symptoms following smoked marijuana in humans. Psychopharmacology (Berl) 141:395–404, 1999b

Haney M, Ward AS, Comer SD, et al: Bupropion SR worsens mood during marijuana withdrawal in humans. Psychopharmacology (Berl) 155:171–179, 2001

Haney M, Hart CL, Ward AS: Nefazodone decreases anxiety during marijuana withdrawal in humans. Psychopharmacology (Berl) 165:157–165, 2003

Haney M, Hart CL, Vosburg SK, et al: Marijuana withdrawal in humans: effects of oral THC or divalproex. Neuropsychopharmacology 29: 158–170, 2004

Hart CL, Haney M, Ward AS, et al: Effects of oral THC maintenance on smoked marijuana self-administration. Drug Alcohol Depend 67:301–309, 2002

Huestis MA, Gorelick DA, Heishman SJ, et al: Blockade of effects of smoked marijuana by the CB1-selective cannabinoid receptor antagonist SR141716. Arch Gen Psychiatry 58:322–328, 2001

Hughes JR, Goldstein MG, Hurt RD, et al: Recent advances in the pharmacotherapy of smoking. JAMA 281:72–76, 1999

Hutcheson DM, Tzavara ET, Smadja C, et al: Behavioral and biochemical evidence for signs of abstinence in mice chronically treated with delta-9-tetrahydrocannabinol. Br J Pharmacol 125:1567–1577, 1998

Johnston LD, O'Malley PM, Bachman JG: Monitoring the Future National Survey Results on Drug Use, 1975–2002, Vol I: Secondary School Students (NIH Publ No 03–5375). Bethesda, MD, National Institute on Drug Abuse, 2003a

Johnston LD, O'Malley PM, Bachman JG: Monitoring the Future National Survey Results on Drug Use, 1975–2002, Vol II: College Students and Adults Ages 19–40 (NIH Publ No 03–5376). Bethesda, MD, National Institute on Drug Abuse, 2003b

Johnston LD, O'Malley PM, Bachman JG, et al: Monitoring the Future National Results on Adolescent Drug Use: Overview of Key Findings, 2003 (NIH Publ No 04–5506). Bethesda, MD: National Institute on Drug Abuse, 2004

Jorda MA, Rayman N, Valk P, et al: Identification, characterization, and function of a novel oncogene: the peripheral cannabinoid receptor Cb2. Ann N Y Acad Sci 996:10–16, 2003

Jorenby DE, Leischow SJ, Nides MA, et al: A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. N Eng J Med 340:685–691, 1999

Kandel DB: Marijuana users in young adulthood. Arch Gen Psychiatry 42:200–209, 1984

Kouri EM, Pope HG Jr: Abstinence symptoms during withdrawal from chronic marijuana use. Exp Clin Psychopharmacol 8:483–492, 2000

Kouri EM, Pope HG Jr, Lukas SE: Changes in aggressive behavior during withdrawal from long-term marijuana use. Psychopharmacology 143:302–308, 1999

Ledent C, Valverde L, Cossu G, et al: Unresponsiveness to cannabinoids and reduced addictive effects of opiates in CB1 receptor knockout mice. Science 283:401–404, 1999

Lepore M, Vorel SR, Lowinson J, et al: Conditioned place preference induced by delta-9-tetrahydrocannabinol: comparison with cocaine, morphine, and food reward. Life Sci 56:2073–2080, 1995

Lichtman AH, Martin BR: Marijuana withdrawal syndrome in the animal model. J Clin Pharmacol 42:S20–S27, 2002

Lichtman AH, Wiley JL, LaVecchia KL, et al: Acute and chronic cannabinoid effects: characterization of precipitated withdrawal in dogs. Eur J Pharmacol 357:139–148, 1998

Lichtman AH, Sheikh SM, Loh HH, et al: Opioid and cannabinoid modulation of precipitated withdrawal in delta(9)-tetrahydrocannabinol and morphine-dependent mice. J Pharmacol Exp Ther 298:1007–1014, 2001

Lynskey MT, Heath AC, Nelson EC, et al: Genetic and environmental contributions to cannabis dependence in a national young adult twin sample. Psychol Med 32: 195–207, 2002

Mannion V: Case report: adverse effects of taking tricyclic antidepressants and smoking marijuana. Can Fam Physician 45:2683–2684, 1999

Martellotta MC, Cossu G, Fattore L, et al: Self-administration of the cannabinoid receptor agonist WIN 55,212–2 in drug-naive mice. Neuroscience 85:327–330, 1998

Matsuda LA, Lolait SJ, Brownstein MJ, et al: Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature 364: 561–564, 1990

Mechoulam R: The pharmacohistory of cannabis sativa, in Cannabinoids as Therapeutic Agents. Edited by Mechoulam R. Boca Raton, FL, CRC Press, 1986, pp 1–20

Nowell KW, Pettit DA, Cabral WA, et al: High-level expression of the human CB2 cannabinoid receptor using a baculovirus system. Biochem Pharmacol 55:1893–1905, 1998

Parker LA, Gillies T: THC-induced place and taste aversions in Lewis and Sprague-Dawley rats. Behav Neurosci 109:71–78, 1995

Pope HG, Yurgelun-Todd D: The residual cognitive effects of heavy marijuana use in college students. JAMA 275:521–527, 1996

Robson P: Therapeutic aspects of cannabis and cannabinoids. Br J Psychiatry 178:107–115, 2001

Roffman RA, Barnhart R: Assessing need for marijuana dependence treatment through an anonymous telephone interview. Int J Addict 22:639–651, 1987

Russo EB: Clinical endocannabinoid deficiency (CECD): can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions? Neuro Endocrinol Lett 25(1–2):31–39, 2004

Stephens RS, Roffman RA, Simpson EE: Adult marijuana users seeking treatment. J Consult Clin Psychol 61:1100–1104, 1993

Stephens RS, Roffman RA, Simpson EE: Treating adult marijuana dependence: a test of the relapse prevention model. J Consult Clin Psychol 62:92–99, 1994

Stephens RS, Roffman RA, Curtin L: Comparison of extended versus brief treatments for marijuana use. J Counsul Clin Psychol 68:898–908, 2000

Substance Abuse and Mental Health Services Administration: The DASIS Report: Marijuana Treatment Admissions Increase: 1993–1999. Rockville, MD, Substance Abuse and Mental Health Services Administration, 2002a

Substance Abuse and Mental Health Services Administration: Results from the 2001 National Household Survey on Drug Abuse: Vol I. Summary of National Findings. Rockville, MD, Substance Abuse and Mental Health Services Administration, 2002b

Substance Abuse and Mental Health Services Administration: The DASIS Report: Marijuana Use Secondary to Other Substances of Abuse. Rockville, MD, Substance Abuse and Mental Health Services Administration, 2003

Tanda G, Munzar P, Goldberg SR: Self-administration behaviour is maintained by the psychoactive ingredient of marijuana in squirrel monkeys. Nat Neurosci 3:1073–1074, 2000

Teesson M, Lynskey M, Manor B, et al: The psychometric properties of DSM-IV cannabis use disorders. Drug Alcohol Depend 68:255–262, 2002

Tsou K, Patrick SL, Walker JM. Physical withdrawal in rats tolerant to delta 9-tetrahydrocannabinol precipitated by a cannabinoid receptor antagonist. Eur J Pharmacol 280:R13–R15, 1995

Tzavara ET, Valjent E, Firmo C, et al: Cannabinoid withdrawal is dependent upon PKA activation in the cerebellum. Eur J Neuroscience 12:1038–1046, 2000

Young S, Corley R, Stallings M, et al: Substance use, abuse and dependence in adolescence: prevalence, symptom profiles and correlates. Drug Alcohol Depend 68: 309–322, 2002

Wachtel SR, El Sohly MA, Ross SA, et al: Comparison of the subjective effects of delta9-tetrahydrocannabinol and marijuana in humans. Psychopharmacology (Berl) 161:331–339, 2002

Wall J, Davis S, Ridgway S: Cannabis: its therapeutic use. Nurs Stand 16:39–44, 2001

Wiesbeck GA, Shuckit MA, Kalmijn JA, et al: An evaluation of the history of a marijuana withdrawal syndrome in a large population. Addiction 91:1469–1478, 1996

Wilens TE, Biederman J, Spencer TJ: Case study: adverse effects of smoking marijuana while receiving tricyclic antidepressants. J Am Acad Child Adolesc Psychiatry 36: 481–485, 1997

World Health Organization: International Statistical Classification of Diseases and Related Health Problems, 10th Revision. Geneva, World Health Organization, 1992

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5

Cocaine and Psychostimulants

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Stimulants include a wide range of substances from cocaine to caffeine, or from amphetamine to xanthenes, for those preferring a broader alphabetical range. In this chapter, we focus on cocaine and amphetamine dependence, which are primarily treated with behavioral interventions, because no U.S. Food and Drug Administration (FDA)–approved pharmacotherapies are available. Pharmacotherapies for dependence on these psychoactive agents, which increase central nervous system (CNS) activity and produce powerful reinforcing effects (e.g., euphoria, elevated mood, "highs"), have been widely tested for more than 20 years with many promising leads, but treatment is complex, and it appears that a combination of behavioral interventions with a few selected medications is best.

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The peak of the cocaine epidemic occurred in the mid 1980s, and localized epidemics of amphetamine abuse continue, particularly in the Western United States (Rawson et al. 2002a). Methamphetamine abuse is an international public health problem, with two-thirds of the world's 33 million amphetamine abusers living in Asia (Ahmad 2003). In Hong Kong, the prevalence of amphetamine abuse rose from 1% in 1995 to 17% in 2000. The rate of stimulant abuse grew considerably among adolescents in the United States during the 1990s; between 1991 and 1997 the 30-day prevalence of cocaine abuse among eighth-, tenth-, and twelfth-graders increased more than twofold (Johnston et al. 1998). Annual prevalence among twelfth-graders fell from 12.7% in 1986 to 3.1% in 1992; by 1999, it had increased to 6.2%, and since then, it has remained around 5% (Johnston et al. 2005). The percentage of youths ages 12–17 years who had ever used cocaine increased from 2.3% in 2001 to 2.7% in 2002 (Substance Abuse and Mental Health Services Administration 2003). During the same period the rate of use by young adults (ages 18–25 years) increased from 14.9% to 15.4% (Substance Abuse and Mental Health Services Administration 2003). The prevalence of stimulant abuse reported in the 2002 National Survey on Drug Use and Health is shown in Table 5–1.

During the past 15 years, casualties from stimulant use have continued to accumulate; cocaine involvement in emergency department accident and violence cases remains prominent. National Institute of Justice figures showed that in the mid-1990s 40%–80% of male and female arrestees in major cities had cocaine-positive urine test results (Johanson and Shuster 1995). Presently about 2 million stimulant-dependent individuals are in serious need of treatment because of the dangers associated with stimulant use, including increased risk of human immunodeficiency virus (HIV) infection, detrimental effects on the unborn and newborn, and increased crime and violence, as well as medical, financial, and psychological problems. Because of these consequences, the task of identifying, characterizing, and developing treatments for stimulant abuse is more important than ever.

In this chapter, we review the current understanding of the biological basis for stimulant reinforcement and describe the clinical characteristics resulting from its use, as a foundation for a discussion of the pharmacological treatment of stimulant abuse. We conclude by providing specific treatment guidelines for managing stimulant-abusing individuals.

Table 5–1. Use of selected illicit drugs in lifetime, past year, and past month among persons age 12 years or older in the United States, 2002

	Lifetime				Past year				Past month			
	2002		2003		2002		2003		2002		2003	
Drug	*N* (1000s)	%	*N* (1000s)	%	*N* (1000s)	%	*N* (1000s)	%	*N* (1000s)	%	*N* (1000s)	%
Cocaine	33,910	14.4	34,891	14.7	5,902	2.5	5,908	2.5	2,020	0.9	2,281	1.0
Crack	8,402	3.6	7,949	3.3	1,554	0.7	1,406	0.6	567	0.2	604	0.3
Stimulants	21,072	9.0	20,798	8.8	3,181	1.4	2,751	1.2	1,218	0.5	1,191	0.5
Metham-phetamine	12,383	5.3	12,303	5.2	1,541	0.7	1,315	0.6	597	0.3	607	0.3

Source. Substance Abuse and Mental Health Services Administration, Office of Applied Studies, National Survey on Drug Use and Health, 2002 and 2003.

Chemistry and Pharmacology

The various stimulants have no obvious chemical relationships and do not share primary neurochemical effects, despite their similar behavioral effects. Cocaine's chemical structure does not resemble that of caffeine, nicotine, or amphetamine. Cocaine binds to the dopamine reuptake transporter in the central nervous system, effectively inhibiting dopamine reuptake. It has similar effects on the transporters that mediate norepinephrine and serotonin reuptake. As discussed later in this chapter in the section on neurochemical actions mediating stimulant reward, dopamine is very important in the reward system of the brain; the increase of dopamine associated with use of cocaine probably accounts for the high dependence potential of the drug.

Amphetamines probably act centrally mainly by increasing the release of catecholaminergic neurotransmitters, including dopamine. Amphetamines act through the vesicular monoamine transporter (VMAT), preventing catecholamines from being stored in intracellular vesicles and leading to the release of these catecholamines into the synapse (White and Kalivas 1998). Amphetamines are also weak inhibitors of monoamine oxidase and, by virtue of structural similarity, possibly of direct catecholaminergic agonists in the brain. Dextroamphetamine is the major member of the class, although many other amphetamines and amphetamine surrogates, such as methamphetamine (Methedrine, "speed"), phenmetrazine (Preludin), and methylphenidate (Ritalin), were subsequently introduced. The number of amphetamine analogs with psychoactive effects continues to multiply. The first of the newer members of the group was 2,5-dimethoxy-4-methylamphetamine (DOM, "STP"), and the list now includes 3,4-methylenedioxyamphetamine (MDA) and 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). The latter drugs have more amphetamine-like than hallucinogenic effects (Reneman et al. 2001). A closely related natural alkaloid, cathinone, is found in the leaves and stems of *Catha edulis*, or khat, a plant found and cultivated in the Middle East and Africa. Chewing freshly harvested khat results in effects indistinguishable from those of the amphetamines. The pharmacology of this compound is probably similar to amphetamine, but it has been less studied (Kalix and Braenden 1985).

Caffeine and nicotine have more complex reinforcing effects on dopamine. Caffeine, a methylxanthine compound, appears to exert its central ac-

tions (and perhaps some of its peripheral ones as well) by blocking adenosine receptors. Other methylxanthines (e.g., theophylline) have the same actions. Adenosine modulates adenylyl cyclase activity, probably accounting for the central stimulant actions of the methylxanthines. At high concentrations, the methylxanthines inhibit phosphodiesterase, thereby inhibiting the breakdown of cyclic adenosine monophosphate (cAMP) and increasing its concentration inside cells. However, it is doubtful that this action is important at the dosage that commonly produces psychoactive effects. Caffeine's ultimate effect on dopaminergic reinforcement pathways in the nucleus accumbens is not clear (Garrett and Griffiths 1997). Nicotine enhances the activity of dopamine in the nucleus accumbens and the ventral tegmental area, an effect that may be mediated by several neuroreceptors, including nicotinic, muscarinic, D_1/D_2 dopaminergic, *N*-methyl-D-aspartate (NMDA), cannabinoid (CB1), and γ-aminobutyric acid B ($GABA_B$) receptors (Sziraki et al. 2002).

The rewarding effects of stimulants such as cocaine and amphetamine are enhanced by the intravenous or smoked route of administration because these routes produce more immediate onset of euphoria. The preferred method of self-administering cocaine has been snorting and, more recently, smoking. The effects of snorted cocaine generally occur within 15–20 minutes, whereas the effects from intravenously injected cocaine can be felt within minutes. A smokable form of cocaine (crack cocaine), which results from the conversion of cocaine hydrochloride into a free base, also produces euphoria within minutes. Amphetamines come in a variety of forms (e.g., pill, liquid, or powder form) but are usually taken orally or intravenously. Similar to cocaine, amphetamine is available in a smokable version ("ice"); because of its long duration of action, smokable amphetamine can produce euphoria lasting 12–24 hours. Methamphetamine can be synthesized in illegal, unsophisticated laboratories from readily available precursors, and smoked ("ice"), snorted ("crystal meth"), injected ("crank"), or taken orally ("speed").

Neurochemical Actions Mediating Stimulant Reward

The rewarding effects of stimulants are mediated through the mesocorticolimbic dopamine neurons of the ventral tegmental area and their target

projections to the nucleus accumbens and prefrontal cortex (Johanson and Fischman 1989; Kosten 2002). Behavioral and neurochemical studies indicate that reinforcement is dependent on rapid entry of cocaine into the brain to rapidly raise dopamine levels as cocaine inhibits the dopamine transporter (Volkow et al. 1996a, 1997). Because cocaine and amphetamine have actions on the norepinephrine and serotonin neurotransmitter systems, these systems are also important targets for medication development (Rothman et al. 2000). Such medications might be used to block this acute reinforcement, but they may also target brain changes caused by chronic stimulant use. Sensitization in brain reward centers (Robinson and Berridge 1993) also may be critical to the development of an increased response to the abused drug and its cues, leading to greater reward and drug-seeking behavior, although this topic remains controversial (Ben-Shahar et al. 2004; Cornish and Kalivas 2001; Koob and LeMoal 2001). Sensitization is induced by repeated administration of stimulants such as amphetamine and may be caused by increases in dopaminergic activity and an imbalance in the regulatory activity of dopamine receptor subtypes or interactions with excitatory amines (Almodovar-Fabregas et al. 2002; Klawans and Margolin 1975; Richtand et al. 2001; Schuster 1981; Segal and Mandell 1974). Glutamate transmission, particularly that involving the NMDA receptor, may be especially important in cocaine sensitization, probably through connections with the prefrontal cortex (Vanderschuren and Kalivas 2000).

Neurobiological Effects of Chronic Stimulant Abuse

Because stimulants can produce a constellation of neurochemical, physiological, and neuropsychological impairments following chronic use, a useful concept in treatment of these patients is normalization of disrupted neurobiology. Abnormalities in neurotransmitter receptors and transporters that have been noted in animal models have been confirmed in human neuroimaging studies of both the dopamine and serotonin neurotransmitter systems (Malison et al. 1998; Sevarino et al. 2000; Volkow et al. 1990, 1992, 1996b). Single photon emission computed tomography (SPECT) and positron emission tomography (PET) studies showed increases in dopamine transporter (DAT) during acute cocaine abstinence in cocaine-abusing subjects, relative to com-

parison subjects (Malison et al. 1998), decreases in dopamine D_2 receptor binding in detoxified cocaine abusers (Volkow et al. 1996b), and reduced cerebral blood flow (CBF) among chronic cocaine users (Holman et al. 1991; Kosten et al. 1998; Volkow et al. 1988). During abstinence this reduced CBF has been shown to improve in cocaine-dependent individuals, suggesting that drug-induced alterations may be reversed to some extent (Holman et al. 1993; Kosten 1998). Alterations in glucose metabolism have also been observed with chronic and acute stimulant administration. When tested during early withdrawal, cocaine users showed an increase in glucose metabolism, relative to comparison subjects, but during late withdrawal, metabolic activity was decreased in cocaine-dependent subjects (Volkow et al. 1991, 1992). Such reductions in glucose metabolism have also been observed following acute administration of cocaine (London et al. 1990). More recently, decreased gray matter concentration has been described in a variety of cortical areas, including the frontal, cingulate, and temporal regions (Franklin et al. 2002).

Neuroendocrine challenge studies showed functional deficits consistent with these neuroimaging findings; norepinephrine systems, which may also be disrupted by stimulants, showed parallel pharmacological challenge abnormalities, such as lowered thresholds for yohimbine induction of panic attacks (Aronson et al. 1995; Bowers et al. 1998; McDougle et al. 1992, 1994; Swartz et al. 1990). Monamine neurotransmitter systems show the direct actions of chronic stimulants; other neurotransmitter systems that are indirectly affected include glutamate, GABA, and κ opioid systems (Johanson and Fischman 1989; Koob 1992). Abnormalities in any of these systems are appropriate targets for pharmacotherapy and have been studied in clinical trials of a range of available agents, which are reviewed later in this chapter, in the section on specific pharmacological treatments.

The disturbed brain structure and function following stimulant use may be the substrate for the cognitive deficits frequently described in these patients. Impairments in verbal learning, memory, and attention have been well documented in cocaine-abusing individuals (Beatty et al. 1995; Bolla et al. 1998; Di Sclafani et al. 2002; Gottschalk et al. 2001) and are correlated with reductions in CBF among cocaine users (Woods et al. 1991). DAT reduction also appears to correlate with psychomotor impairment in methamphetamine abusers (Volkow et al. 2001a, 2001b). Thus, neurochemical and physiological alterations from chronic stimulant abuse may lead to cognitive impairments.

Behavioral Effects

In humans, subjective and behavioral responses to stimulants are very complex and depend on many variables, including 1) drug dose, 2) drug route of administration (intravenous administration and smoking produce an intensely pleasurable response), 3) previous experience with stimulants, 4) the environment in which the drug is taken, and 5) the unique response pattern of the individual user, which may in part be genetically determined. In most subjects, low doses administered orally produce a sense of relaxation, well-being, diminished fatigue, self-confidence, and mental alertness (see Kosten 2002; Martin et al. 1971). Increasing doses result in greater activation, anxiety, insomnia, and anorexia, and dose escalation is necessary to maintain the reinforcing properties (Foltin et al. 2003). The mood response can vary from elation to extreme dysphoria. An antidepressant effect is seen in some depressed patients (Silberman et al. 1981), and cocaine abusers with milder depressive symptoms experience beneficial effects on mood after cocaine administration (Sofuoglu et al. 2001; Uslaner et al. 1999). However, some studies suggested that individuals with primary depression (i.e., not substance-induced depression) have dysphoric responses to cocaine (Rosenblum et al. 1999).

Stimulants induce both tolerance and sensitization to their behavioral effects. Tolerance develops to the anorectic and euphoric effects of stimulants (Schuster 1981); however, chronic intermittent use of low doses of stimulants delays the development of tolerance. With the doses commonly used in clinical practice, patients treated for narcolepsy or for depressive or apathetic states find that the stimulant properties usually persist without development of tolerance; however, the persistence of antidepressant effects remains a matter of controversy. Sensitization has been linked to the development of amphetamine-induced psychosis (Yui et al. 1999). Sensitization to the induction of psychosis is suggested because psychosis is induced by progressively lower doses and shorter periods of consumption of amphetamine following repeated use over time (Sato 1986). Sensitization for amphetamine-induced psychosis may persist despite long periods of abstinence.

The development of psychosis is the most striking clinical characteristic of high-dose stimulant abuse. The amphetamines, methylphenidate, and phenmetrazine all produce psychosis (Ellinwood et al. 1973; Harris and Batki 2000; Iversen et al. 1978; Lucas and Weiss 1971; McCormick and McNeil 1962).

Some authorities believe that psychosis is more common with binge patterns of use and escalating dosages (Gawin 1991; Segal and Kuczenski 1997). Compared with other stimulants, cocaine appears less likely to lead to psychosis, which is probably related to dose and patterns of use. Most individuals use cocaine intermittently, whereas daily use of amphetamines is common (see King and Ellinwood 1997). Susceptibility to stimulant-induced psychosis may also be related to differences in the effects of various stimulants on monoamines (Fleckenstein et al. 2000; Vanderschuren and Kalivas 2000). Some (Janowsky et al. 1973) but not all (Kornetsky 1976) studies have found that schizophrenic patients are sensitive to exacerbation of psychosis from stimulants. Paranoid delusions can probably be induced in most people if they are given an adequate dose of stimulant (Griffith et al. 1968). Schizophrenic patients with cocaine dependence may have more hallucinations than patients presenting with either disorder alone, although there is considerable similarity in clinical presentations (Serper et al. 1999). The dose required to produce psychosis varies greatly among individuals (Bell 1973). It has been estimated that 50% of people who abuse 30–100 mg/day of amphetamine for 3 months will develop psychotic symptoms (Sato 1986). In one study of normal volunteers, 100 mg of amphetamine was sufficient to produce psychosis in one subject, whereas another subject required 955 mg (Angrist and Gershon 1970).

Before the onset of overt psychosis, most stimulant users begin to exhibit suspiciousness and a fascination with details of objects in their environment; they often will begin to perform repetitive behaviors, such as picking at their skin, disassembling mechanical objects, and engaging in prolonged masturbation or coitus (Connell 1958). With higher doses or continued administration, users begin to experience paranoid delusions; ideas of reference; visual, auditory, or olfactory hallucination; and agitation (Ellinwood 1967). Cocaine-induced paranoia is relatively common and may even have genetic determinants related to DAT and dopamine hydroxylase (Cubells et al. 2000; Gelernter et al. 1994; Satel et al. 1991). Violence, including homicide, has been reported as a consequence of this activated, paranoid state (Ellinwood 1967; Kramer 1969). The combination of alcohol and cocaine appears to be an especially high risk factor for violent behavior, even in the absence of psychotic symptoms (Chermack and Blow 2002). Disorientation ("stimulant delirium") appears in some instances. A syndrome of hyperthermia and agitation that resembles neuroleptic malignant syndrome has also been reported (Kosten and Kleber 1988).

The clinical presentation of stimulant psychosis has frequently been described as being indistinguishable from that of paranoid schizophrenia (Angrist and Gershon 1970; Ellinwood 1971). Supporting the similarity is a study that examined the symptoms of psychosis in 168 methamphetamine-dependent inpatients in Australia, Japan, the Philippines, and Thailand (Srisurapanont et al. 2003). The investigators found that 77% of the subjects had experienced persecutory delusions during their lifetime, "followed by auditory hallucinations, strange or unusual beliefs, and thought reading" in almost half of the subjects. Twenty percent of the subjects exhibited negative symptoms, such as "poverty of speech, psychomotor retardation, and flattened/incongruous affects," resembling the symptoms of schizophreniform disorder. Some clinical presentations may be confused with acute mania, characterized by agitation, hypersexuality, affective lability, and grandiosity. In addition, many symptoms are suggestive of temporal lobe epilepsy, such as olfactory hallucinations, déjà vu, philosophical preoccupation, and the very atypical course of the illness (Ellinwood 1968). Stimulant psychosis generally clears within a few days of discontinuation of the drug (Beamish and Kiloh 1960; Spear and Alderton 2003), although prolonged psychoses may sometimes occur (Ahmad 2003; Iversen et al. 1978). Stimulant psychosis is generally managed by close psychiatric and medical supervision and by judicious use of benzodiazepines and atypical antipsychotic medications (Jha and Fourie 1999; Misra and Kofoed 1997).

Dependence and withdrawal can occur with all of the stimulants. Cocaine is one of the most strongly reinforcing drugs in self-administration paradigms in animals and also has a psychological withdrawal syndrome. A typical pattern of withdrawal includes a ravenous appetite, exhaustion, and mental depression, which may last for several days after the drug is withdrawn. Because tolerance develops quickly, abusers may take large doses, compared with those used medically, for example, as anorexiants.

Treatment Guidelines for Stimulant Abuse

A comprehensive assessment of the stimulant-dependent patient's psychological, medical, forensic, and drug use history may be difficult, because information may be incomplete or unreliable. In recognition of this deficiency, it is important that the patient receives a thorough physical examination, as well

as laboratory testing, including testing of supervised urine samples for toxicological analysis of potential polydrug abuse. Patients may ingest large amounts of one or more drugs at potentially lethal doses, and therefore it is important that the physician be aware of the dangers of possible drug combinations, such as cocaine with alcohol or heroin (Goldsmith 1997).

Pharmacological intervention for stimulant-induced drug states may include neuroleptics for controlling stimulant-induced psychosis or delirium. Pharmacological interventions should be followed by treatments aimed at relapse prevention. In the future, antidepressants or even vaccines may be an appropriate choice for relapse prevention. Medication treatment is typically initiated in outpatients, and it is critical to warn the patient of the potential adverse interactions between cocaine and prescribed medication. For instance, high blood pressure could result from the release of epinephrine by cocaine combined with the reuptake blockade by a tricyclic antidepressant, although later in the course of treatment, tricyclics decrease the sensitivity of the postsynaptic adrenergic receptors (Fischman et al. 1976; Kosten et al. 1992). In general, the potential role of pharmacotherapy in patients with stimulant dependence is to initiate abstinence, to prevent relapse, and to treat psychiatric comorbidity.

Specific Pharmacological Treatments for Stimulant Abuse

The development of effective pharmacotherapy has lagged behind progress in understanding the reward mechanisms and chronic impairments underlying stimulant abuse. Pharmacological and behavioral treatment approaches that have been used for cocaine abuse have not been as widely tested for the treatment of amphetamine abuse, limiting what can be offered for treatment of this disorder. No treatment agents are approved by the FDA for treatment of cocaine or amphetamine dependence.

The targets for treatment can include withdrawal relief for abstinence initiation and relapse prevention. Stimulant withdrawal, which occurs after cessation of cocaine or amphetamine use, can produce a wide range of dysphoric symptoms. Following binge use, individuals may initially experience symptoms of depression, anxiety, agitation, and intense drug craving (Gawin and

Ellinwood 1988). After this initial phase of agitation individuals may experience fatigue, a loss of physical and mental energy, and decreased interest in the surrounding environment (Gawin and Ellinwood 1988). Addressing these withdrawal symptoms may facilitate abstinence initiation. After attaining more sustained abstinence from stimulants, the patient may experience brief periods of intense drug craving in which objects and people in the patient's life become conditioned triggers for craving and relapse. Relapse prevention, which targets individuals who have minimal symptoms except drug craving as responses to environmental cues, probably involves a different set of potential pharmacotherapies.

Pharmacotherapy for Primary Stimulant Dependence

More than 40 medications have been investigated but none have shown consistent efficacy for primary cocaine or amphetamine dependence. These medications include dopaminergic agonists, antidepressants, and more recently disulfiram, selegiline, and a cocaine vaccine (see Table 5–2 for summary). Studies have been relatively brief and have focused on abstinence initiation rather than on relapse prevention, but even these modest treatment goals have not been attained. The focus in the discussion that follows is on pharmacotherapies for cocaine dependence, because very few clinical trials have been completed with amphetamine-dependent patients. Furthermore, none of the studies of amphetamine dependence have shown results different from those described for cocaine dependence (Rawson et al. 2002b; Srisurapanont et al. 2001).

We begin this overview with a listing of some of the approaches and representative agents. Cocaine agonists that mimic some of cocaine's effects have included other stimulants such as methylphenidate, amphetamine, pemoline, modafinil, and slow-onset agonist treatment with oral cocaine in the form of a coca tea used in South America. Cocaine antagonists that block cocaine effects by blocking cocaine binding at the dopamine transporter site include bupropion, mazindol, and GBR-12909. Agents that block dopamine receptors include D_1 antagonists (ecopipam), D_2 antagonists (antipsychotics), and D_1/D_3 antagonists (atypical antipsychotics). Putative antikindling agents include carbamazepine, valproate, and phenytoin. Agents that affect the GABA system include gabapentin, vigabatrin, tiagabine, topiramate,

Table 5–2. Strategies for medication development in stimulant abuse

Medication class or mechanism of action	Common examples	Comments
Dopamine agonists	Amantidine, bromocriptine, mazindol, pergolide, cabergoline, L-dopa/carbidopa, pramipexole, ABT-431, catecholamine metabolism inhibitors (disulfiram, phenelzine, selegiline), amineptine	Findings are mixed, but some agents are promising (e.g., disulfiram, amineptine); class deserves further study.
Stimulant agonist replacement	Methylphenidate, *d*-amphetamine, tropanes, GBR-12909 (partial agonist that may also act as antagonist), modafinil, coca tea	Partial agonists are in early developmental stages. Agonist replacement is an attractive strategy, because of the successs of methadone and buprenorphine in opioid dependence.
Stimulant antagonists	Antipsychotics (conventional agents have nonspecific dopamine receptor antagonsim; atypical agents also have serotonin antagonist activity), ecopipam, GBR-12909 and other partial dopamine agonists (may be functional antagonists)	Partial agonists may act as antagonists under certain conditions. These agents hold promise.
Anticonvulsants	Vigabatrin (not marketed in United States), tiagabine, topiramate, gabapentin, carbamazepine, lamotrigine	Vigabatrin has an unacceptable adverse effect profile, but consistent findings in animal studies suggest that GABA agonists deserve further study. α-AMPA antagonism, or antikindling action, may also be important for some anticonvulsants.
GABA agonists (non-anticonvulsants)	Baclofen, riluzole	Baclofen is most promising agent at present, but studies with negative findings exist.

Table 5–2. Strategies for medication development in stimulant abuse *(continued)*

Medication class or mechanism of action	Common examples	Comments
Antidepressants	Desipramine, imipramine, sertraline, fluoxetine, paroxetine, venlafaxine, bupropion, nefazodone, mirtazapine, gepirone, amineptine	Mixed findings suggest that better designed studies may find a niche for some of these drugs. Amineptine was effective for withdrawal symptoms.
Serotonergic agents (nonantidepressants)	Ondansetron, ritanserin, buspirone	Large controlled studies are not encouraging.
Catecholamine depletion or blockade	Reserpine, propranolol, and other β blockers; clonidine and other α_2 agonists	Placebo-controlled trial of reserpine had negative findings. Other agents require further study.
Opioids	Buprenorphine, κ agonists	Buprenorphine probably not effective in treating stimulant abuse. κ Agonists have not been adequately studied.
Cocaine vaccine	Passive monoclonal antibodies, active vaccinations	Further studies are required for this novel approach.
Neurosteroids	Progesterone, dexamethasone, dehydroepiandrosterone	Study findings have been negative.
N-methyl-D-aspartate antagonists	Dextromethorphan	Limited number of drugs in this class are available for human use. Study findings have been negative.
Cerebral blood flow enhancers	Piracetam, hydergine	Study findings have been negative.
Herbals	*Hypericum perforatum*, L-carnitine/coenzyme Q10, *Ginkgo biloba*	Study findings have been negative.
Phosphodiesterase inhibitors	Pentoxifylline, rolipram	Study findings have been negative.

Note. AMPA=amino-3-hydroxy-5-methyl-4-isoxazole propionate; GABA=γ-aminobutyric acid.

baclofen, and progesterone. Stress response modulators include ketoconazole, dehydroepiandrosterone, dexamethasone, propranolol, and biofeedback with electroencephalogram monitoring. Cerebral blood flow enhancers include piracetam, hydergine, and pentoxifylline (also a nonselective phosphodiesterase inhibitor). Finally, nutritional supplements and herbal products include *Ginkgo biloba*, amino acid mixtures, L-carnitine/coenzyme Q10, *Hypericum perforatum* (St. John's wort), and ibogaine, which might be more appropriately considered a hallucinogen. The controlled studies with these agents have yielded variable findings, and none of these agents have shown consistent efficacy.

A number of the agents examined as cocaine pharmacotherapy, including carbamazepine, buprenorphine, and GABA agonists, have been examined extensively enough to merit citation of particular studies. Carbamazepine failed to show therapeutic effects in three controlled studies (Cornish et al. 1995; Kranzler et al. 1995; Montoya et al. 1995). Buprenorphine also has had more negative than positive findings for its efficacy in treating cocaine-abusing, opioid-dependent patients (Kosten et al. 1989, 1993; Schottenfeld et al. 1997). The GABA agonists showed promise in an initial study using baclofen (Ling et al. 1998), a study of vigabatrin (Brodie et al. 2003), and a study showing efficacy for tiagabine, a GABA reuptake inhibitor (Gonzalez et al. 2003).

Recent advances in understanding dopamine neuronal systems and in considering ways to alter the brain pharmacokinetics of cocaine have led to innovative approaches for medication development. For example, the effects of κ agonists to reduce dopamine activity is opposite to that observed with cocaine or amphetamine, thereby suggesting a potential mechanism by which κ agonists could be efficacious (Maisonneuve et al. 1994). Furthermore, several groups have shown that mice with the dopamine transporter gene deleted will still self-administer cocaine, suggesting a role for other neurotransmitter systems (Rocha et al. 1998; Sora et al. 1998, 2001). Finally, several cocaine vaccines, including both passive monoclonal antibodies and active vaccinations, are being developed for use in humans, and animal studies have shown that these vaccines suppress cocaine administration (Kosten and Biegel 2002; Kosten et al. 2002b).

We will now examine two classes of agents—dopaminergic agents and antidepressants—in more detail.

Dopaminergic Agents

Because chronic cocaine use appears to reduce the efficiency of central dopamine neurotransmission, a number of dopaminergic compounds, including amantadine, bromocriptine, mazindol, and methylphenidate, have been examined as treatments for cocaine abuse. It is thought that these relatively slow-onset dopaminergic agents, with low or relatively low abuse potential, would correct the dopamine dysregulation and alleviate withdrawal symptoms following chronic stimulant use.

Dopaminergic medications that have been examined include dopamine agonists, such as the D_1 receptor agonist ABT-431, D_2 receptor agonists (bromocriptine, pergolide, cabergoline), relatively more selective D_3 receptor agonists (e.g., pramipexole), and amantidine (which may increase dopamine release, reduce synaptic reuptake, act as a dopamine receptor agonist, enhance postsynaptic dopamine receptor sensitivity, or inhibit NMDA activity). Amineptine also showed some efficacy for amphetamine withdrawal, although the medication was withdrawn from major markets because of abuse liability (Rawson et al. 2002b; Srisurapanont et al. 2001). The effects of monoamine oxidase inhibitors such as phenelzine and selegiline and an inhibitor of dopamine β-hydroxylase–disulfiram–have been examined. Precursors of dopamine synthesis, such as tyrosine and L-dopa, have also been examined.

Direct dopamine agonists such as pergolide have shown no efficacy, but some suggestion of efficacy has been found for indirect agents such as sustained-release amphetamine and disulfiram (Carroll et al. 2004; Kosten et al. 2002a; Malcolm et al. 2000). Open screening trials have shown some potential for methylphenidate in cocaine-dependent subjects with attention-deficit/hyperactivity disorder (ADHD) (Somoza et al. 2004). In the absence of ADHD, a controlled study found no difference between methylphenidate and placebo treatment groups in cocaine use (Grabowski et al. 1997). Sustained-release amphetamine showed more promise (Grabowski et al. 2001). No published placebo-controlled study has examined the effects of selegiline, which blocks the breakdown of dopamine by monoamine oxidase inhibition. Disulfiram has an indirect action on dopamine through inhibition of the enzyme dopamine β-hydroxylase, which converts dopamine to norepinephrine. Studies with disulfiram at doses of 250 mg/day showed promise in reducing cocaine

abuse, with or without comorbid alcohol dependence (Carroll et al. 1998, 2004; George et al. 2000).

Antidepressants

The second class of medications used to treat cocaine dependence consists of antidepressants, which are thought to down-regulate synaptic catecholamine receptors—an action opposite to the presynaptic up-regulation caused by chronic stimulant use (Gawin and Ellinwood 1988). Selective serotonin reuptake inhibitors (SSRIs) that have been examined as treatments for cocaine abuse include fluoxetine, sertraline, and paroxetine. Serotonin receptor agonists with potential antidepressant or antianxiety effects that have been tested include buspirone and gepirone, both of which act at serotonin$_{1A}$ (5-HT$_{1A}$) receptors. Receptor antagonists include ritanserin (at 5-HT$_2$ receptors), odansetron (5-HT$_3$), and mirtazapine (5-HT$_2$, 5-HT$_3$, and others). The precursor in the synthesis of serotonin, L-tryptophan, has also been tried unsuccessfully. Antidepressants that affect dopamine, serotonin, and norepinephrine as reuptake blockers appear to show the most success. They include desipramine, imipramine, and venlafaxine. Although newer SSRI antidepressants have a relatively benign side effect profile, good patient adherence rates, and lack of abuse liability, only the older agent desipramine has shown efficacy in selected populations. Although early studies suggested some efficacy for fluoxetine, this finding has not been confirmed in controlled trials (Grabowski et al. 1995; Schmitz et al. 2001).

A meta-analysis of placebo-controlled studies by Levin and Lehman (1991) showed that desipramine produced greater cocaine abstinence than placebo. Although a more recent review did not concur (Lima et al. 2001), secondary analyses of studies with imipramine, desipramine, and bupropion suggested that depressed cocaine abusers are more likely to show significant reductions in cocaine abuse than nondepressed cocaine abusers (Margolin et al. 1995; Nunes et al. 1991; Ziedonis and Kosten 1991). Furthermore, recent work with desipramine supported its efficacy in opioid-dependent patients, particularly in combination with contingency management therapies (Kosten et al. 2004; Oliveto et al. 1999).

Pharmacotherapy and Psychiatric Comorbidity

The rates of comorbid psychiatric disorders such as depression, ADHD, and antisocial personality disorder are significantly higher in stimulant abusers

than in community control subjects (Rounsaville et al. 1991; Weiss et al. 1986). Because psychiatric disorders may increase the risk for drug use (e.g., individuals may self-medicate to ease psychiatric symptoms), it is important that treatment addresses both the stimulant addiction and the comorbid disorder. Particularly useful pharmacotherapies for stimulant abusers with comorbid psychopathology include antidepressants to ameliorate depressive symptoms and reduce cocaine use and craving in depressed cocaine-dependent patients (Ciraulo et al. 2000; Nunes et al. 1991; Ziedonis and Kosten 1991). Also, methylphenidate has been reported to be effective in treating cocaine-dependent patients with ADHD (Khantzian et al. 1984; Somoza et al. 2004), although a controlled trial has yet to be published.

Conclusion

Although no medications are currently approved by the FDA to treat stimulant dependence, neurobiological abnormalities in dopamine receptors and transporters after chronic stimulant use suggest potential treatment approaches. Studies of dopamine receptor agonists and antagonists have not shown clinical efficacy, but more sophisticated approaches are being developed. On the basis of clinical phenomenology, treatment with antidepressants has been examined in depressed cocaine abusers, who may reduce their cocaine use when depressive symptoms are reduced. CBF defects also appear to be relatively common among stimulant abusers and appear to correlate with neuropsychological deficits. CBF defects in cocaine abusers may benefit from the application of findings from the rapidly evolving field of stroke pharmacotherapy. Finally, vaccines may reduce cocaine's rewarding effects and prevent relapse among abstinent patients.

With all of these pharmacotherapies, concurrent behavioral treatment is critical to retain the patient in treatment and maintain adherence to medication treatment. Contingency management programs in which patients receive vouchers that can be used to purchase pro-social goods and services are the most common reinforcer approaches used to initiate and maintain stimulant-free urine test results (Anker and Crowley 1982; Boudin 1972; Higgins et al. 1991, 1993, 1994). The major problem with these approaches has been maintaining abstinence after the reinforcers are withdrawn completely and devel-

oping a mechanism to produce sufficient reinforcement outside of a research setting. A more typical time-limited therapy for use in clinical programs is cognitive-behavioral therapy, which has shown interesting additive effects with antidepressants (Carroll et al. 1994). For example, after a 3-month treatment period, patients who received both pharmacotherapy and cognitive-behavioral therapy showed more sustained abstinence than those who received either therapy alone. Although both pharmacological and behavioral interventions may be useful in treating the majority of stimulant-dependent patients, individuals with significant medical risks, psychiatric comorbidity, or neuroadaptation resulting from heavy stimulant use are particularly likely to benefit from pharmacological treatment (Kosten 2002). Thus, combined treatment is often needed, and outcome at 1 year is substantially enhanced by the use of psychotherapy in combination with medications.

References

Ahmad K: Asia grapples with spreading amphetamine abuse. Lancet 361:1878–1879, 2003

Almodovar-Fabregas LJ, Segarra O, Colon N, et al: Effects of cocaine administration on VTA cell activity in response to prefrontal cortex stimulation. Ann N Y Acad Sci 965:157–171, 2002

Angrist BM, Gershon S: The phenomenology of experimentally induced amphetamine psychosis—preliminary observations. Biol Psychiatry 2:95–107, 1970

Anker AL, Crowley TJ: Use of contingency contracts in specialty clinics for cocaine abuse. NIDA Res Monogr 41:452–459, 1982

Aronson SC, Black JE, McDougle CJ, et al: Serotonergic mechanisms of cocaine effects in humans. Psychopharmacology (Berl) 119:179–185, 1995

Beamish P, Kiloh LG: Psychoses due to amphetamine consumption. J Ment Sci 106: 337–343, 1960

Beatty WW, Katzung VM, Moreland VJ, et al: Neuropsychological performance of recently abstinent alcoholics and cocaine abusers. Drug Alcohol Depend 37:247–253, 1995

Bell DS: The experimental reproduction of amphetamine psychosis. Arch Gen Psychiatry 29:35–40, 1973

Ben-Shahar O, Ahmed SH, Koob GF, et al: The transition from controlled to compulsive drug use is associated with a loss of sensitization. Brain Res 995:46–54, 2004

Bolla KI, Cadet JL, London ED: The neuropsychiatry of chronic cocaine abuse. J Neuropsychiatry Clin Neurosci 10:280–289, 1998

Boudin HM: Contingency contracting as a therapeutic tool in the declaration of amphetamine use. Behav Res Ther 3:604–608, 1972

Bowers MB Jr, Malison RT, Seibyl JP, et al: Plasma homovanillic acid and the dopamine transporter during cocaine withdrawal. Biol Psychiatry 43:278–281, 1998

Brodie JD, Figueroa E, Dewey SL: Treating cocaine addiction: from preclinical to clinical trial experience with gamma-vinyl GABA. Synapse 50:261–265, 2003

Carroll KM, Rounsaville BJ, Gordon LT, et al: Psychotherapy and pharmacotherapy for ambulatory cocaine abusers. Arch Gen Psychiatry 51:177–187, 1994

Carroll KM, Nich C, Ball SA, et al: Treatment of cocaine and alcohol dependence with psychotherapy and disulfiram. Addiction 93:713–727, 1998

Carroll KM, Fenton LR, Ball SA, et al: Efficacy of disulfiram and cognitive behavior therapy in cocaine-dependent outpatients: a randomized placebo-controlled trial. Arch Gen Psychiatry 61:264–272, 2004

Chermack ST, Blow FC: Violence among individuals in substance abuse treatment: the role of alcohol and cocaine consumption. Drug Alcohol Depend 66:29–37, 2002

Ciraulo DA, Rotrosen J, Leiderman D, et al: Nefazodone induced alterations of cocaine craving and use in dysphoric cocaine users. Drug Alcohol Depend 60:S38, 2000

Connell PH: Amphetamine Psychosis (Maudsley Monographs No 5). London, Oxford University Press, 1958

Cornish JL, Kalivas PW: Cocaine sensitization and craving: differing roles for dopamine and glutamate in the nucleus accumbens. J Addict Dis 20:43–54, 2001

Cornish JW, Maany I, Fudala PJ, et al: Carbamazepine treatment for cocaine dependence. Drug Alcohol Depend 38:221–227, 1995

Cubells JF, Kranzler HR, McCance-Katz E, et al: A haplotype at the DBH locus, associated with low plasma dopamine beta-hydroxylase activity, also associates with cocaine-induced paranoia. Mol Psychiatry 5:56–63, 2000

Di Sclafani V, Tolou-Shams M, Price LJ, et al: Neuropsychological performance of individuals dependent on crack-cocaine, or crack-cocaine and alcohol, at 6 weeks and 6 months of abstinence. Drug Alcohol Depend 66:161–171, 2002

Ellinwood EH Jr: Amphetamine psychosis: I. description of the individuals and process. J Nerv Ment Dis 144:273–283, 1967

Ellinwood EH Jr: Amphetamine psychosos: II. theoretical implications. Int J Neuropsychiatry 4:45–54, 1968

Ellinwood EH Jr: Assault and homicide associated with amphetamine abuse. Am J Psychiatry 127:1170–1175, 1971

Ellinwood EH Jr, Sudilovsky A, Nelson LM: Evolving behavior in the clinical and experimental amphetamine (model) psychosis. Am J Psychiatry 130:1088–1093, 1973

Fischman MW, Schuster CR, Resnekov L, et al: Cardiovascular and subjective effects of intravenous cocaine administration in humans. Arch Gen Psychiatry 33:983–989, 1976

Fleckenstein AE, Gibb JW, Hanson GR: Differential effects of stimulants on monoaminergic transporters: pharmacological consequences and implications for neurotoxicity. Eur J Pharmacol 406:1–13, 2000

Foltin RW, Ward AS, Haney M, et al: The effects of escalating doses of smoked cocaine in humans. Drug Alcohol Depend 70:149–157, 2003

Franklin TR, Acton PD, Maldjian JA, et al: Decreased gray matter concentration in the insular, orbitofrontal, cingulate, and temporal cortices of cocaine patients. Biol Psychiatry 51:134–142, 2002

Garrett BE, Griffiths RR: The role of dopamine in the behavioral effects of caffeine in animals and humans. Pharmacol Biochem Behav 57:533–541, 1997

Gawin FH: Cocaine addiction: psychology and neurophysiology. Science 251:1580–1586, 1991

Gawin FH, Ellinwood EH Jr: Cocaine and other stimulants: actions, abuse, and treatment. N Engl J Med 318:1173–1182, 1988

Gelernter J, Kranzler HR, Satel SL, et al: Genetic association between dopamine transporter protein alleles and cocaine-induced paranoia. Neuropsychopharmacology 11:195–200, 1994

George TP, Chawarski MC, Pakes J, et al: Disulfiram versus placebo for cocaine dependence in buprenorphine-maintained subjects: a preliminary trial. Biol Psychiatry 47:1080–1086, 2000

Goldsmith RJ: The elements of contemporary treatment, in The Principles and Practice of Addictions in Psychiatry. Edited by Miller NS. Pennsylvania, PA, WB Saunders, 1997, pp 392–399

Gonzalez G, Sevarino K, Sofuoglu M, et al: Tiagabine increases cocaine-free urines in cocaine-dependent methadone-treated patients: results of a randomized pilot study. Addiction 98:1625–1632, 2003

Gottschalk C, Beauvais J, Hart R, et al: Cognitive function and cerebral perfusion during cocaine abstinence. Am J Psychiatry 158:540–545, 2001

Grabowski J, Rhoades H, Elk R, et al: Fluoxetine is ineffective for treatment of cocaine dependence or concurrent opiate and cocaine dependence: two placebo-controlled double-blind trials. J Clin Psychopharmacol 15:163–174, 1995

Grabowski J, Roache JD, Schmitz JM, et al: Replacement medication for cocaine dependence: methylphenidate. J Clin Psychopharmacol 17:485–488, 1997

Grabowski J, Rhoades H, Schmitz J, et al: Dextroamphetamine for cocaine-dependence treatment: a double-blind randomized clinical trial. J Clin Psychopharmacol 21: 522–526, 2001

Griffith JD, Oates JA, Cavanaugh JH: Paranoid episodes induced by drugs. JAMA 205:39–46, 1968

Harris D, Batki SL: Stimulant psychosis: symptom profile and acute clinical course. Am J Addict 9:28–37, 2000

Higgins ST, Delaney DD, Budney AJ, et al: A behavioral approach to achieving initial cocaine abstinence. Am J Psychiatry 148:1218–1224, 1991

Higgins ST, Budney AJ, Bickel WK, et al: Achieving cocaine abstinence with a behavioral approach. Am J Psychiatry 150:763–769, 1993

Higgins ST, Budney AJ, Bickel WK, et al: Incentives improve outcome in outpatient behavioral treatment of cocaine dependence. Arch Gen Psychiatry 51:568–576, 1994

Holman BL, Carvalho PA, Mendelson J, et al: Brain perfusion is abnormal in cocaine-dependent polydrug users: a study using technetium-99m-HMPAO and ASPECT. J Nucl Med 32:1206–1210, 1991

Holman BL, Mendelson J, Garada B, et al: Regional cerebral blood flow improves with treatment in chronic cocaine polydrug users. J Nucl Med 34:723–727, 1993

Iversen LL, Iversen SD, Snyder SH: Stimulants: Handbook of Psycopharmacology, Vol 11. New York, Plenum, 1978

Janowsky DS, el-Yousel MK, Davis JM, et al: Provocation of schizophrenic symptoms by intravenous administration of methylphenidate. Arch Gen Psychiatry 28:185–191, 1973

Jha A, Fourie H: Risperidone treatment of amphetamine psychosis (letter). Br J Psychiatry 174:366, 1999

Johanson CE, Fischman MW: The pharmacology of cocaine related to its abuse. Pharmacol Rev 41:3–52, 1989

Johanson C-E, Shuster CR: Cocaine, in Psychopharmacology: The Fourth Generation of Progress. Edited by Bloom FE, Kupfer DJ. New York, Raven, 1995, pp 1685–1697

Johnston LD, O'Malley PM, Bachman JG, et al: The National Survey Results on Drug Use from Monitoring the Future Study, 1975–1997. Rockville, MD, National Institute on Drug Abuse, 1998

Johnston LD, O'Malley PM, Bachman JG, et al: Monitoring the Future: National Results on Adolescent Drug Use : Overview of Key Findings (NIH Publ No 05-5726). Bethesda, MD, National Institute on Drug Abuse, 2005

Kalix P, Braenden O: Pharmacological aspects of the chewing of khat leaves. Pharmacol Rev 37:149–164, 1985

Khantzian EJ, Gawin F, Kleber HD, et al: Methylphenidate (Ritalin) treatment of cocaine dependence—a preliminary report. J Subst Abuse Treat 1:107–112, 1984

King GR, Ellinwood EH: Amphetamines and other stimulants, in Substance Abuse: A Comprehensive Textbook, 3rd Edition. Edited by Lowinson JH, Ruiz P, Millman RB, et al. Baltimore, MD, Williams & Wilkins, 1997, pp 207–233

Klawans HL, Margolin DI: Amphetamine-induced dopaminergic hypersensitivity in guinea pigs: implications in psychosis and human movement disorders. Arch Gen Psychiatry 32:725–732, 1975

Koob GF: Neural mechanisms of drug reinforcement. Ann N Y Acad Sci 654:171–191, 1992

Koob GF, LeMoal M: Drug addiction, dysregulation of reward, and allostatis. Neuropsychopharmacology 24:97–129, 2001

Kornetsky C: Hyporesponsivity of chronic schizophrenic patients to dextroamphetamine. Arch Gen Psychiatry 33:1425–1428, 1976

Kosten TR: Pharmacotherapy of cerebral ischemia in cocaine dependence. Drug Alcohol Depend 49:133–144, 1998

Kosten TR: Pathophysiology and treatment of cocaine dependence, in Neuropsychopharmacology: The Fifth Generation of Progress. Edited by Davis KL, Charney D, Coyle JT, et al. Baltimore, MD, Lippincott Williams & Wilkins, 2002, pp 1461–1473

Kosten TR, Biegel D: Therapeutic vaccines for substance dependence. Expert Rev Vaccine 1:363–371, 2002

Kosten TR, Kleber HD: Rapid death during cocaine abuse: a variant of the neuroleptic malignant syndrome? Am J Drug Alcohol Abuse 14:335–346, 1988

Kosten TR, Kleber HD, Morgan C: Treatment of cocaine abuse with buprenorphine. Biol Psychiatry 26:637–639, 1989

Kosten TR, Gawin FH, Silverman DG, et al: Intravenous cocaine challenges during desipramine maintenance. Neuropsychopharmacology 7:169–176, 1992

Kosten TR, Schottenfeld RS, Ziedonis D, et al: Buprenorphine versus methadone maintenance for opioid dependence. J Nerv Ment Dis 181:358–364, 1993

Kosten TR, Cheeves C, Palumbo J, et al: Regional cerebral blood flow during acute and chronic abstinence from combined cocaine-alcohol abuse. Drug Alcohol Depend 50:187–195, 1998

Kosten TR, George TP, Kosten TA: The potential of dopamine agonists in drug addiction. Expert Opin Investig Drugs 11:491–499, 2002a

Kosten TR, Rosen M, Bond J, et al: Human therapeutic cocaine vaccine: safety and immunogenicity. Vaccine 20:1196–1204, 2002b

Kosten T, Falcioni J, Oliveto A, et al: Depression predicts higher rates of heroin on desipramine with buprenorphine than with methadone. Am J Addict 13:191–201, 2004

Kramer JC: Introduction to amphetamine abuse. J Psychedelic Drugs 2:1, 1969

Kranzler HR, Bauer LO, Hersh D, et al: Carbamazepine treatment of cocaine dependence: a placebo-controlled trial. Drug Alcohol Depend 38:203–211, 1995

Levin FR, Lehman AF: Meta-analysis of desipramine an adjunct in the treatment of cocaine addiction. J Clin Pharmacol 11:374–378, 1991

Lima MS, Reisser AA, Soares BG, et al: Antidepressants for cocaine dependence. Cochrane Database Syst Rev 4:CD002950, 2001

Ling W, Shoptaw S, Majewska D: Baclofen as a cocaine anti-craving medication: a preliminary clinical study (letter). Neuropsychopharmacology 18:403–404, 1998

London ED, Cascella NG, Wong DF, et al: Cocaine-induced reduction of glucose utilization in human brain: a study using positron emission tomography and [fluorine 18]-fluorodeoxyglucose. Arch Gen Psychiatry 47:567–574, 1990

Lucas AR, Weiss M: Methylphenidate hallucinosis. JAMA 217:1079–1081, 1971

Maisonneuve IM, Archer S, Glick SD: U50, 488, a kappa opioid receptor agonist, attenuates cocaine-induced increases in extracellular dopamine in the nucleus accumbens of rats. Neurosci Lett 181:57–60, 1994

Malcolm R, Kajdasz DK, Herron J, et al: A double-blind, placebo-controlled outpatient trial of pergolide for cocaine dependence. Drug Alcohol Depend 60:161–168, 2000

Malison RT, Best SE, van Dyck CH, et al: Elevated striatal dopamine transporters during acute cocaine abstinence as measured by [123I] beta-CIT SPECT. Am J Psychiatry 155:832–834, 1998

Margolin A, Kosten TR, Avants SK, et al: A multicenter trial of bupropion for cocaine dependence in methadone-maintained patients. Drug Alcohol Depend 40:125–131, 1995

Martin WR, Sloan JW, Sapira JD, et al: Physiologic, subjective, and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine, and methylphenidate in man. Clin Pharmacol Ther 12:245–258, 1971

McCormick TC Jr, McNeil TW: Acute psychosis and Ritalin abuse. Tex State J Med 59:99–100, 1962

McDougle CJ, Price LH, Palumbo JM, et al: Dopaminergic responsivity during cocaine abstinence: a pilot study. Psychiatry Res 43:77–85, 1992

McDougle CJ, Black JE, Malison RT, et al: Noradrenergic dysregulation during discontinuation of cocaine use in addicts. Arch Gen Psychiatry 51:713–719, 1994

Misra L, Kofoed L: Risperidone treatment of methamphetamine psychosis (letter). Am J Psychiatry 154:1170, 1997

Montoya ID, Levin FR, Fudala PJ, et al: Double-blind comparison of carbamazepine and placebo for treatment of cocaine dependence. Drug Alcohol Depend 38:213–219, 1995

Nunes EV, Quitkin FM, Brady R, et al: Imipramine treatment of methadone maintenance patients with affective disorder and illicit drug use. Am J Psychiatry 148: 667–669, 1991

Oliveto AH, Feingold A, Schottenfeld R, et al: Desipramine in opioid-dependent cocaine abusers maintained on buprenorphine vs methadone. Arch Gen Psychiatry 56:812–820, 1999

Rawson RA, Gonzales R, Brethen P: Treatment of methamphetamine use disorders: an update. J Subst Abuse Treat 23:145–150, 2002a

Rawson RA, Huber A, Brethen P, et al: Status of methamphetamine users 2–5 years after outpatient treatment. J Addict Dis 21:107–119, 2002b

Reneman L, Lavalaye J, Schmand B, et al: Cortical serotonin transporter density and verbal memory in individuals who stopped using 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy"): preliminary findings (comment). Arch Gen Psychiatry 58:901–906, 2001

Richtand NM, Woods SC, Berger SP, et al: D3 dopamine receptor, behavioral sensitization, and psychosis. Neurosci Biobehav Rev 25:427–443, 2001

Robinson TE, Berridge KC: The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Brain Res Rev 18:247–291, 1993

Rocha BA, Fumagalli F, Gainetdinov RR, et al: Cocaine self-administration in dopamine-transporter knockout mice. Nat Neurosci 1:132–137, 1998

Rosenblum A, Fallon B, Magura S, et al: The autonomy of mood disorders among cocaine-using methadone patients. Am J Drug Alcohol Abuse 25:67–80, 1999

Rothman RB, Partilla JS, Baumann MH, et al: Neurochemical neutralization of methamphetamine with high-affinity nonselective inhibitors of biogenic amine transporters: a pharmacological strategy for treating stimulant abuse. Synapse 35:222–227, 2000

Rounsaville BJ, Anton SF, Carroll K, et al: Psychiatric diagnoses of treatment-seeking cocaine abusers. Arch Gen Psychiatry 48:43–51, 1991

Satel SL, Southwick SM, Gawin FH: Clinical features of cocaine-induced paranoia. Am J Psychiatry 148:495–498, 1991

Sato M: Psychotoxic manifestations in amphetamine abuse. Psychopharmacol Bull 22:751–756, 1986

Schmitz JM, Averill P, Stotts AL, et al: Fluoxetine treatment of cocaine-dependent patients with major depressive disorder. Drug Alcohol Depend 63:207–214, 2001

Schottenfeld RS, Pakes JR, Oliveto A, et al: Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. Arch Gen Psychiatry 54:713–720, 1997

Schuster CR: The behavioral pharmacology of psychomotor stimulant drugs, in Psychotropic Agents, Part II. Edited by Hoffmeister F, Stille G. New York, Springer-Verlag, 1981, pp 587–605

Segal DS, Mandell AJ: Long-term administration of d-amphetamine: progressive augmentation of motor activity and stereotypy. Pharmacol Biochem Behav 2:249–255, 1974

Segal DS, Kuczenski R: Behavioral alterations induced by an escalating dose-binge pattern of cocaine administration. Behav Brain Res 88:251–260, 1997

Serper MR, Chou JC, Allen MH, et al: Symptomatic overlap of cocaine intoxication and acute schizophrenia at emergency presentation. Schizophr Bull 25:387–394, 1999

Sevarino KA, Oliveto A, Kosten TR: Neurobiological adaptations to psychostimulants and opiates as a basis of treatment development. Ann N Y Acad Sci 909:51–87, 2000

Silberman EK, Reus VI, Jimerson DC, et al: Heterogeneity of amphetamine response in depressed patients. Am J Psychiatry 138:1302–1307, 1981

Sofuoglu M, Brown S, Babb DA, et al: Depressive symptoms modulate the subjective and physiological response to cocaine in humans. Drug Alcohol Depend 63:131–137, 2001

Somoza EC, Winhusen TM, Bridge TP, et al: An open-label pilot study of methylphenidate in the treatment of cocaine-dependent patients with adult attention deficit/hyperactivity disorder. J Addict Dis 23:77–92, 2004

Sora I, Wichems C, Takahashi N, et al: Cocaine reward models: conditioned place preference can be established in dopamine- and in serotonin-transporter knockout mice. Proc Natl Acad Sci U S A 95:7699–7704, 1998

Sora I, Hall FS, Andrews AM, et al: Molecular mechanisms of cocaine reward: combined dopamine and serotonin transporter knockouts eliminate cocaine place preference. Proc Natl Acad Sci U S A 98:5300–5305, 2001

Spear J, Alderton D: Psychosis associated with prescribed dexamphetamine use (letter). Aust N Z J Psychiatry 37:383, 2003

Srisurapanont M, Jarusuraisin N, Kittirattanapaiboon P: Treatment for amphetamine dependence and abuse. Cochrane Database Syst Rev 4:CD003022, 2001

Srisurapanont M, Ali R, Marsden J, et al: Psychotic symptoms in methamphetamine psychotic in-patients. Int J Neuropsychopharmacol 6:347–352, 2003

Substance Abuse and Mental Health Services Administration: Overview of Findings From the 2002 National Survey on Drug Use and Health (DHHS Publ No SMA 03–3774). Rockville, MD, Substance Abuse and Mental Health Services Administration, 2003

Swartz CM, Breen K, Leone F: Serum prolactin levels during extended cocaine abstinence. Am J Psychiatry 147:777–779, 1990

Sziraki I, Sershen H, Hashim A, et al: Receptors in the ventral tegmental area mediating nicotine-induced dopamine release in the nucleus accumbens. Neurochem Res 27:253–261, 2002

Uslaner J, Kalechstein A, Richter T, et al: Association of depressive symptoms during abstinence with the subjective high produced by cocaine. Am J Psychiatry 156: 1444–1446, 1999

Vanderschuren LJ, Kalivas PW: Alterations in dopaminergic and glutamatergic transmission in the induction and expression of behavioral sensitization: a critical review of preclinical studies. Psychopharmacology (Berl) 151:99–120, 2000

Volkow ND, Mullani N, Gould KL, et al: Cerebral blood flow in chronic cocaine users: a study with positron emission tomography. Br J Psychiatry 152:641–648, 1988

Volkow ND, Fowler JS, Wolf AP, et al: Effects of chronic cocaine abuse on postsynaptic dopamine receptors. Am J Psychiatry 147:719–724, 1990

Volkow ND, Fowler JS, Wolf AP, et al: Changes in brain glucose metabolism in cocaine dependence and withdrawal (see comments). Am J Psychiatry 148:621–626, 1991

Volkow ND, Hitzemann R, Wang GJ, et al: Long-term frontal brain metabolic changes in cocaine abusers (published erratum appears in Synapse 12:86, 1992). Synapse 11:184–190, 1992

Volkow ND, Ding YS, Fowler JS, et al: Cocaine addiction: hypothesis derived from imaging studies with PET. J Addict Dis 15:55–71, 1996a

Volkow ND, Fowler JS, Gatley SJ, et al: PET evaluation of the dopamine system of the human brain. J Nucl Med 37:1242–1256, 1996b

Volkow ND, Wang GJ, Fischman MW, et al: Relationship between subjective effects of cocaine and dopamine transporter occupancy. Nature 386:827–830, 1997

Volkow ND, Chang L, Wang GJ, et al: Low level of brain dopamine D2 receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex. Am J Psychiatry 158:2015–2021, 2001a

Volkow ND, Chang L, Wang GJ, et al: Association of dopamine transporter reduction with psychomotor impairment in methamphetamine abusers. Am J Psychiatry 158:377–382, 2001b

Weiss RD, Mirin SM, Michael JL, et al: Psychopathology in chronic cocaine abusers. Am J Drug Alcohol Abuse 12:17–29, 1986

White FJ, Kalivas PW: Neuroadaptations involved in amphetamine and cocaine addiction. Drug Alcohol Depend 51:141–153, 1998

Woods SW, O'Malley SS, Martini BL, et al: SPECT regional cerebral blood flow and neuropsychological testing in non-demented HIV-positive drug abusers: preliminary results. Prog Neuropsychopharmacol Biol Psychiatry 15:649–662, 1991

Yui K, Goto K, Ikemoto S, et al: Neurobiological basis of relapse prediction in stimulant-induced psychosis and schizophrenia: the role of sensitization. Mol Psychiatry 4:512–523, 1999

Ziedonis DM, Kosten TR: Depression as a prognostic factor for pharmacological treatment of cocaine dependence. Psychopharmacol Bull 27:337–343, 1991

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6

Hallucinogens and Phencyclidine

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The term *hallucinogens* refers to a chemically and pharmacologically heterogeneous group of substances that have in common the capacity to cause in the user a distortion of perception (i.e., hallucinations) and a mental state resembling psychosis. The term *hallucinogenic* emphasizes the perceptual effects. The term *psychotomimetic*, which is alternatively used to describe these drugs, emphasizes the similarity between their effect on affect, cognition, and perception and the symptoms of naturally occurring psychosis. The term *psychedelic* (mind-manifesting) is more vague but less restrictive and is also frequently used to describe these drugs. Aside from naturally occurring plant-derived drugs (e.g., mescaline and psilocybin), these psychotomimetic substances include semisynthetic compounds (e.g., lysergic acid diethylamide [LSD]) and synthetic compounds (e.g., 3,4-methylenedioxyamphetamine [MDA]). Frequently included in this group, but discussed elsewhere in this volume, is cannabis (see Chapter 4, "Cannabis"). For practical purposes, the hallucinogens described here can be divided into tryptamine-related compounds, phenylalkylamines, *N*-methyl-D-aspartate (NMDA) receptor antagonists, and anticholinergics (see Table 6–1).

Table 6–1. Major groups of hallucinogens

Tryptamine-related compounds
LSD (lysergic acid diethylamide)
LSD derivatives contained in plants (e.g., morning glory seeds)
Dialkyltryptamines
Psilocybin and psilocin
DMT (*N,N*-dimethyltryptamine)
DET (*N,N*-diethyltryptamine)

Phenylalkylamines
Mescaline
Synthetic amphetamine derivatives
- DOM (2,5-dimethoxy-4-methylamphetamine)
- MDA (3,4-methylenedioxyamphetamine)
- MDMA (3,4-methylenedioxymethamphetamine)

Phencyclidine (PCP) and ketamine

Anticholinergics
Herbal anticholinergics
- Deadly nightshade (*Solarium dulcamara*)
- *Atropa belladonna*
- Jimsonweed (*Datura stramonium*)

Prescription and nonprescription anticholinergics
- Antiparkinson drugs
- Trihexyphenidyl (Artane)
- Benztropine (Cogentin)
- Anticholinergics used in gastrointestinal disorders
- Over-the-counter antiasthma drugs

Note. Cannabis not included here.

Tryptamine-Related Hallucinogens (Indolealkylamines)

Tryptamine-related hallucinogens are naturally occurring plant alkaloids or their chemically synthesized derivatives. Some of them are related to sub-

stances (ergot alkaloids) produced by a rye-plant-inhabiting fungus (*Claviceps purpurea*).

Tryptamine itself is found in all major centers of the brain. Its physiologic role in central nervous system (CNS) function, however, remains unclear. 5-Hydroxytryptamine (5-HT, serotonin) is an important neurotransmitter in the CNS. The structural similarity of the tryptamine-related hallucinogens with 5-HT presumably forms the neurochemical basis for their action within the CNS.

History and Prevalence of Abuse

The hallucinogenic and psychotomimetic effects of LSD were serendipitously discovered in 1943 by A. Hofmann, a chemist with a major Swiss pharmaceutical company, who accidentally ingested a minute quantity of the substance while working on ergot derivatives. His detailed report of his hallucinatory experience prompted intense research on this class of substances. It was believed that their experimental administration to healthy volunteers could give new insights into the biochemical basis of psychosis. In the 1950s and 1960s, LSD was used by some psychiatrists in a variety of psychiatric patient populations, with the intention of accelerating the psychotherapeutic process by increasing insight and resurrecting repressed material. However, results from this "LSD-assisted psychotherapy" were not proven to be useful, and the therapeutic use of this substance was abandoned (Hollister 1986).

In the mid-1960s, with the increasing public interest in the recreational use of mind-altering drugs, LSD found its way into American and European university campuses and countercultures. LSD was outlawed in the United States in 1968. Its abuse, however, increased during the 1970s and started to decline by 1980. LSD abuse is now of a low-dose recreational type, the level of which has been relatively stable since 1985 (Robinson et al. 1987). The Monitoring the Future survey found the rate of LSD use among high school students in 2002 to be the lowest since the survey began in 1975 (Johnston et al. 2003). Increased knowledge among users about dealing with "bad trips" (see the later section on acute and chronic effects of tryptamine-related hallucinogens) has had an effect on the incidence of LSD-induced acute hallucinogenic crisis seen in emergency departments. However, other drugs (e.g., phencyclidine [PCP] and MDA), deceptively sold as LSD, as well as adulterants

Table 6–2. Street names of hallucinogens

Hallucinogen	Street name
LSD (lysergic acid diethylamide)	Acid, blotter, blue devils, California sunshine, haze, microdot(s), mickeys, Mr. Natural, paper acid, purple haze, sunshine, wedges, window pane(s)
Morning glory seeds	Flying saucers, licorice drops, heavenly gates, pearly gates
Psilocybin	Magic mushrooms, mushroom
DMT (*N*,*N*-dimethyltryptamine), DET (*N*,*N*-diethyltryptamine)	Businessman's lunch, snuff
Peyote/mescaline	Button(s), cactus, mesc, mescal, mescal buttons, moon, peyote
DOM (2,5-dimethoxy-4-methylamphetamine)	Golden eagle, STP, psychodrine, tile
MDA (3,4-methylenedioxyamphetamine)	Love drug
MDMA (3,4-methylenedioxymethamphetamine	Adam, ecstasy, MDM, XTC
MDEA (3,4-methylenedioxyethylamphetamine)	Eve

in street preparations of LSD (e.g., strychnine), continue to cause acute problems. The fact that LSD can be manufactured easily without profound knowledge of chemistry has helped make it a popular and profitable drug of abuse. Most of the street names (Table 6–2) for LSD allude to the various forms in which the drug is offered to the consumer: as tablets (microdot), as capsules (blue devils or Mr. Natural), in gelatinous form (window pane), soaked on paper (blotter), or in Mickey Mouse decals (mickeys) (Giannini et al. 1986). Besides its oral use, LSD is also occasionally mixed with tobacco and smoked or injected intravenously or subcutaneously.

Morning glory seeds have been used in some cultures for religious ceremonies (Lewin et al. 1986). The small, black, round-shaped seeds of the flower *Ipomoea purpurea* and related varieties can be purchased from seed companies. Seeds sold commercially are sometimes sprayed with the herbicide paraquat to discourage inappropriate usage. However, dipping the seeds in ether effectively dissolves the herbicide (Giannini et al. 1986). Ingestion of the seeds pro-

duces a hallucinatory state that is due to the LSD-related compounds lysergol, *d*-lysergic acid amide, and *d*-isolysergic acid amide. Street names refer to the appearance of the seeds or to the commercial names by which the seeds are marketed by seed companies (Table 6–2).

Psilocybin and psilocin were isolated and identified from the hallucinogenic mushroom *Psilocybe mexicana* in 1958 by Hoffman (Nichols 1986). "Magic" or "sacred" mushrooms have been used by American Indians for religious purposes since pre-Columbian times. Many of the psilocybin-containing mushrooms are found in different parts of the United States. Most of them belong to the genus *Psilocybe*, which includes about 100 species; not all species of *Psilocybe* contain psilocybin (Lincoff and Mitchel 1977). The outstanding feature of the psychotropic *Psilocybe* species is the color change to blue or blue-green on the cap or stalk from handling or age. *Psilocybe caerulipes* (blue foot) grows on debris under trees or rotting logs; *Psilocybe cubensis* can be found on rich pastures where it grows on dung (Lincoff and Mitchel 1977).

Psilocybin intoxication is seen either as a result of accidental poisoning from ingestion of mushrooms falsely regarded as edible or as a result of intentional ingestion by individuals seeking a hallucinogenic "high." Although U.S. law prohibits shipping of hallucinogenic mushrooms across state lines, the purchase of *Psilocybe cubensis* spores as mail-order kits for domestic cultivation became part of the drug culture (Kulberg 1986; Kulberg et al. 1986). Sporadic cases of intravenous use of hallucinogenic mushrooms have been reported in the United States (Curry and Rose 1985) and in Australia (Sivyer and Dorington 1984).

DMT (*N*,*N*-dimethyltryptamine) and DET (*N*,*N*-diethyltryptamine) are constituents of snuff (cohoba) prepared from the seeds and pods of *Piptademia peregrina*, a plant native to the West Indies and to Central and South America. Similar snuffs from other South American plants (Epena and Yopo snuffs) have been found to contain DMT, 5-methoxy-DMT, and bufotenine (5-hydroxy-DMT), a hallucinogenic substance originally isolated from the secretion of the skin glands of the poisonous toad *Bufo vulgaris*. DMT- and DET-containing *Piptademia* preparations can be smoked, and the synthetic form of DMT is sometimes used by means of intravenous or intramuscular injection. DMT is known as snuff or "businessman's lunch," the latter name referring to the high incidence of abuse in this particular population and the short duration of action (about 30 minutes).

Pharmacology

Pharmacokinetics

All drugs of this class are well absorbed from the gastrointestinal tract. LSD is the most potent hallucinogen known, with oral doses as low as 20–25 μg being sufficient for a marked sympathomimetic effect (Strassman 1984). Twice that amount ingested by a 180-pound man can produce a hallucinatory state lasting up to 12 hours. Illicit LSD usually contains 40–60 μg per dose, somewhat lower than the 100–250 μg doses typically available in the 1960s and 1970s (Nichols 2004). All of the structural modifications made to the LSD molecule have yielded less potent compounds. Also, plant preparations containing LSD-like substances cause psychotomimetic symptoms at relatively low dosages; for example, five morning glory seeds may be sufficient for a high lasting 12 hours or longer (Giannini et al. 1986). LSD is longer acting (8–12 hours) and more potent than psilocybin and psilocin, which have an average duration of action of 4–12 hours. One or two mushrooms of the *Psilocybe* family (equivalent to about 20–70 mg of active substance) can produce a hallucinosis lasting 4–12 hours. When inhaled, smoked, or used parenterally, DMT and DET show a short duration of action, limiting the psychotomimetic experience to not more than 30 minutes.

The impairment of cognitive functioning in healthy volunteers receiving LSD intravenously has been shown to correlate positively with the plasma concentration of the drug. Tryptamine-related compounds are mainly cleared by the liver; LSD concentrations in the urine are extremely low. Furthermore, because the complete, intact structure of the LSD molecule is crucial for its biological activity, there are no active metabolites excreted in the feces (Strassman 1984). Psilocybin is hydrolyzed in vivo to generate psilocin, which represents the active hallucinogen (Nichols 1986). DMT and DET undergo extensive first-pass oxidation, which makes these drugs ineffective after oral ingestion (Nichols 1986).

Mechanism of Action

Although the exact mechanisms of action of LSD and tryptamine-related compounds are incompletely understood (Freedman 1987), there is convincing evidence relating the psychotomimetic effects of these substances to serotonergic transmission in the brain (Davis 1987; Freedman 1987; McCall 1986; Nichols 2004). An antagonism of 5-HT in the rat brain is sufficient to cause a fourfold decrease in the threshold dose of LSD (Appel and Freedman 1964).

Receptor binding studies have shown that ^{3}H-LSD labels 5-HT$_2$ receptors in neuronal tissue (Peroutka 1987). LSD has also been shown to bind with high affinity to a subtype of the 5-HT$_1$ receptor (5-HT$_{1C}$), a site that also displays a high affinity for 5-HT (Glennon et al. 1986; Peroutka 1987).

Hallucinogens have agonist actions at the 5-HT$_{2A}$ receptor. Studies in rodents indicated that hallucinogens have approximate equal potency at the 5-HT$_{2A}$ and 5-HT$_{2C}$ receptor subtypes, but the psychoactive and behavioral effects of hallucinogens are blocked by 5-HT$_{2A}$ antagonists and not by 5-HT$_{2C}$ antagonists (Nichols 2004). Tachyphylaxis is associated with down-regulation of the 5-HT$_{2A}$ receptor (Buckholtz et al. 1990). These findings suggest that the 5-HT$_{2A}$ receptor is of primary functional importance in the behavioral effects of hallucinogens. On the other hand, the behavioral potency of LSD does not correlate well with its activity at the 5HT$_{2A}$ receptor, where it is a partial agonist (Kurrasch-Orbaugh et al. 2003). The functional significance of the receptor subtypes is further complicated by the fact that there is no known hallucinogen that is selective for the 5-HT$_{2A}$ receptor over the 5-HT$_{2C}$ receptor. It is possible that agonist effects at both receptors are necessary for hallucinogenic activity (Burris et al. 1991).

Agonist effects at the 5-HT$_{2A}$ receptor enhance glutamatergic (Arvanov et al. 1999) and dopaminergic neurotransmission (Yan 2000) and activate inhibitory γ-aminobutyric acid (GABA) interneurons. Other receptors may also be involved (Appel et al. 2004). LSD binds to both D$_1$ and D$_2$ dopamine receptors, and Nichols (2004) has suggested that D$_2$ stimulation may potentiate agonist effects at the 5-HT$_{2A}$ receptor. The tryptamines, but not the phenylalkylamines, have high activity at the 5-HT$_{1A}$ receptor, which reduces firing of cells in the dorsal raphe nucleus, probably through an effect on GABA interneurons (Nichols 2004). Activation of 5-HT$_{1A}$ receptors produces functional antagonism of 5-HT$_{2A}$ receptors (Schreiber et al. 1995). Pindolol, a 5-HT$_{1A}$ receptor antagonist, potentiates the effects of DMT (Strassman 1996), presumably by permitting unopposed stimulation of 5-HT$_{2A}$ receptors.

The action of 5-HT on brain neuronal systems is complex; depending on the neurons involved, it can induce inhibition or excitation. Experiments with iontophoretic application of LSD to neurons have shown that 5-HT-induced excitation is invariably blocked by LSD, whereas LSD mimics inhibition at sites where 5-HT exerts an inhibiting effect (Aghajanian et al. 1987; Martin and Sloane 1986). Tryptamine itself is found in all major regions of

the brain and produces pharmacologic effects that are similar to those seen with LSD, psilocybin, DMT, and the hallucinogens of the phenylalkylamine group (mescaline and 2,5,-dimethoxy-4-methylamphetamine [DOM]) (Martin and Sloane 1986). Inhibitory serotonergic input to the raphe nuclei, the cortex, and the limbic system is regarded as essential for the filtering of extracerebral (perception) and intracerebral (feeling and cognition) stimuli (Strassman 1984). It has been hypothesized that an inhibition of these serotonergic functions, which normally process physical and mental events as they arise, may lead to the experience of common stimuli as novel or "psychedelic." The dense innervation of the limbic and visual systems by 5-HT axons could make them a major target for this hallucinogenic disinhibition, leading to the major clinical effects of these drugs: alterations in affect and visual hallucinations. LSD and other tryptamine-related compounds (psilocin and DMT) have been shown to produce a complete but reversible inhibition of the 5-HT-mediated neuronal discharges in the raphe nucleus (McCall 1986). The relationship of this phenomenon to the hallucinogenic action of these compounds is underscored by the finding that brom-LSD, a nonhallucinogenic analog of LSD, does not influence 5-HT neuronal discharge.

However, simple disinhibition of 5-HT neurons originating in the raphe cannot fully explain the pharmacological effects of LSD. First, lisuride, which is devoid of hallucinogenic properties, is 5–10 times more potent than LSD in blocking neuronal firing in the raphe. Second, the psychotomimetic effect of LSD lasts considerably longer than its inhibitory effect on raphe neuron firing. Third, although tolerance develops to the behavioral effects of LSD, no such tolerance can be seen for its neurophysiologic action. It has been proposed that 5-HT receptor sensitization may account for the psychedelic action of the hallucinogens (McCall 1986). This mechanism of action is similar to the 5-HT_2 agonist effect of the phenylalkylamines (Davis 1987; Hollister 1986), which may actually be the neurochemical substrate of hallucinogenic action in general (Lyon et al. 1988).

Acute and Chronic Effects

Clinical Symptoms of LSD Intoxication

Because the minimal lethal or toxic dose of LSD is not well established, assessment of severity of intoxication should always be made on clinical grounds. The

DSM-IV-TR (American Psychiatric Association 2000) criteria for hallucinogen intoxication are presented in Table 6–3. The normally used quantity of LSD ingested ranges from 30 to 400 μg, but doses as low as 20 μg may cause clinically detectable symptoms (Strassman 1984). However, tolerance to the effect of LSD develops relatively quickly, so that chronic users increase their dose over time.

Because of the rapid absorption of LSD from the gastrointestinal tract, symptoms start to occur within 30 minutes. Drug effects are at a maximum at 1–4 hours after ingestion of the drug, with the symptoms subsiding during the following 8–16 hours. The predominant effects with small doses are autonomic nervous system changes and alterations of mood; higher doses cause the typical perceptional distortions and changes in body image. Vegetative symptoms are mostly sympathomimetic (tachycardia, increased blood pressure, mydriasis, and hyperthermia). However, a central parasympathomimetic component (diaphoresis, vomiting, and diarrhea) may complicate the clinical picture. Observation of extreme agitation and marked muscular rigidity, causing lactic acidosis in combination with hyperthermia, should raise suspicion of adulteration of the ingested LSD by strychnine (Kulberg 1986).

The subjective experience under LSD is dependent on the personality of the user, his or her expectations, and the setting in which the drug is taken. Although some subjects experience a state of excitement and activity, others become quiet and passive and withdraw from their surroundings. Changes of mood range from anxiety to ecstasy. Feelings of euphoria with symptoms of excitation are the most consistently occurring mood changes during an LSD high. Episodes of depression and panic ("bad trip") may follow, or alternate with, the elevated state of affect (Strassman 1984).

The effect of LSD on perception is sometimes referred to as "illusiogenic," because, rather than creating a perception of a nonexisting stimulus, LSD produces a distortion of sensory input from the environment (Kulberg 1986). Visual symptoms are most frequently experienced; for example, vision may be blurred, and the perception of distance and depth may be changed. Objects in the surroundings may be perceived as unusually intense in color, shape, and/or size. With the eyes closed, geometric and kaleidoscopic patterns are perceived. Synesthesia, by which a sensory stimulus of one modality is transformed into a perception from another sense, is a type of a perceptual distortion typically experienced under the influence of LSD; for example, smells

Table 6–3. DSM-IV-TR diagnostic criteria for hallucinogen intoxication

A. Recent use of a hallucinogen.

B. Clinically significant maladaptive behavioral or psychological changes (e.g., marked anxiety or depression, ideas of reference, fear of losing one's mind, paranoid ideation, impaired judgment, or impaired social or occupational functioning) that developed during, or shortly after, hallucinogen use.

C. Perceptual changes occurring in a state of full wakefulness and alertness (e.g., subjective intensification of perceptions, depersonalization, derealization, illusions, hallucinations, synesthesias) that developed during, or shortly after, hallucinogen use.

D. Two (or more) of the following signs, developing during, or shortly after, hallucinogen use:
   (1) pupillary dilation
   (2) tachycardia
   (3) sweating
   (4) palpitations
   (5) blurring of vision
   (6) tremors
   (7) incoordination

E. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

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and tactile stimuli seem to be visible, and colors become audible (Kulberg 1986). "Out-of-body" experiences, loss of ego boundaries causing the perception of being one with objects or others, and depersonalization are typical LSD-induced distortions of body image. Delusions of supernatural capabilities (e.g., the ability to fly) may lead to injury or death; suicidal impulses may also emerge during or after the acute state of intoxication. Tactile, gustatory, and olfactory hallucinations are frequently reported; auditory hallucinations are only rarely experienced. Insight into the drug-induced nature of these experiences is usually retained. Following the euphoric state characterized by intense and vivid perceptions, reality is frequently experienced as dull and uninteresting after the acute toxic symptoms have subsided.

"Bad trip" describes a state of frightening illusions and panic that may be experienced instead of heightened emotions and enjoyable hallucinations. This experience is frequently accompanied by the fear of insanity (Frosch et al. 1965; Kulberg 1986). Flashbacks in LSD users are reported to occur with an incidence of 15%–77% (Kulberg 1986). The term *flashback* has been replaced by the DSM-IV-TR diagnosis of hallucinogen persisting perception disorder (American Psychiatric Association 2000). The criteria for DSM-IV-TR hallucinogen persisting perception disorder (flashbacks) are presented in Table 6–4.

The spontaneous recurrences of symptoms may range from mild confusion to repeated intrusions into awareness of images from a previous LSD state. Flashbacks are most frequent during the first months after drug use and may be precipitated by periods of stress and anxiety. If the drug is not taken again, the frequency of flashbacks gradually decreases with time (Kulberg 1986).

Prolonged adverse reactions after the use of LSD (such as psychosis, paranoid states, or depression) have been reported (Cohen and Ditman 1962; Frosch et al. 1965; Hatrick and Dewhurst 1970; Strassman 1984). However, many of the reported cases have occurred in chronic schizophrenic patients and in subjects with personality disorders. It is not known whether healthy subjects are at risk for psychosis as a late adverse reaction after the use of LSD. Neuropsychological effects of prolonged use have been difficult to study but appear to be "modest," if present at all (Halpern and Pope 1999). Heavy users of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") on the other hand, show impaired performance on tests of mental processing and impulsivity (Halpern et al. 2004), although these findings have been challenged (Lyvers and Hasking 2004).

High doses of LSD may cause chromosome damage in experimental animals (Dishotsky et al. 1971). Chromosomal aberrations in humans have been related to drug abuse in general. Pharmacologically pure LSD, however, has not been demonstrated to cause a detectable increase in chromosome damage (Li and Lin 1998).

Treatment of LSD Intoxication

Patients with LSD-induced disorders come to the attention of medical care providers because of an acute overdose, because of a panic reaction during

Table 6–4. DSM-IV-TR diagnostic criteria for hallucinogen persisting perception disorder

A.	The reexperiencing, following cessation of use of a hallucinogen, of one or more of the perceptual symptoms that were experienced while intoxicated with the hallucinogen (e.g., geometric hallucinations, false perceptions of movement in the peripheral visual fields, flashes of color, intensified colors, trails of images of moving objects, positive afterimages, halos around objects, macropsia, and micropsia).
B.	The symptoms in Criterion A cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C.	The symptoms are not due to a general medical condition (e.g., anatomical lesions and infections of the brain, visual epilepsies) and are not better accounted for by another mental disorder (e.g., delirium, dementia, Schizophrenia) or hypnopompic hallucinations.

Source. Reprinted from American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders,* 4th Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000. Used with permission.

acute intoxication (bad trip), or because of episodes of flashbacks (Kulberg 1986; Slaby et al. 1981; Strassman 1984). LSD concentrations in body fluids are extremely low because of its high potency and its extensive metabolism, which poses a difficult analytical problem. Radioimmunoassay, high-pressure liquid chromatography, and gas chromatograph-mass spectrometry methods have been developed to detect LSD, but routine drug screens are not sensitive enough to accomplish detection. A drug screen can, however, help to rule out other intoxications.

If the patient has ingested a substantial amount (>200 μg/kg) of the drug fairly recently (within 30 minutes) and is not obtunded, comatose, or convulsing, gastric lavage is most efficient in removing unabsorbed drug from the stomach. If this approach is not possible, emesis may be induced with ipecac syrup (15 mL for children ages 1–12 years; 30 mL for older children and adults). If emesis does not occur after the first dose, ipecac may be repeated once after 30 minutes. In most patients seen in the emergency department for symptoms of LSD intoxication, nearly complete absorption of the drug is most likely to have already occurred.

Convulsions are treated with slow intravenous administration of diazepam (0.1–0.3 mg/kg for children; 10 mg for adults); this treatment may be

repeated if necessary. Acute anxiety can be managed with oral diazepam (5–20 mg for adults) or equivalent doses of other benzodiazepines such as lorazepam. In the treatment of hallucinosis or acute delusions, neuroleptics should be used with great caution because they may induce or worsen hypotension and may cause convulsions by lowering the seizure threshold. Reassuring the patient that the alterations in his or her perception are due to the ingested drug ("talking down") is helpful in cases of acute anxiety. Placing the patient in a dimly lighted, quiet room and giving cues for orientation to place and time will assist in calming the patient. If hospitalization does not seem necessary, an outpatient clinic appointment should be made. Steps should be taken to ensure that a reliable person looks after the patient until symptoms have subsided completely.

Patients seen for flashbacks are treated with oral diazepam (15–30 mg/day for adults) if symptoms of anxiety are severe (Rumack 1987). Neuroleptics, especially haloperidol, have been implicated in a transient increase in visual flashbacks and are not recommended (Moskowitz 1971; Strassman 1984). Risperidone and selective serotonin reuptake inhibitors may also worsen symptoms of hallucinogen persisting perception disorder (Halpern and Pope 2003). The patient needs assurance of the self-limiting nature of the phenomenon and its decreasing frequency of reoccurrence with time. The patient should be reminded that any future use of hallucinogens or marijuana may precipitate similar symptoms (Strassman 1984).

Symptoms and Treatment of Intoxication With Other Tryptamine-Related Compounds

Clinical symptoms after ingestion of other tryptamine-related compounds, such as morning glory seeds, psilocybin, DMT, and DET, are quite similar to those of LSD toxicity, including restlessness, nausea, and autonomic hyperactivity. Intoxication from mushrooms of the *Psilocybe* variety causes ataxia, hyperkinesis, anticholinergic effects, and chromatopsia (in which colorless objects are perceived to be in color) (Halpern 2003; Giannini et al. 1986). *Psilocybe cubensis* usually contains 10–12 mg of psilocybin per gram of dried mushroom, and 1–2 grams of mushroom are typically ingested (Halpern 2004). Clinical symptoms start 15–30 minutes after ingestion of the poisonous mushrooms. Intoxication with psilocybin or morning glory seeds is rarely fatal. DET and DMT may cause LSD-like clinical symptoms that are, however, much shorter lasting.

Therapeutic measures for the treatment of intoxication from psilocybin or morning glory seeds are the same as described earlier for LSD—that is, gastric lavage or induction of emesis with ipecac, treatment of anxiety with diazepam, and reassurance and psychological support (Rumack 1987). Acute treatment of DET or DMT intoxication in an emergency department setting is rarely necessary. Antipsychotics should be used with great caution, because the patient may have been exposed to PCP or DOM, which are frequently found as adulterants of street drugs. If these drugs are responsible for the clinical condition of the patient, antipsychotics may make symptoms worse.

Phenylalkylamine Hallucinogens

The phenylalkylamine hallucinogens show a close structural resemblance to the catecholamines, noradrenaline and dopamine. The prototype structure is found in mescaline, a naturally occurring substance. Modification of the mescaline molecule has led to synthetic amphetamine derivatives with hallucinogenic action.

History and Prevalence of Abuse of Mescaline (Peyote)

Mescaline (3, 4, 5-trimethoxyphenylethylamine) is the hallucinogenic substance found in the peyote cactus (*Lophophora williamsii*), which is characterized by red or pink flowers and soft spikes. One dried flower top of the cactus (mescal button) contains 6–45 mg of the active substance (Kulberg 1986), which represents up to 6% of its mass. Mescaline was isolated from peyote in 1896 and was synthesized in 1918. For centuries, peyote has played an important role in the religious ceremonies of the Indians of northern Mexico and the southwestern United States. A "peyote cult" was established in the United States in the late nineteenth century, leading to the foundation of the Native American Church in 1918. In this congregation, the use of peyote as a religious sacrament during church services is legal under U.S. law.

Peyote is ingested fresh (as whole dried buttons) or as powder (loose in capsules or pressed into tablets). Mescaline sold on the street (see Table 6–2) is generally not what it is claimed to be but is most likely one of the following: DOM, PCP, LSD, caffeine, or amphetamine-related stimulants (Kulberg

1986). Only when the cactus buttons are found with the patient can there be certainty that the drug in question is peyote (mescaline) (Giannini et. al. 1986).

Pharmacology of Mescaline

Mechanism of Action

The behavioral effects of mescaline apparently result from an agonist action at 5-HT_2 receptors (Aghajanian and Haigler 1975). This hypothesis is supported by the findings that 5-HT_2 receptor antagonists are able to block selectively the increased reactivity of locus coeruleus neurons produced by these substances and that the potency of various phenylethylamine hallucinogens in producing this effect correlates well with their order of potency in binding to the 5-HT_2 receptor (Aghajanian et al. 1987). In fact, because the agonist action at the 5-HT_2 receptor is the one characteristic that the hallucinogenic indolealkylamines and phenylethylamines have in common, it has been proposed that this could be the ultimate neurochemical substrate for their behavioral and psychological effects (Aghajanian and Haigler 1975).

The mode of action of the amphetamine derivatives MDA and MDMA seems to be dissimilar, with MDMA possessing mescaline-like psychoactive properties. MDMA demonstrates greater serotonergic effects than does the more amphetamine-like MDA.

Pharmacokinetics

Mescaline is considerably less potent than LSD; equipotent amounts are 5 mg and 1 μg, respectively. Peyote is readily absorbed from the gastrointestinal tract. Mescaline is mainly concentrated in the liver, spleen, and kidney. Up to 60% is excreted unchanged in the urine; mescaline metabolites are devoid of any psychoactive effect.

Clinical symptoms of mescaline intoxication are similar to those seen in LSD intoxication. Nausea and vomiting occur 30 minutes to 2 hours after ingestion. Other symptoms are mydriasis, diaphoresis, hypertension, dizziness, and chills (Mack 1986). The hallucinogenic effects peak at 5–6 hours after ingestion of the drug (Kulberg 1986). Vivid colors, kaleidoscopic visions, and synesthesias similar to those experienced with LSD have been reported. The user may hallucinate that he or she is followed by marching geometric shapes;

this symptom may be pathognomonic for mescaline intoxication. After about 14 hours, when the effects of the drug have vanished, excellent recall of the experience is maintained. Because this phenomenon is different from the state after PCP intoxication, it can have some practical significance for the differential diagnosis; on the street, PCP is frequently sold as mescaline (Giannini et al. 1986).

The lethal dose of mescaline varies because of the development of tolerance to the action of the drug. After a massive overdose, hypotension, bradycardia, CNS depression, and respiratory failure may be life threatening. Fatal intoxications from mescaline are rare, and fatalities associated with mescaline use are usually attributed to traumas resulting from altered perceptions.

Treatment of Mescaline Intoxication

The active drug and metabolites can be detected from the urine by thin-layer chromatography, gas-liquid chromatography, or gas chromatography–mass spectrometry. However, assays are available only at specialized centers. Treatment of acute intoxication with mescaline is virtually identical to the treatment outlined for LSD intoxication. DOM-induced vasospasm responds well to intra-arterial tolazoline or sodium nitroprusside. Major life-threatening complications of hallucinogenic amphetamine derivatives include hyperthermia, hypertension, convulsions, cardiovascular collapse, and self-inflicted trauma.

History, Prevalence of Abuse, and Pharmacology of Hallucinogenic Phenylalkylamine Derivatives

The substituted phenethylamines, consisting of approximately 50 substances, form the largest chemical group of hallucinogenic substances known. The almost unlimited possibility of modification of the amphetamine molecule has encouraged the development of "designer drugs." These are clandestinely produced substances, some of which may still be uncontrolled by national or international law, despite their being chemically and pharmacologically similar to strictly controlled substances. Thus, the drug scene tends to remain one step ahead of the law (Ghodse 2002). Hallucinogenic amphetamine analogs have a chemical substitution on the benzene ring of the molecule, which is also typical for mescaline. Several of these "ring-substituted amphetamines" were synthesized in the 1960s and represent the oldest group of designer drugs. Later they became part of the so-called club drugs (a term that refers to a wide

variety of substances, including LSD, ketamine, γ-hydroxybutyrate [GHB], and others), which are used at dancing and partying venues (see Chapter 7, "Club Drugs"). However, in the past few years, these drugs have been found increasingly in more mainstream settings (National Institute on Drug Abuse 2004a).

Methamphetamine is sold on the street under a variety of slang or street names (e.g., speed, ice, chalk, crystal, crank, fire, glass). Several of these names seem to refer to the tiny white crystals of which it consists. The drug can be consumed in many different ways (e.g., by mouth, intravenously, snorted, or smoked with tobacco). A particularly intense and long-lasting euphoria is seen when the vaporized substance is inhaled. For this purpose methamphetamine is heated in a glass tube. Like amphetamine, methamphetamine is highly water soluble in its pure salt form, and it can easily be injected in large quantities, also leading to an intense feeling of well-being. When used in "runs" by injecting it several times per day over a period of several days, methamphetamine leads to increased agitation, pseudohallucinations (visual images identified as unreal by the user), hallucinations, and exhaustion (Brands et al. 2001).

The half-life of methamphetamine is about 11 hours, although half-life is dependent on the pH of the urine, with acidification leading to increased elimination. Methamphetamine is metabolized in the liver, but about 30% is excreted unchanged. It is a potent stimulant with less peripheral effects than amphetamine. Abusers typically show agitation, excited speech, decreased appetite, and increased physical activity (National Institute on Drug Abuse 2004a). Reports of its violence-inducing properties have caused concern, and its psychotomimetic properties (hallucinations, paranoia, mania, impaired judgment) can be very frightening to the user and to people in the user's surroundings. Withdrawal reactions may also be very severe. According to data from the National Institute on Drug Abuse (NIDA) 2003 Monitoring the Future survey, use of methamphetamine among U.S. high-school students remains at a high level and is of concern (National Institute on Drug Abuse 2004a).

3,4-Methylenedioxymethamphetamine (MDMA), known by the street names ecstasy, XTC, X, Adam, clarity, and lover's speed, was synthesized in 1914 as an appetite suppressant but was never marketed. In the early 1970s, it appeared on the U.S. drug scene under various street names. More recently, the name "ecstasy" has become synonymous for MDMA, even in the scien-

tific literature. Until the mid-1980s, MDMA was used by some psychiatrists as an adjunct to psychotherapy, because it was believed to reduce feelings of hatred and increase emotional harmony (Verebey et al. 1988). During that period, the substance was also popular among American college students, but dangerous health effects led to an emergency Schedule I controlled substance classification in 1985. Later, it began to play a major role as part of the "rave" culture, because it helped users dance for a prolonged period of time (see the section on MDMA (ecstasy) in Chapter 7, "Club Drugs"). MDMA sold on the street may in reality be MDA or 3,4-methylenedioxyethylamphetamine (MDEA) or some other designer drug of the amphetamine type. According to NIDA's 2003 Monitoring the Future study, use of MDMA among junior and senior high school students has decreased since 2001 (National Institute on Drug Abuse 2004a).

MDMA is taken orally in the form of tablets or capsules. Typical doses range between 75 and 200 mg, depending on the tolerance of the individual. An experienced user, who has developed some tolerance to the drug, would take a starting dose at the upper end of the range and a smaller dose some hours later to maintain the desired euphoria. MDMA is also used in combination with other drugs (e.g., alcohol, opiates, benzodiazepines) in order to enhance the effect or reduce withdrawal symptoms. MDMA has been shown to deplete central 5-HT transmission and destroy serotonergic neurons (Ricaurte et al. 2000). Individuals, aware of this effect, may take "smart-drug" drinks containing 5-HT precursors in an attempt to prevent CNS damage (Wills 1997). The average elimination half-life of MDMA is 7.6 hours (Baselt and Cravey 1989). About 60% of the drug is eliminated in the urine unchanged (Alrazy and Verebey 1988), and a small fraction is eliminated as the psychoactive metabolite MDA (see the discussion of MDA later in this section).

The effective dose of MDMA ranges from 50 to 150 mg. The drug is well absorbed after ingestion, and its peak effect is experienced after about 1–5 hours. MDMA users frequently describe three phases of MDMA's action. First, there is disorientation. This is followed by a "rush," during which tingling and jerking movements in the extremities are experienced. The paresthesias and myoclonus subside within 1–4 hours and are followed by a short period (30–60 minutes) of happy sociability (Dowling et al. 1987). MDMA-positive subjects participating in a study of the effect of this substance on driving showed muscle twitching, body tremors, dilated pupils, slow papillary re-

action to light, elevated pulse and blood pressure, profuse perspiration, and lack of balance and coordination (Logan and Cooper 2001). Other effects reported by MDMA users include a reduction in defensive and aggressive impulses, a feeling of tranquil euphoria, and an enhanced interest in interacting with others. As with LSD, the effects of MDMA often depend on the mindset of the person using it. Anxiety, paranoia, psychosis, and hallucinations have been reported after its use (Winstock 1991).

After the acute effects of MDMA have worn off, lethargy and depression are seen, and late flashback-type experiences have been reported (Creighton et al. 1991). During rave culture-related dancing events, the stimulant properties of the drug may lead individuals to dance for prolonged periods of time. Especially in a hot and crowded place, this activity may lead to exhaustion, dehydration, electrolyte disturbances, and hyperpyrexia, which may trigger convulsions (Screaton et al. 1992). Rhabdomyolysis may lead to disseminated intravascular coagulation (DIC). Death related to hyperpyrexia has been reported, especially in the United Kingdom (Randall 1992). Impaired thermoregulation may be the result of a neurotoxic effect on 5-HT transmission in the hypothalamus. Treatment includes rapid cooling (Bordo and Dorfman 2004) and the use of dantrolene (Rusyniak et al. 2004). In the United Kingdom, practical advice has been given to participants of "rave" venues to avoid dancing for long periods of time, to rest in a cool place, wear loose clothes, and consume plenty of fluids (Wills 1997). Fluids with electrolyte replacement are preferred, because intake of large volumes of hypotonic fluid may cause hyponatremia (Holden and Jackson 1996). MDMA has also been suspected of causing a syndrome of inappropriate antidiuretic hormone secretion (SIADH) (Satchell and Connaughton 1994). In addition to being exposed to the health risks related to ecstasy use in crowded, hot venues, users of the drug may also experience cardiac arrhythmias and cardiomyopathy. There are also reports of jaundice and liver damage after the use of ecstasy (Gorard et al. 1992; Shearman et al. 1992). Heavy use of MDMA has been associated with a decline in nonverbal (visual) memory (Back-Madruga et al. 2003), which may indicate damage to hippocampal neurons (National Institute on Drug Abuse 2004b). No specific treatments for MDMA abuse are available. Cognitive-behavioral interventions are used in a manner similar to that for the treatment of other addictions, and long-term recovery may be supported through participation in recovery support groups.

MDA is the *N*-methylated derivative of MDMA. It is a potent stimulant that was originally investigated by the U.S. Army as an incapacitating agent. In the 1960s, it became a popular drug of abuse. Its reputation as a safe recreational drug ("love drug") that provides the user with a tranquil psychedelic experience has been contradicted by reports of several cases of fatal intoxication. With increased availability of MDMA, the popularity of MDA has decreased in the United States and Canada (Brands et al. 2001). At low doses, MDA is reported to induce peaceful relaxation without significant hallucinations; at moderately high doses its effect is LSD-like, and at high doses it can cause extreme, sometimes fatal, excitation. High doses may also lead to delirium, seizures, coma, respiratory distress, hyperpyrexia, rhabdomyolysis, and DIC (Brands et al. 2001).

MDEA has effects similar to those of MDMA. MDEA appeared on the market following restrictions placed on MDMA.

Paramethoxyamphetamine (PMA) has a hallucinogenic potency about five times that of mescaline and three times that of MDA. Because of its high toxicity, it caused fatal intoxications shortly after it became available on the street in the early 1970s (Cimbura 1974). Some of the fatalities were apparently due to the fact that the substance was sold to users as MDA; because of the higher potency of PMA, severe intoxication (i.e., hypertensive crisis, seizures, death) occurred.

3,4,5-Trimethoxyamphetamine (TMA) causes perceptual distortions, LSD-like synesthesias, and dissociative states. At high doses, it may produce unprovoked anger, aggressive behavior, and "homicidal violence" (Shulgin 1978).

DOM is the active compound in the street drug STP. The origin of the abbreviation STP remains obscure. DOM appeared on the North American drug scene in the late 1960s (Snyder et al. 1967), but then its use waned. Effective doses of DOM range from 1 to 5 mg. At low doses DOM produces mild euphoria and CNS stimulation. Higher doses of the drug cause an LSD- or mescaline-like effect, which may last up to 24 hours. Its potency has been estimated to be eight times that of mescaline (McKim 1996). Acute adverse reactions ("bad trips") seem to be more common with DOM than with most other hallucinogens, and this phenomenon may explain why DOM has remained less popular than other, related substances. Because of its strong peripheral serotonin agonist effects, DOM may cause severe vasospasm (Bowen et al. 1983).

Death after the use of MDMA or MDEA is rare but may occur because of induction of cardiac arrhythmias or as a consequence of risk-taking behavior. Following its acute effects, MDMA may produce symptoms such as anxiety, depression, and confusion, which, in some cases, continue for several weeks (Dowling et al. 1987).

Phencyclidine and Ketamine

History and Prevalence of Abuse

Phencyclidine (1-[1-phenylcyclohexyl] piperidine, PCP) was originally developed as an intravenous anesthetic in the 1950s. Used for this indication, it causes a trance-like state without loss of consciousness and was hence classified as a dissociative anesthetic. However, it was soon withdrawn from human use because it produced unpleasant hallucinations, agitation, and delirium. The product was later used in veterinary medicine. Ketamine, a chemically closely related substance, was developed to replace PCP and is still in use as a dissociative anesthetic in children. Ketamine is less potent than PCP, and its effects are of shorter duration. However, it may also cause hallucinations (see the section on ketamine in Chapter 7, "Club Drugs"). Much of the ketamine sold on the street (special K, cat Valium) has been diverted from veterinarians' offices.

In the United States, PCP abuse started in the mid 1960s, when it entered the illegal drug market under the name of "angel dust" and other street names (peace pill, crystal, hob, love boat, dummy dust, peace, supergrass, zombie, synthetic THC, or synthetic marijuana). Like LSD, PCP has effects on perception (time, space, body image) and thought processes, and an increase in its use coincided with the decline in LSD use in the 1970s. After a period of substantial popularity in the 1980s, phencylclidine abuse declined. The drug seems to be more popular among men, with males age 18 and older showing the highest prevalence in North America. Because the synthesis of PCP is easy and relatively cheap, in the United States it has been used to adulterate other illicit drugs or has been substituted for other abused substances (e.g., methamphetamine, mescaline, psilocybin, cannabis).

Originally, PCP entered the illegal drug market in the form of tablets, which had a slow onset of action. Since the 1970s, PCP has been produced in

illegal laboratories and is generally sold in crystalline form. In this form it can be mixed with tobacco, mint leaves, parsley, or cannabis (super or killerweed, supergrass) and smoked. Typical oral doses range from 5–10 mg to 80–100 mg, two to three times a day. The bitter-tasting, water-soluble crystals are also snorted or injected intravenously. Effects of PCP begin within minutes of its being smoked, reaching their greatest intensity after about 30 minutes. The effects start to decline after 4–6 hours and disappear after about 24 hours. Because PCP-induced psychotic experiences may last for several days or even weeks, the drug has been used in laboratory animals to produce an experimental model of schizophrenia.

A wide variety of perceptual, cognitive, and emotional experiences may be encountered after the use of PCP. Abusers seek euphoria, which develops within minutes after smoking and is accompanied by a sense of warmth and numbness, as well as unusual delusions and hallucinations.

Inexperienced users or individuals who are exposed to the drug unexpectedly (e.g., who unknowingly consume PCP-adulterated cannabis) may develop severe anxiety and panic because of the intensity and variety of symptoms. Perceptual distortions have sometimes led to extremely violent behavior, accidents, or self-damaging acts. An especially high risk of violent behavior has been reported in acutely intoxicated PCP users who have a history of psychiatric problems. Intoxication with doses in excess of 150 mg may lead to convulsions, coma, and death from respiratory arrest. Other complications include hypertensive crisis, intracerebral hemorrhage, and renal failure (Table 6–5).

Pharmacology of PCP and Ketamine

PCP and ketamine act as noncompetitive NMDA receptor antagonists. They have been shown to bind to a site deep in the ion channel. It is still unknown how this mode of action is related to the hallucinogenic and addictive effects of these drugs. At substantially higher doses (i.e., those that cause blockade of the NMDA receptor), PCP (but not ketamine) blocks monoamine reuptake, increasing synaptic levels of dopamine and noradrenaline. This action may explain the stimulatory effects during high-dose intoxication, which may lead to agitation and violence. Other pharmacologic effects (e.g., blockade of Na and K channels; effects on cholinergic, opiate, and GABA/benzodiazepine

Table 6–5. Adverse effects of phencyclidine

Acute effects

- Hypertension
- Tachycardia
- Nausea, vomiting
- Hypersalivation
- Hyperpyrexia, fever, sweating
- Rhabdomyolysis
- Flushing
- Bronchospasm, aspiration pneumonia
- Anesthesia, somnolence, sleep
- Neurological signs: nystagmus, miosis, blurred vision, tremor, slurred speech, dystonia, convulsion, amnesia, confusion, peripheral numbness
- Psychiatric signs: euphoria, dysphoria, agitation, hallucinations, delusions, aggression, violence, bizarre behavior, schizophrenia-like "body trip"

Chronic effects

- Psychological and physical dependence
- Chronic anxiety, confusion, depression
- Memory loss, speech difficulties (mutism, stuttering)
- Psychosis, personality changes, flashbacks

Source. Adapted from Will 1997.

receptors) are also related to high doses and may explain some of the clinical effects during intoxication, such as convulsions. Hence, it may be that the effects of PCP result from perturbation of multiple neurotransmitter systems.

PCP has very complex pharmacokinetics. A lipophilic drug, it is stored in fatty tissue, from which it may be liberated for several days, causing long-lasting and/or recurring psychotic symptoms. The half-life of the drug varies from 7 to more than 72 hours. PCP is primarily eliminated by hepatic hydroxylation and subsequent renal excretion. About 10% of total PCP is excreted in the urine unchanged and may be detected by suitable urine screening methods.

Treatment of Intoxication

Treatment of acute PCP intoxication includes efforts to decrease gastrointestinal absorption of the drug (e.g., by activated charcoal) and to increase renal

excretion (e.g., by acidification of the urine through administration of ascorbic acid). PCP-users typically use the drug in binges lasting 2–3 days (which may occur several times per month), similar to the "runs" in amphetamine users, which are followed by a hypersomnia and depressed mood. Effects of chronic use are listed in Table 6–5 and include social isolation and a schizophrenia-like clinical picture that can occur among patients with no prior psychiatric disturbance.

With chronic use of PCP, tolerance develops, resulting in use of higher doses to achieve the desired subjective effects. Other clinical signs of addiction may also be seen, including difficulty discontinuing use of the drug despite adverse consequences and craving for the drug. Although withdrawal symptoms following abrupt discontinuation of PCP use have been reported in animals, there are no clear reports from chronic PCP users that support the existence of an abstinence syndrome. Recently, PCP treatment in rats has been shown to result in a protracted depression of brain reward function that may be analogous to the dysphoric and anhedonic symptoms of PCP dependence (Spielewoy and Markou 2003).

Anticholinergic Plants and Synthetic Agents

Atropine and its ether analog scopolamine (hyoscine) are potent alkaloids that are found as active compounds in a large number of plants around the world (belladonna alkaloids). The "deadly nightshades" ("European bittersweet," *Solanum dulcamara* or "belladonna," *Atropa belladonna*) were used in the Middle Ages as witches' brew. Intoxication from both plants occurs mainly in children who ingest the fruits or flowers because of their attractive appearance.

Jimsonweed (*Datura stramonium*, thorn apple, or "locoweed"), another member of the Solanaceae family, is found throughout the United States. The plant has large, jagged, bitter-tasting leaves and large white or purple trumpet-like flowers. In the fall, the plant bears fruit in the form of thorny capsules, which contain brown or black seeds. All parts of the plant are poisonous; about 4% of the seeds consist of anticholinergic alkaloids (scopolamine, hyoscyamine, and atropine). Although accidental childhood poisonings with jimsonweed were seen in the past, more recently, these events have been replaced by an increased incidence of inadvertent overdoses in persons experimenting with the drugs for their mind-altering effects (Goldfrank 1986). Leaves of the plant

can be eaten raw, prepared as a tea, or smoked. There is even a preparation of *Datura stramonium* available in health food stores, where it is sold as an asthma drug (Goldfrank 1986). Alkaloid contents of plants of the Solanaceae family vary between seasons and from year to year, which makes it difficult to make clinical inferences from the amount ingested; as little as 4–5 g of crude leaf from jimsonweed may be lethal for a child. Adolescents and young adults are known to smoke the dried leaves or consume the dried seeds to induce a state of toxic delirium.

Trihexyphenidyl (Artane) and benztropine (Cogentin) are prescription drugs used in the treatment both of Parkinson's disease and the extrapyramidal side effects produced by neuroleptic medication. They are occasionally abused for their mind-altering properties, which occur at toxic doses (Perry et al. 1978). Abusers often try to obtain these drugs by false representation of extrapyramidal symptoms, which are claimed to result from the use of phenothiazines or other neuroleptics (Rubinstein 1978).

Certain antiasthma drugs available in health food stores contain preparations from belladonna or stramonium leaves (Goldfrank 1986). Gastrointestinal anticholinergics containing atropine sulfate are used as adjunctive therapy for peptic ulcers and in other gastrointestinal conditions (e.g., functional diarrhea). Scopolamine is prescribed for the treatment of motion sickness. Over-the-counter sleeping pills containing scopolamine are also occasionally abused for their effects on the CNS.

Clinical Findings in Anticholinergic Intoxication

The clinical picture of anticholinergic intoxication is governed by the muscarinic effects of the drug (Table 6–6). Mydriasis is a consistent finding. Dry mouth, decreased gastrointestinal motility, urinary retention, tachycardia with dysrhythmias, and hyperpyrexia with a dry, flushed skin are also typically seen. These symptoms are markedly different from the sympathomimetic effects seen after exposure to the majority of the hallucinogens discussed earlier. Lilliputian hallucinations are frequently reported as a symptom of anticholinergic intoxication (Goldfrank 1986). Insight into the drug-induced nature of the sensory distortions and recall of the vivid illusions are typically lost following resolution of the intoxication (Shulgin 1981). In patients with narrow-angle glaucoma, anticholinergics may precipitate an acute attack.

Table 6–6. Symptoms of anticholinergic intoxication

Peripheral signs	Central symptoms
Mydriasis	Visual hallucinations
Tachycardia	Drowsiness
Hyperthermia	Distortion of body image
Decreased salivation	Amnesia
Dryness of skin and mucous membranes	Heatstroke (from hyperthermia at high environmental temperatures)
Facial flushing	
Difficulty urinating	

Treatment of Anticholinergic Intoxication

If the ingestion of an anticholinergic has been recent, and the patient is not obtunded or convulsing, gastric lavage or emesis with ipecac is indicated. Because absorption of the drug is slow (due to the reduced motility of the gut), oral administration of activated charcoal and a cathartic enhances the probability of removing substantial amounts of unabsorbed drug.

In case of severe hallucinations, myoclonic seizures, hypertension, or arrhythmias, the anticholinesterase physostigmine is the drug of choice (Goldfrank 1986); it also can help to confirm the diagnosis in unclear cases. The effective dose of physostigmine is 0.5 mg in children and 1–2 mg (0.01–0.03 mg/kg) in adults, given intramuscularly or intravenously over 2–5 minutes. Slow administration is essential because physostigmine may cause seizures if administered too rapidly. This dose may be repeated in 20–30 minutes if toxic effects persist and no cholinergic effect is produced. Because the signs of cholinergic excess (bradycardia, heart block, and excessive secretions) may develop rapidly, use of physostigmine should be reserved for the intensive care setting. Neostigmine and pyridostigmine, which are quaternary amines, do not cross the blood-brain barrier and hence lack effect on the CNS.

Relative contraindications to the use of anticholinesterase treatment include a history of cardiovascular disease, asthma, glaucoma, and gastrointestinal or genitourinary obstruction. Symptomatic treatment of tachyarrhythmias with propranolol may be considered; β blockers, however, are less effective than physostigmine.

References

Aghajanian GK, Haigler HJ: Hallucinogenic indoleamines: preferential action upon presynaptic serotonin receptors. Psychopharmacol Commun 1:619–629, 1975

Aghajanian GK, Sprouse JS, Rasmussen K: Physiology of the midbrain serotonin system, in Psychopharmacology: The Third Generation of Progress. Edited by Meltzer HY. New York, Raven, 1987, pp 141–149

Alrazy J, Verebey K: MDMA biological disposition in man: MDA is a biotransformation product. NIDA Res Monogr 90:34, 1988

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000

Appel JB, Freedman DX: Chemically induced alterations in the behavioral effects of LSD-25. Biochem Pharmacol 13:861–869, 1964

Appel JB, West WB, Buggy J: LSD, 5-HT (serotonin), and the evolution of a behavioral assay. Neurosci Biobehav Rev 27:693–701, 2004

Arvanov VL, Liang X, Magro P, et al: A pre- and postsynaptic modulatory action of 5-HT and the 5-$HT_{2A,\ 2C}$ receptor agonist DOB on NMDA-evoked responses in the rat medial prefrontal cortex. Eur J Neurosci 11:2917–2934, 1999

Back-Madruga C, Boone KB, Chang L, et al: Neuropsychological effects of 3,4-methyldioxymthamphetamine (MDMA or ecstasy) in recreational users. Clin Neuropsychol 17:446–459, 2003

Baselt RC, Cravey RH: The Disposition of Toxic Drugs and Chemicals in Man, 3rd Edition. London, Year Book Medical, 1989

Bordo DJ, Dorfman MA: Ecstasy overdose: rapid cooling leads to successful outcome. Am J Emerg Med 22:326–327, 2004

Bowen JS, Davis GB, Kearney TE, et al: Diffuse vascular spasm associated with 4-bromo-2,5-dimethoxyamphetamine ingestion. JAMA 249:1477–1479, 1983

Brands B, Sproule B, Marshman J: Drugs and Drug Abuse, 3rd Edition. Toronto, Ontario, Addiction Research Foundation, Fondation de la recherché sur la toxicomanie, 2001

Buckholtz NS, Zhou DF, Freedman DX, et al: Lysergic acid diethylamide (LSD) administration selectively downregulates $serotonin_2$ receptors in rat brain. Neuropsychopharmacology 3:137–148, 1990

Burris KD, Breeding M, Sanders-Bush E: (+)Lysergic acid diethylamide, but not its nonhallucinogenic congeners, is a potent serotonin $5HT_{IC}$ receptor agonist. J Pharmacol Exp Ther 258:891–896, 1991

Cimbura G: PMA deaths in Ontario. Can Med Assoc J 110:1263–1265, 1974

Cohen S, Ditman K: Complications associated with lysergic acid diethylamide (LSD-25). JAMA 181:161–162, 1962

Creighton FJ, Black DL, Hyde CE: 'Ecstasy' psychosis and flashbacks. Br J Psychiatry 159:713–715, 1991

Curry SC, Rose MC: Intravenous mushroom poisoning. Ann Emerg Med 14:900–902, 1985

Davis M: Mescaline: excitatory effects on acoustic startle are blocked by serotonin 2 antagonists. Psychopharmacology (Berl) 93:286–291, 1987

Dishotsky NI, Lougham WD, Mogar RE, et al: LSD and genetic damage. Science 172: 431–440, 1971

Dowling GP, McDonough ET 3rd, Bost RO: 'Eve' and 'ecstasy': a report of five deaths associated with the use of MDEA and MDMA. JAMA 257: 1615–1617, 1987

Freedman DX: Hallucinogenic drug research: if so, so what? symposium summary and commentary. Pharmacol Biochem Behav 24:407–415, 1987

Frosch WA, Robbins ES, Stern M: Untoward reactions to lysergic acid diethylamide (LSD) resulting in hospitalization. N Engl J Med 273:1235–1239, 1965

Ghodse H: Drugs and Addictive Behaviour, A Guide to Treatment, 3rd Edition. Cambridge, UK, Cambridge University Press, 2002

Giannini AJ, Price WA, Giannini MC: Contemporary drugs of abuse. Am Fam Physician 33:207–216, 1986

Glennon RA, Titeler M, Young R: Structure-activity relationships and mechanism of action or hallucinogenic agents based on drug discrimination and radioligand binding studies. Psychopharmacol Bull 22:953–958, 1986

Goldfrank LR: Anticholinergic plant poisoning: jimson weed, in Goldfrank's Toxicologic Emergencies, 3rd Edition. Edited by Goldfrank LR, Flomenbaum NE, Lewin NA, et al. Norwalk, CT, Appleton-Century-Crofts, 1986, pp 602–608

Gorard DA, Davies SE, Clark ML: Misuse of ecstasy (letter). BMJ 305:309, 1992

Halpern JH: Hallucinogens: an update. Curr Psychiatry Rep 5:347–354, 2003

Halpern JH: Hallucinogens and dissociative agents naturally grown in the United States. Pharmacol Ther 102:131–138, 2004

Halpern JH, Pope HG Jr: Do hallucinogens cause residual neuropsychological toxicity? Drug Alcohol Depend 69:247–256, 1999

Halpern JH, Pope HG Jr: Hallucinogen persisting perception disorder: what do we know after 50 years? Drug Alcohol Depend 69:109–119, 2003

Halpern JH, Pope HG Jr, Sherwood AR, et al: Residual neuropsychological effects of illicit 3,4-methylenedioxymethamphetamine (MDMA) in individuals with minimal exposure to other drugs. Drug Alcohol Depend 7:149–152, 2004

Hatrick JA, Dewhurst K: Delayed psychosis due to LSD. Lancet 2:742–744, 1970

Holden R, Jackson MA: Near-fatal hyponatraemic coma due to vasopressin oversecretion after "ecstasy" (3,4-MDMA). Lancet 347(9007):1052, 1996

Hollister L: Clinical aspects of abuse of phenylalkylamine and indolealkylamine hallucinogens. Psychopharmacol Bull 22:977–979, 1986

Johnston LD, O'Malley PM, Bachman JG: Monitoring the Future National Survey Results on Drug Use, 1975–2002, Vol I: Secondary School Students (NIH Publ No 03–5375). Bethesda, MD, National Institute on Drug Abuse, 2003

Kulberg A: Substance abuse: clinical identification and management. Pediatr Clin North Am 33:325–361, 1986

Kulberg AG, Goldfrank LR, Bresnitz EA: Mushrooms: toxic and hallucinogenic, in Goldfrank's Toxicologic Emergencies, 3rd Edition. Edited by Goldfrank LR, Flomenbaum NE, Lewin NA, et al. Norwalk, CT, Appleton-Century-Crofts, 1986, pp 545–557

Kurrasch-Orbaugh DM, Parrish JC, Watts VJ, et al: A complex signaling cascade links the serotonin$_{2A}$ receptor to phospholipase A2 activation: the involvement of MAP kinases. J Neurochem 86:980–991, 2003

Lewin NA, Howland MA, Goldfrank LR, et al: Herbal preparations, in Goldfrank's Toxicologic Emergencies, 3rd Edition. Edited by Goldfrank LR, Flomenbaum NE, Lewin NA, et al. Norwalk, CT, Appleton-Century-Crofts, 1986, pp 560–577

Li JH, Lin LF: Generic toxicology of abused drugs: a brief review. Mutagenesis 13:557–565, 1998

Lincoff GH, Mitchel DH: Toxic and Hallucinogenic Mushroom Poisoning: A Handbook for Physicians and Mushroom Hunters. Edited by Williams WK. New York, Van Nostrand Reinhold, 1977

Logan BK, Cooper FJ: 3,4-Methylenedioxymethamphetamine (MDMA, ecstasy) and driving impairment. J Forensic Sci 46:1426–1433, 2001

Lyon RA, Titeler M, Seggel MR, et al: Indolealkylamines analogs share 5-HT$_2$ binding characteristics with phenylalkylamine hallucinogens. Eur J Pharmacol 145:291–297, 1988

Lyvers M, Hasking P: Have Halpern et al. (2004) detected 'residual neuropsychological effects' of MDMA? not likely. Drug Alcohol Depend 75:149–152, 2004

Mack RB: Marching to a different cactus: peyote (mescaline) intoxication. N Engl J Med 47:137–138, 1986

Martin WR, Sloan JW: Relationship of CNS tryptaminergic processes and the action of LSD-like hallucinogens. Pharmacol Biochem Behav 24:393–399, 1986

McCall R: Effects of hallucinogenic drugs on serotoninergic neuronal systems. Pharmacol Biochem Behav 24:359–363, 1986

McKim WA: Drugs and Behavior: An Introduction to Behavioral Pharmacology, 3rd Edition. Englewood Cliffs, NJ, Prentice-Hall, 1996

Moskowitz D: Use of haloperidol to reduce LSD flashbacks. Milit Med 136:754–757, 1971

National Institute on Drug Abuse: NIDA Community Drug Alert Bulletin: Club Drugs. Rockville, MD, National Institute on Drug Abuse, 2004a. Available at: http://www.drugabuse.gov/ClubAlert/ClubDrugAlert.html. Accessed May 9, 2005.

National Institute on Drug Abuse: Research Report Series: MDMA (Ecstasy) Abuse. Rockville, MD, National Institute on Drug Abuse, 2004b. Available at: http://www.drugabuse.gov/ResearchReports/MDMA/MDMA5.html. Accessed May 9, 2005.

Nichols DE: Studies of the relationship between molecular structure and hallucinogenic activity. Pharmacol Biochem Behav 24:335–340, 1986

Nichols DE: Hallucinogens. Pharmacol Ther 101:131–191, 2004

Peroutka SJ: Serotonin receptors, in Psychopharmacology: The Third Generation of Progress. Edited by Meltzer HY. New York, Raven, 1987, pp 303–311

Perry PJ, Wilding OC, Juhl RP: Anticholinergic psychosis. Am J Hosp Pharm 35:725–728, 1978

Randall T: Ecstasy-fueled "rave" parties become dances of death for English youths. JAMA 268:1505–1506, 1992

Ricaurte GA, McCann UD, Szabo Z, et al: Toxicodynamics and long-term toxicity of the recreational drug 3,4-methylenedioxy-methamphetamine (MDMA, "Ecstasy"). Toxicol Lett 112–113:143–146, 2000

Robinson TN, Killen JD, Taylor CB, et al: Perspectives on adolescent substance use: a defined population study. JAMA 258:2072–2076, 1987

Rubinstein JS: Abuse of antiparkinson drugs: feigning of extrapyramidal symptoms to obtain trihexyphenidyl. JAMA 239:2365, 1978

Rumack BH (ed): LSD, in Poisindex, Vol 54. Denver, CO, Micromedex, 1987

Rusyniak DE, Banks ML, Mills EM, et al: Dantrolene use in 3,4-methylenedioxymethamphetamine ("ecstasy")–medicated hyperthermia (letter). Anesthesiology 10:263, 2004

Satchell SC, Connaughton M: Inappropriate antidiuretic hormone secretion and extreme rises in serum creatinine kinase following MDMA ingestion. Br J Hosp Med 51:495, 1994

Schreiber R, Brocco M, Audinot V, et al: (1-(2,5-Dimethoxy-4 iodophenyl)-2-aminopropane)-induced head-twitches in the rat are mediated by 5-hydroxytryptamine (5-HT) 2A receptors: modulation by novel 5-$HT_{2A/2C}$ antagonists, D_1 antagonists and 5-HT_{1A} agonists. J Pharmacol Exp Ther 273:101–112, 1995

Screaton GR, Singer M, Cairns HS, et al: Hyperpyrexia and rhabdomyolysis after MDMA ("ecstasy") abuse. Lancet 399:667–668, 1992

Shearman JD, Chapman RW, Satsangi J, et al: Misuse of ecstasy (letter) BMJ 305:309, 1992

Shulgin AT: Hallucinogens, in Burger's Medicinal Chemistry, 4th Edition, Part 3. Edited by Wolff ME. New York, Wiley, 1981, pp 1109–1137

Shulgin AT: Psychotomimetic drugs: structure-activity relationships, in Handbook of Psychopharmacology, Vol 11. Edited by Iversen LD, Iversen SD, Snyder SH. New York, Plenum, 1978, pp 243–336

Sivyer G, Dorrington L: Intravenous injection of mushrooms (letter). Med J Aust 140:182, 1984

Slaby AE, Lieb J, Trancredi LR: Handbook of Psychiatric Emergencies, 2nd Edition. Garden City, NY, Medical Examination Publishing, 1981

Snyder SH, Faillace L: 2,5-Dimethoxy-4-methyl-amphetamine (STP): a new hallucinogenic drug. Science 1588: 669–670, 1967

Spielewoy C, Markou A: Withdrawal from chronic phencyclidine treatment induces long-lasting depression in brain reward function. Neuropsychopharmacology 28:1106–1116, 2003

Strassman R: Adverse reactions to psychedelic drugs: a review of the literature. J Nerv Ment Dis 172:577–595, 1984

Strassman R: Human psychopharmacology of N,N-dimethyltryptamine. Behav Brain Res 73:121–124, 1996

Verebey K, Alrazi J, Jaffe JH: The complications of "ecstasy" (MDMA) (letter). JAMA 259:1649–1650, 1988

Wills S: Drugs of Abuse. London, Pharmaceutical Press, 1997

Winstock AR: Chronic paranoid psychosis after misuse of MDMA. BMJ 302:1150–1151, 1991

Winstock AR: Chronic paranoid psychosis after misuse of MDMA. BMJ 302:6785, 1997

Yan QS: Activation of 5-$HT_{2A/2C}$ receptors within the nucleus accumbens increases local dopaminergic transmission. Brain Res Bull 51:75–81, 2000

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7

Club Drugs

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The use of "club drugs," which include GHB (γ-hydroxybutyrate), 3,4-methylenedioxymethamphetamine (MDMA) ("ecstasy"), and ketamine, particularly among adolescents and young adults, has raised concern (Chatlos 1996). Although, overall, more recent studies of adolescents and adults have shown a slight decrease in drug use, adolescent substance abuse remains a public health concern, particularly as it relates to the use of designer drugs (Armentano 1995; Johnston et al. 2002). Moreover, given their popularity among a subgroup of the homosexual community, the club drugs may also represent a unique challenge in working with patients in this group.

Club drugs originally received their name from their use in nightclubs and "raves." Raves are all-night dance parties that feature "techno" music, which is intended to enhance drug effects. These parties tend to attract adolescents and young adults ages 15–25 years (Koesters et al. 2002). As part of the rave experience, party-goers are often looking for "euphoric transcendence," which

is reached through the combination of frenetic dancing and club drug use (Weir 2000). Increasingly, however, clinicians must be concerned with non-club uses of the club drugs, particularly among high school and college students (Pederson and Skrondal 1999). Although technically, any drug used in a club could be considered a "club drug," general interest has focused on three agents: GHB, MDMA, and ketamine.

GHB and Related Compounds

GHB has been used both for legitimate clinical and clinical research purposes and for a range of illicit purposes. It was marketed legally in the United States until 1990, when the U.S. Food and Drug Administration (FDA) banned its sale to consumers. Except for the one indication described later in this section, GHB is a Schedule I controlled substance without other FDA-approved indications. The FDA has also declared γ-butyrolactone (GBL) as a List I chemical and 1,4-butanediol (1,4-BD) as a Class I health hazard, practically designating these GHB precursors, which are also industrial solvents, as illicit and unapproved new drugs (National Institute on Drug Abuse 2000).

Epidemiology and Clinical Presentation

Emergency department (ED) episodes related to GHB as reported to the Drug Abuse Warning Network (DAWN) increased more than fivefold from 1994 to 2001, with weighted estimates of 3,340 GHB mentions in 2001, compared to 638 mentions in 1994 (Kissin and Ball 2002). More than 74% of GHB mentions in 2001 were concurrent mentions with other drugs, and 54% were concurrent mentions with alcohol. Fifty-eight percent of ED mentions of GHB were for patients ages 18–25 years, and GHB mentions typically involved patients who are white and male (Kissin and Ball 2002). Although ED visits related to GHB are rare, the complaints that precipitate them may reflect the pattern of GHB sequelae in users in the community.

Miotto and colleagues (2001) surveyed 42 recreational users of GHB and found that 66% reported episodes of unpredictable loss of consciousness and 26% had overdosed. Forty-five percent of daily users had experienced frequent amnesia during or after use of the drug, suggestive of blackouts typically attributed to severe alcohol abuse. The rate of adverse events was greater

among those who used higher GHB doses and among those who used GHB together with other drugs of abuse.

Aside from the use of GHB and its analogs by body builders for purported anabolic effects, the main abuse of this class of compounds is recreational use, which produces sedation, euphoria, and sexual disinhibition (Miotto et al. 2001). The sedative effects of GHB may be related to inhibition of dopamine release and a subsequent increase in the intraneuronal dopamine level (Itzhak and Ali 2002). In an attempt to sidestep the FDA ban on human use of GHB and its precursors, GBL and 1,4-BD, these drugs are frequently represented and sold on the Internet as cleaning fluids. Recent "brands" sold over the Internet include the GBL preparations such as Fire Water, Revivarant, Revivarant G, RenewTrient, GH Revitalizer, GH Release, Gamma-G, InvigorateX, Furomax, Insom-X, and Blue Nitro Vitality and the 1,4-BD preparations such as Revitalize Plus, Serenity, Enliven, Zen, GHRE, SomatoPro, InnerG, NRG3, Weight Belt Cleaner, and Thunder Nectar (Centers for Disease Control and Prevention 1999; Hall and Maxwell 2000; Zvosec et al. 2001). Because GHB potentially causes coma and anterograde amnesia, especially in conjunction with alcohol, with which its effects are synergistic, it has reportedly been used as a drug to facilitate sexual assault. Reflecting street awareness of the side effects of loss of consciousness and decreased coordination, users usually avoid driving motor vehicles (Miotto at al. 2001).

Because GHB induces slow-wave sleep, a peak period of sleep for release of growth hormone (Gerra et al. 1994; Takahara et al. 1977), it has been marketed as a nonregulated anabolic health-food supplement to body builders since the 1980s. However, Addolorato and colleagues (1999b) found no evidence of purported anabolic effects during long-term administration of GHB, and no other evidence from case reports or clinical trials exists for the efficacy of GHB in increasing muscle mass.

Acute Effects

Taken for recreational use as an intoxicant, typical acute effects described by misusers are euphoria, relaxation, and increased sexuality (Galloway et al. 1997; Miotto et al. 2001). On the street, GHB is taken in capfuls or teaspoons of a salty/sour liquid, which because of variations in concentration, may range in dose from 0.5 to 5.0 g. Common side effects are nausea, headache, itching, and vomiting (Borgen et al. 2003). Doses of 10–20 mg/kg of GHB typically

produce anxiolysis with hypotonia and amnesia, 20–30 mg/kg induces sleep, and 50–60 mg/kg induces anesthesia (Craig et al. 2000). In the context of rave-type parties, GHB or its precursors are often taken together with other club drugs (e.g., ketamine, MDMA), so as to offset the sedating properties of GHB and modulate the stimulants' adverse effects such as teeth grinding and jaw-clenching, while increasing the subjective euphoria and disinhibition. GHB has also gained notoriety as a common drug of abuse at gay circuit parties. Similar to alcohol, GHB may cause impairment of judgment in addition to disinhibition when used to facilitate sexuality. In Liverpool, United Kingdom, 61% of gay men identified in one study as infected with syphilis had used GHB as an aphrodisiac in the context of unprotected sex (Cook et al. 2001).

Chronic Effects

In a conditioned place preference paradigm, mice treated repeatedly for a week with 250 mg/kg of GHB demonstrate place preference, suggesting that GHB cues are rewarding (Itzhak and Ali 2002). However, highly reinforcing drugs (e.g., cocaine, opioids) typically produce conditioned place preference after only two to three drug exposures, so GHB, which appears to require a greater number of exposures, may have less reinforcing effects (Nicholson and Balster 2001). Nonetheless, it appears that a small percentage of human users of GHB or its precursors become addicted. In addition to evidence of physiologic dependence, including tolerance and withdrawal, there is evidence that patients may quickly relapse to GHB or GBL use after complicated withdrawal (McDaniel and Miotto 2001), thus meeting the DSM-IV-TR criteria for substance dependence (American Psychiatric Association 2000). Part of the high relapse risk may be due to what McDaniel and Miotto (2001) have described as a protracted abstinence syndrome, characterized by dysphoria, anxiety, memory problems, and insomnia, which may last for 3–6 months after the acute withdrawal has stabilized.

Basic and Clinical Pharmacology

Biosynthetic and Metabolic Pathways

GHB is an endogenous, water-soluble, four-carbon fatty acid that is found in peripheral organs, including the heart, liver, kidney, and cardiac and skeletal

muscle, as well as in the brain of mammals, where it is thought to play a role as a neurotransmitter (Maitre 1997; Nelson et al. 1981). This metabolite of γ-aminobutyric acid (GABA) appears to be synthesized in the central nervous system (see Figure 7–1), and in rodents it has been shown to bind to high-affinity receptors in neurons of the hippocampus, cortex, striatum, olfactory bulb and tubercle, and dopaminergic nuclei (Maitre 1997). In the mitochondria, GABA is transaminated by GABA-transaminase into succinic semialdehyde (SSA). Most of the SSA is oxidized into succinate in the mitochondria for use in the Krebs cycle, but a small amount, 1%–2%, appears to be transported back into the cytosol, where it is reduced into GHB by succinic semialdehyde reductase, an enzyme found only in neurons (Maitre et al. 2000). In the brain, 1,4-BD is also converted into GHB (Snead et al. 1989), whereas peripheral lactonases appear to convert naturally occurring GBL into GHB, which then freely diffuses across the blood-brain barrier (Maitre 1997; Roth and Giarman 1968). In the liver, 1,4-BD is oxidized by alcohol dehydrogenase to γ-hydroxybutyraldehyde, which is oxidized to GHB by aldehyde dehydrogenase (Dyer et al. 2001). Inhibiting the enzyme GABA-transaminase will block the formation of GHB from GABA; however, neither this effect nor the blocking of alcohol dehydrogenase affects the formation of GHB from 1,4-BD in the brain, demonstrating at least two different pathways for GHB synthesis in the central nervous system (CNS) (Snead et al. 1989). GHB is ultimately metabolized to carbon dioxide (CO_2), which is eliminated through the lungs, although a small percentage is excreted in the urine (Galloway et al. 2000; Nicholson and Balster 2001).

GHB is rapidly absorbed from the gastrointestinal tract, and is present in free form in the serum without protein binding (Li et al. 1998a), with peak plasma concentrations usually appearing 40–60 minutes after ingestion, often more quickly (Borgen et al. 2003). However, absorption is capacity-limited, and larger doses will increase the time to peak plasma concentration (Palatini et al. 1993). Food, especially that of high fat content, significantly reduces bioavailability of GHB, reducing peak plasma concentration and increasing median time to peak concentration (Borgen et al. 2003). As the main enzyme for degradation of GHB is saturable and the elimination pharmacokinetics of GHB is nonlinear, plasma clearance of GHB decreases as the dose of GHB increases (Borgen et al. 2000). At low doses such as 12.5 mg/kg, the elimination half-life is as brief as 20 minutes, with clearance of 14 mL/min/kg,

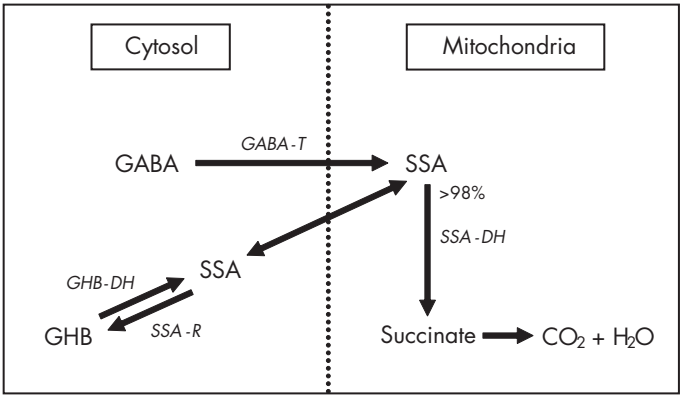

Figure 7–1. γ-Hydroxybutyrate (GHB) synthesis in the neuron. Succinic semialdehyde (SSA) is synthesized in the mitochondria through transamination of γ-aminobutyric acid (GABA) by GABA transaminase (GABA-T). Most of the SSA is oxidized by SSA dehydrogenase (SSA-DH) to form succinate, which is used for energy metabolism and results in the end products CO_2 + H_2O, which are expired. A small portion of SSA (<2%) is converted by SSA reductase (SSA-R) in the cytosol to GHB. GHB may also be oxidized back to SSA by GHB dehydrogenase (GHB-DH).

whereas at moderate doses such as 32 mg/kg, the mean clearance is reduced to 6.6 mL/min/kg and is further reduced by almost 40% with doses of approximately 60 mg/kg (Borgen et al. 2000; Roth and Giarman 1966; Scharf et al. 1998). Plasma levels of GHB are negligible 6 hours after a single 64-mg/kg (4.5-g) dose in healthy adults (Borgen et al. 2003). Because of the rapid elimination of the drug, the alteration in clearance with increased dose is not usually clinically relevant, except in the case of overdose, where coma may be extended with high doses, or where there is a pattern of high-dose administration at frequent intervals. The effect of the latter is discussed later in this chapter, in the section on abstinence syndrome.

Clinical Pharmacology

GHB has sedative, anxiolytic, and euphoric effects similar to ethanol, likely because of potentiation of cerebral GABAergic and dopaminergic activities.

In general, GHB is thought to exert tonic inhibitory control over dopamine and GABA release through high-affinity GHB receptors (Howard and Feigenbaum 1997; Kemmel et al. 2003). Increases in neuronal pools of dopamine are mediated by induction of tyrosine hydroxylase (Gessa et al. 1966), the rate-limiting enzyme in the catecholaminergic synthetic pathway. There also may be a serotonergic effect of GBH that is mediated by increased transport of tryptophan into serotonergic cells (Gobaille et al. 2002). Although GHB does not interact directly with known sites of action of other drugs of abuse, including the $GABA_A$ receptor, in pharmacologic doses it may be an agonist at $GABA_B$ sites (Nicholson and Balster 2001).

In addition, high-dose GHB causes epileptiform electroencephalogram (EEG) effects that are distinctly different from those of ethanol, and in preclinical studies it produced EEG changes that are more suggestive of petit mal absence seizures than of true sedation (Godschalk et al. 1977). However, the sedation caused by GHB is usually not thought to reflect absence seizures. Compared to the sedation induced by benzodiazepines and barbiturates, sedation induced by GHB at higher doses possesses distinct excitatory properties similar to that seen with dissociative anesthetics such as ketamine (Nicholson and Balster 2001; Winters and Kott 1979). This effect may contribute to its role as a club drug. GHB also differs from other sedative-hypnotics such as ethanol or benzodiazepines in that it consolidates REM sleep.

GHB has been investigated as a potential treatment for several disorders including those related to sleep, such as narcolepsy (Scrima et al. 1990) and sleep apnea (Sériès et al. 1992), and those postulated to involve dopamine and GABA systems, such as schizophrenia (Levy et al. 1983) and alcohol withdrawal (Addolorato et al. 2000). GHB, developed under FDA orphan drug status as sodium oxybate (Xyrem), was approved by the FDA in July 2002 as a Schedule III drug for the treatment of cataplexy in patients with narcolepsy. GHB reduces cataplexy and induces and consolidates the type of brain EEG changes seen in normal sleep, such as slow-wave sleep, without affecting REM sleep (Sériès et al. 1992). As such, it has demonstrated efficacy in controlled clinical trials in patients with narcolepsy (Lammers et al. 1993; Scrima et al. 1990).

Another potential clinical use of GHB is in the treatment of alcohol withdrawal and alcohol dependence. In preclinical studies, GHB inhibited voluntary ethanol consumption in ethanol-preferring rats and suppressed the

ethanol withdrawal syndrome in alcohol-dependent animals (Gessa et al. 2000). These results set the foundation for investigating the potential use of GHB in the clinical treatment of alcohol dependence. Although an alcohol treatment indication is not currently approved in the United States, in Europe there have been several open studies and a few randomized clinical trials suggesting that GHB is efficacious in preventing or controlling symptoms of alcohol withdrawal (Addolorato et al. 1999a; Moncini et al. 2000; Nimmerrichter 2002) and that GHB may have a role in reducing alcohol craving, increasing treatment retention (Moncini et al. 2000), and preventing relapse to drinking (Gallimberti et al. 1992, 2000) in detoxified alcoholic patients. The potential role of GHB as a substitution pharmacotherapy for alcoholism is confounded by its short plasma half-life; the role of longer-acting GHB analogues remains to be explored (Galloway et al. 2000).

Toxicology

Overdose Effects

The most frequent presentation of GHB-related syndromes in EDs is that of overdose characterized by coma or stupor and respiratory depression and usually complicated by ingestion of other recreational drugs, but fatalities have been reported in the context of GHB and 1,4-BD use alone (Centers for Disease Control and Prevention 1997; Zvosec et al. 2001). Other common findings are bradycardia, respiratory acidosis, and vomiting (Chin et al. 1998). Because GHB is frequently taken together with other psychoactive substances, it is important to note that alcohol acts synergistically with GHB to produce respiratory and CNS depression (Mamelak 1989). GHB overdose also presents certain unusual clinical characteristics: patients may rapidly shift from an unconscious, apneic state requiring respiratory support to a markedly agitated, combative state, and back again (Li et al. 1998a), as well as become combative upon recovery of consciousness (Chin et al. 1998). These combative states are frequently triggered by the stimulus of intubation attempts, which reveal an exaggerated gag reflex (Li et al. 1998b; Ross 1995).

Abstinence Syndrome

The development of tolerance for GHB has been repeatedly described in clinical vignettes and demonstrated in animal models. For example, with repeated

GHB treatment in mice, tolerance develops to both the hypolocomotion and cataleptic effects of the drug (Itzhak and Ali 2002). There is also preclinical evidence of cross-tolerance and cross-dependence of GHB with alcohol (Colombo et al. 1995; Fadda et al. 1989). As described in the earlier section on clinical pharmacology, GHB and its analogues have been used in humans in the treatment of alcohol withdrawal. Nicholson and Balster (2001) reviewed the evidence for cross-tolerance and cross-dependence of GHB with alcohol.

In clinical trials with GHB, discontinuation syndromes were rarely mentioned (Addolorato et al. 1999c). However, there are now numerous reports of withdrawal syndromes clearly related to GHB or its precursors GBL and 1,4-BD (Craig et al. 2000; Dyer et al. 2001; McDaniel and Miotto 2001; Mycyk et al. 2001; Sivilotti et al. 2001). Craig and colleagues (2000) identified several probable antecedent factors that contribute to GHB withdrawal, including a history of prolonged GHB abuse with gradual dose escalation, the experience of dysphoria, anxiety and tremor upon stopping, and numerous attempts to cut down or stop GHB use.

It is important for the clinician to obtain a clear history of the pattern of use of GHB or its precursors once the patient recovers from acute overdose. In the case of frequent dosing, the patient may be at high risk for severe withdrawal. This high risk exists because a dose causing intoxication severe enough to require clinical treatment for overdose would have to be large enough to overcome the tolerance associated with repeated dosing. Most reports suggest that the distinguishing characteristic of patients presenting with clinically severe GHB withdrawal is a pattern of dosing at 2–4 hour intervals around the clock (Dyer et al. 2001; Hernandez et al. 1998; McDaniel and Miotto 2001; Miotto et al. 2001). This pattern of use is necessary in GHB-dependent patients, because of the drug's short half-life. Severe withdrawal syndromes, which typically include delirium in daily users of more than 25 g, have been described in numerous case studies and surveys (Chin 2001; Craig et al. 2000; Hernandez et al. 1998; Hodges and Everett 1998; Sivilotti et al. 2001; Zvosec et al. 2001). Such withdrawal syndromes share similarities in symptom patterns to withdrawal from both alcohol and benzodiazepines.

The onset of GHB withdrawal symptoms typically begins 1–5 hours after the last dose; initial symptoms include anxiety, tremor, tachycardia, nausea, and insomnia (Table 7–1). Untreated, the symptoms may progress within 24 hours to a more severe pattern that is similar to delirium tremens, with dys-

Table 7–1. γ-Hydroxybutyrate (GHB) withdrawal syndrome

Severity of withdrawal	Symptoms
Mild	Tremor, anxiety, insomnia, mood lability, abdominal cramping, nausea, vomiting, palpitations, diaphoresis, tachycardia, meiosis
Severe	Delirium with auditory or visual hallucinations and confusion, delusional thinking, autonomic instability with hypertension, increased temperature, severe agitation, horizontal nystagmus

Source. Dyer et al. 2001; Mycyk et al. 2001.

function of cognition and sensorium, bouts of severe agitation, and autonomic dysregulation lasting up to 1–2 weeks (Dyer et al. 2001). Concurrent abuse of other sedative-hypnotics, in particular alcohol, may exacerbate the GHB withdrawal syndrome. The more severe forms of withdrawal typically occur within 48 hours of the last use and are characterized by delirium with auditory or visual hallucinations and confusion, horizontal nystagmus, autonomic instability with hypertension and increased temperature, and episodic agitation. Autonomic dysregulation characterized by tachycardia, fever, hypertension, and diaphoresis is generally milder than that seen in delirium tremens, and although generalized seizures are not reported, myoclonus resembling tonic-clonic movements has been described (see Dyer et al. 2001; Miotto and Roth 2001).

Treatment

Overdose

The general treatment of GBH overdose is supportive medical care with a focus on the respiratory system. Patients typically regain consciousness in 2–5 hours. Commonly used coma reversal agents such as intravenous naloxone, glucose (50% dextrose in water), and flumazenil have demonstrated little benefit in GHB overdose (Li et al. 1998a). In addition, physostigmine has been suggested as a treatment for GHB overdose, but the risks of bradycardia and asystole in the context of GHB's short duration of action outweigh any purported benefits (Boyer et al. 2001).

Withdrawal

Milder forms of withdrawal, typically seen with lower frequency of dosing or lower cumulative daily doses, may be successfully treated with benzodiazepines on an outpatient basis (Addolorato et al. 1999c; Galloway et al. 1997). Severe withdrawal states typically require medical support, high doses of intravenous benzodiazepines, and capacity for physical restraint to prevent the patient from harming self or others during bouts of psychotic agitation (Dyer et al. 2001; Miotto and Roth 2001; Mycyk et al. 2001). Reports of the failure of benzodiazepines to adequately control symptoms of GHB withdrawal (Friedman et al. 1996; Mullins and Fitzmaurice 2001) have raised the question of how best to treat the disorder. The probable explanation for the observed lack of response is underdosing of the benzodiazepines. Many case reports have demonstrated that patients in severe GHB withdrawal may require very high doses of intravenous benzodiazepines such as lorazepam, diazepam, or even midolazam in order to control agitation and autonomic dysregulation. The average intravenous dosage of lorazepam given over a 24-hour period in these cases has ranged from 8–10 mg/hour (Craig et al. 2000; Chin 2001). Craig and colleagues (2000) reported the case of a patient who needed 2,655 mg of diazepam equivalents (507 mg of lorazepam plus 120 mg of diazepam) over 90 hours to control agitation. For patients treated with high doses of benzodiazepines, Miotto and Roth (2001) suggest the use of pulse oximetry to monitor for oxygen desaturation. After a diagnosis of GHB withdrawal is established, it is likely that early aggressive dosing with benzodiazepines under careful medical supervision will reduce the severity and chronicity of acute GHB withdrawal, but this approach remains to be validated.

Other sedative-hypnotic medications, such as barbiturates, may play a useful role in severe withdrawal from this group of drugs. For example, in a case series of GBL withdrawal, use of intravenous pentobarbital in the range of 1–2 mg/kg/hour lowered the total requirement for intravenous lorazepam (Sivilotti et al. 2001). Antipsychotic medications are often used to reduce psychotic agitation. However, because antipsychotic medications lower the seizure threshold and may contribute to loss of central control of temperature leading to hyperthermia or neuroleptic malignant syndrome (NMS), they are not indicated as first-line medications for GHB withdrawal delirium (Dyer and Roth 2001; McDaniel and Miotto 2001; Sharma et al. 2001). If anti-

psychotics are needed, second-generation agents are preferred, in order to lower the risk for dystonia, dyskinesia, and NMS (McDaniel and Miotto 2001; Olivera et al. 1990).

Freese et al. (2002) proposed that anticonvulsants, such as gabapentin, which inhibit glutamate production, may reduce glutamate-induced excitotoxicity, thus reducing the severity of GHB withdrawal. However reasonable this logic may be, there is little evidence to support this intervention at present, except that use of gabapentin, sodium valproate, and carbamazepine administered adjunctively with benzodiazepines has been described in a few published case reports (McDaniel and Miotto 2001).

GHB Dependence

Although the evidence base for this relatively rare disorder is not well developed, patients who are dependent on GHB appear to benefit from cognitive and motivational psychosocial therapies and from support of recovery in a manner similar to alcohol-dependent patients. However, because of the high likelihood of amnesia and cognitive dysfunction during the acute and subacute phases of GHB withdrawal, psychosocial interventions should, when possible, include significant others who can review and reinforce with the patient the negative consequences of GHB dependence.

MDMA (Ecstasy)

MDMA (3,4-methylenedioxymethamphetamine) is commonly known as ecstasy. Other slang names include XTC, X, E, Adam, clarity, and lover's speed. MDMA is chemically similar to the stimulant amphetamine and the hallucinogen mescaline. It was developed in the early 1900s as a chemical precursor in the synthesis of pharmaceutical agents and was patented by Merck in 1914. It was initially thought to have appetite suppressant properties, but it was never marketed for that indication. The first reported "underground" synthesis of MDMA occurred in 1967. The United Kingdom placed MDMA on Schedule I in 1977, and the United States did so in 1985. During the 1970s, MDMA was used by some psychotherapists to enhance the therapy process through its purported empathogenic or "relationship-enhancing" properties. It has never been shown to be effective in this role, and it remains an illegal substance with no accepted medical uses.

Epidemiology and Clinical Presentation

Prior to its designation as a Schedule I drug in the United States in 1985, MDMA had a low level of usage. This usage tapered off in the period immediately following its designation as a Schedule I drug (Koesters et al. 2002). However, the 1990s saw a resurgence in the use of MDMA, and its use continued to increase among adolescents in the early 2000s, becoming more commonly used than cocaine/crack. According to the Monitoring the Future survey for 2001, 11% of twelfth-grade students had used MDMA at least once in the past year and 4% of twelfth-grade students had used MDMA in the month before being surveyed (Johnston et al. 2002). It is generally viewed by high school students as being easily accessible and also as having a low harm potential (Johnston et al. 2002).

Ecstasy is taken orally, usually in a tablet or capsule. The onset of effect is generally sudden, within 30–60 minutes. These effects generally last 3–6 hours, but they may persist as long as 8 hours (Jerrard 1990). Intoxication with MDMA is usually described as occurring in three stages (Koesters et al. 2002; Parrott and Lasky, 1998). The initial stage consists of disorientation. This leads to the second stage of "yielding to tingling and spasmodic jerking" (Koesters et al. 2002). The final ("target") stage of MDMA intoxication consists of the typical response of increased sociability, increased mental clarity, a feeling of emotional warmth and closeness to others, and a general sense of well-being (Cami et al. 2000; Koesters et al. 2002; Parrott and Lasky 1998). At higher doses frank euphoria is experienced. A "hangover" is common the next day and can last for up to 48 hours. Side effects (including confusion, depression, insomnia, anxiety, and paranoia) have been reported to occur for weeks after ingestion (Curran and Travill 1997; Parrott and Lasky 1998).

The threshold dose of MDMA is 30 mg, but the average dose is 80–150 mg, with some users taking in excess of 200 mg. The lethal dose is estimated (from animal data) to be approximately 6,000 mg. On the street, concentrations of MDMA can vary greatly, and tablets may also contain other substances such as methylenedioxyamphetamine (MDA) and methylenedioxyethylamphetamine (MDEA) (Sherlock et al. 1999). The presence of these other substances is often associated with emergency presentations because of their narrower "therapeutic" windows.

Basic and Clinical Pharmacology

Acutely, MDMA acts to increase serotonin, but with chronic use, decreases in serotonin are noted, suggesting loss of serotonergic neurons (Sprague et al. 1998). Moreover, decreases in serotonin transporters have also been reported (McCann et al. 1998). Its use is also correlated with secondary increases in dopamine in the basal ganglia (Sprague et al. 1998). MDMA acts primarily in the frontal cortex, leading to effects on cognition and memory. It also works on the limbic system, leading to MDMA's effects on mood, anxiety, and emotions. Metabolism occurs through the cytochrome P450 2D6 enzyme system (Tucker et al. 1994).

Toxicology

In the emergency setting, MDMA intoxication is usually seen in conjunction with dehydration, hyperthermia, tachycardia, hypertension, liver failure, rhabdomyolysis, and/or renal failure, oftentimes mimicking NMS (Jonas and Graeme-Cook 2001; Lester et al. 2000; Schwartz and Miller 1997). The physical symptoms may be accompanied by symptoms of anxiety, agitation, and even confusion. Because these presentations are nonspecific, they lead to a wide differential diagnosis. Nevertheless, the clinician must have a high index of suspicion of a substance-induced basis for behavioral emergency presentations in most adolescents and young adults (Williams et al. 1998). The diagnosis is complicated by the fact that routine urine toxicology screens do not typically detect the presence of MDMA, although occasionally cross-reactivity with amphetamines may occur (Koesters et al. 2002; Shannon 2000).

MDMA's toxicity may be related to its effects on serotonergic neurons, related to oxidative stress and free radical formation (Bolla et al. 1998; McCann et al. 2000). In animal studies, these processes are associated with exaggerated pruning in those regions of the brain with high serotonergic activity, particularly the hippocampus and amygdala (Ricaurte et al. 1988, 2000). These changes are long lasting, and may be present as long as 7 years after MDMA exposure (Hatzidimitriou et al. 1999).

As a result of the neurochemical changes caused by MDMA, there is significant, observable functional impairment as well. These impairments occur in areas of the brain that have high concentrations of serotonergic neurons. Most notably affected are cognition and memory. Studies have shown decreases

in word recall, as well as poorer functioning in general measures of memory (Morgan 1999; Rodgers 2000; Verkes et al. 2001). It remains unclear if this effect is dose related or independent of dose (Bolla et al. 1998). Moreover, these effects may be compounded when MDMA and marijuana are combined (Gouzoulis-Mayfrank et al. 2000).

Treatment

General principles of the treatment of ecstasy intoxication are the same as those for intoxication with other stimulants, such as cocaine and methamphetamine. Overdoses of MDMA are generally treated with supportive care, as no specific pharmacologic treatments have been identified (Shannon 2000; Solhkhah and Wilens 1998). This approach includes the use of routine laboratory tests to detect electrolyte abnormalities and to assess renal and hepatic functioning (Koesters et al. 2002). Adequate rehydration is crucial. Occasionally the use of sedatives such as the benzodiazepines is indicated, particularly when extreme agitation is present. If pronounced hyperthermia, hypertension, or rhabdomyolysis is present, observation in an intensive care unit may be indicated. Observation may be combined with the use of dantrolene sodium (a skeletal muscle relaxant) at doses of 2–3 mg/kg intravenously three times a day.

MDMA has been associated with significant increases in heart rate and blood pressure, similar to the increases associated with amphetamine use (Lester et al. 2000). This effect may require acute treatment with antihypertensives such as calcium channel blockers or nitroprusside (Koesters et al. 2002). The use of MDMA during raves may lead to dehydration, hypertension, intracerebral hemorrhage, heart failure, liver failure, kidney damage, and malignant hyperthermia (Barrett and Taylor 1993; Harries and De Silva 1992; Jonas and Graeme-Cook 2001). Its use is often associated with jaw-clenching (trismus) and bruxism (Jerrard 1990; Shannon 2000). This effect explains the use of pacifiers or lollipops by teenagers on the dance floor.

As was previously mentioned, a hangover-like syndrome is common the next day after use of MDMA. MDMA withdrawal, which is thought to be caused by serotonin depletion, can last for weeks and includes symptoms of depression, anxiety, restlessness, and insomnia (Allen et al. 1993; McGuire et al. 1994). No specific treatments are currently indicated for this withdrawal syndrome, although the antidepressant bupropion may be helpful (Solhkhah

and Wilens 1998; Solhkhah et al. 2001). Teenage lore has it that use of selective serotonin reuptake inhibitors (SSRIs) may alleviate those symptoms acutely, but some preliminary data may in fact support the opposite effect. In addition, MDMA use may be associated with sexual dysfunction (Buffum and Moser 1986). This effect has led to use of a combination of MDMA and sildenafil (Viagra) ("sexctasy").

Ketamine

Ketamine is a cyclohexane human and veterinary injectable anesthetic that is also known by the slang names K, special K, vitamin K, and cat Valium (Bobo and Miller 2002). It is produced in a liquid form or as a white powder and is usually ingested orally or intranasally but is occasionally administered intramuscularly. Ketamine is a phencyclidine (PCP) analog that was first developed in 1962.

Epidemiology and Clinical Presentation

As with the other club drugs, the use of ketamine has increased over the past decade. Although ketamine use remains much less common than use of MDMA, it is still an important cause of emergency presentations (Koesters et al. 2002). The use of ketamine leads to dose-dependent dissociative episodes (Bowdle et al. 1988). Emergence from ketamine-induced anesthetic effects leads to a variety of symptoms that are generally described as psychedelic by users. These symptoms include "intense alterations in mood, perception, thinking, body awareness, and self-control" (Bowdle et al. 1988).

Basic and Clinical Pharmacology

Ketamine is a noncompetitive *N*-methyl-D-aspartate receptor antagonist and is generally considered a psychotomimetic or schizophrenomimetic. Ketamine also appears to have cholinergic and opiate receptor effects (Koesters et al. 2002). Ketamine has been shown to increase plasma cortisol and prolactin levels, although the physiological significance of these effects is unclear (Krystal et al. 1994). Large doses of ketamine produce reactions similar to reactions to PCP, which include "dreamlike" states, dissociation, and hallucinations (Koesters et al. 2002; Krystal et al. 1994). Important differences between ket-

amine and PCP include ketamine's lower potency, shorter duration of action, and tendency to cause less agitation. In general, the psychotic symptoms associated with ketamine can include both positive and negative symptoms and may even include catatonia (informally described as a "K-hole") (Koesters et al. 2002; Krystal et al. 1994).

For recreational use, ketamine is often snorted or smoked with marijuana or tobacco products, but it may also be injected intramuscularly (Weiner et al. 2000). The typical street dose of ketamine ranges from 30 to 300 mg. These amounts are in contrast to the clinical doses used for anesthesia, which range from 2 to 10 mg/kg. Ketamine has a half-life of less than 2 hours and is metabolized by the cytochrome P450 enzyme system (Koesters et al. 2002; Reich and Silvay 1989).

At low doses, ketamine may result in impairment of attention, learning ability, and memory, and at high doses it has been associated with delirium, amnesia, impaired motor function, hypertension, depression, and respiratory depression (Krystal et al. 1994). Another mechanism of action appears to be a blocking of the reuptake of catecholamines. This effect leads to an increase in heart rate and blood pressure (Reich and Silvay 1989).

Toxicology

In overdose, ketamine may lead to hyperthermia, seizures, hypertensive crisis, coma, and even death. These symptoms are generally thought to be caused by ketamine's catecholaminergic effects (Reich and Silvay 1989). Ketamine is physically addicting, with a described withdrawal syndrome.

In the ED setting, the diagnosis of ketamine intoxication is a clinical one. Ketamine is not routinely detected by urine toxicology tests, although it can be detected with high-performance liquid chromatography (Koesters et al. 2002). As with MDMA, the initial assessment for ketamine intoxication includes the use of routine laboratory tests to detect electrolyte abnormalities and to evaluate renal and hepatic functioning (Koesters et al. 2002).

Treatment

No specific treatments for ketamine intoxication are currently indicated (Solhkhah and Wilens 1998). General supportive care, including providing the patient with a quiet, low-stimulus environment, can be helpful (Koesters et al.

2002; White et al. 1982). Benzodiazepines may be useful, particularly if agitation is present, although clinicians must be mindful of a possible interaction leading to a prolonged half-life for ketamine (Lahti et al. 1995; Lo and Cumming 1975). In general, because of the short half-life of ketamine, patients usually require observation only for several hours and can then be released home (Koesters et al. 2002).

As with many other hallucinogens, ketamine use may be associated with flashbacks. These flashbacks are generally milder and less frequent than those associated with PCP use (Fine and Finestone 1973). Generally, treatment with an antipsychotic is not required and can occasionally make symptoms worse (Solhkhah et al. 2000).

Conclusion

There is an epidemic of club drug use, of greatest concern among adolescents. Use of club drugs is particularly problematic among individuals with psychiatric illness, including mood disorders, anxiety disorders, and attention-deficit/hyperactivity disorder (American Academy of Child and Adolescent Psychiatry 1998; Armentano 1995). Clinicians need to be aware of the ever-changing patterns of drug abuse. The club drugs as a group are not benign, although youths often perceive them as such (Johnston et al. 2002). Use of these drugs often has serious and occasionally fatal consequences.

References

Addolorato G, Balducci G, Capristo E, et al: Gamma-hydroxybutyric acid (GHB) in the treatment of alcohol withdrawal syndrome: a randomized comparative study versus benzodiazepine. Alcohol Clin Exp Res 23:1596–604, 1999a

Addolorato G, Capristo E, Gessa GL, et al: Long-term administration of GHB does not affect muscular mass in alcoholics. Life Sci 65:PL191–PL196, 1999b

Addolorato G, Caputo F, Capristo E, et al: A case of gamma-hydroxybutyric acid withdrawal syndrome during alcohol addiction treatment: utility of diazepam administration. Clin Neuropharmacol 22:60–62, 1999c

Addolorato G, Caputo F, Capristo E, et al: Gamma-hydroxybutyric acid: efficacy, potential abuse, and dependence in the treatment of alcohol addiction. Alcohol 20: 217–222, 2000

Allen RP, McCann UD, Ricaurte GA: Persistent effects of +/- 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") on human sleep. Sleep 16:560–564, 1993

American Academy of Child and Adolescent Psychiatry: Practice parameters for the assessment and treatment of children and adolescents with substance abuse disorders. J Am Acad Child Adolesc Psychiatry 37:122–126, 1998

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000

Armentano M: Assessment, diagnosis, and treatment of the dually diagnosed adolescent. Pediatr Clin North Am 42:479–490, 1995

Barrett PJ, Taylor GT: "Ecstasy" ingestion: a case report of severe complications. J R Soc Med 86:233–234, 1993

Bobo WV, Miller SC: Ketamine as a preferred substance of abuse. Am J Addict 11:332–334, 2002

Bolla KI, McCann UD, Ricaurte GA: Memory impairment in abstinent MDMA ("ecstasy") users. Neurology 51:1532–1537, 1998

Borgen L, Lane E, Lai A: Xyrem (sodium oxybate): a study of dose proportionality in healthy human subjects. J Clin Pharmacol 40:1053, 2000

Borgen LA, Okerholm R, Morrison D, et al: The influence of gender and food on the pharmacokinetics of sodium oxybate oral solution in healthy subjects. J Clin Pharmacol 43:59–65, 2003

Bowdle TA, Radant AD, Crowley DS, et al: Psychedelic effects of ketamine in healthy volunteers: relationship to steady-state plasma concentrations. Anesthesiology 88: 82–88, 1988.

Boyer EW, Quang L, Woolf A, et al: Use of physostigmine in the management of gamma-hydroxybutyrate overdose (letter). Ann Emerg Med 38:346, 2001

Buffum J, Moser C: MDMA and human sexual dysfunction. J Psychoactive Drugs 18:355–359, 1986

Cami J, Farre M, Mas M, et al. Human pharmacology of 3,4-methylenedioxymethamphetamine ("ecstasy"): psychomotor performance and subjective effects. J Clin Psychopharmacol 20:455–466, 2000

Centers for Disease Control and Prevention: Gamma hydroxy butyrate use—New York and Texas, 1995–96. JAMA 277:1511, 1997

Centers for Disease Control and Prevention: Adverse events associated with ingestion of gamma-butyrolactone—Minnesota, New Mexico, and Texas, 1998–1999. MMRW Morb Mortal Wkly Rep 48:137–140, 1999

Chatlos JC: Recent trends and a developmental approach to substance abuse in adolescents. Child Adolesc Psychiatr Clin N Am 5:1–27, 1996

Chin RL: A case of severe withdrawal from gamma -hydroxybutyrate. Ann Emerg Med 37:551–552, 2001

Chin RL, Sporer KA, Cullison B, et al: Clinical course of gamma-hydroxybutyrate overdose. Ann Emerg Med 31:716–722, 1998

Colombo G, Agabio R, Lobina C, et al: Cross-tolerance to ethanol and gamma-hydroxybutyric acid. Eur J Pharmacol 273:235–238, 1995

Cook PA, Clark P, Bellis MA, et al: Re-emerging syphilis in the UK: a behavioral analysis of infected individuals. Commun Dis Public Health 4:253–258, 2001

Craig K, Gomez HF, McManus JL, et al: Severe gamma-hydroxybutyrate withdrawal: a case report and literature review. J Emerg Med 18:65–70, 2000

Curran HV, Travill RA: Mood and cognitive effects of +/− 3,4 methylenedioxymethamphetamine (MDMA, 'ecstasy'): week-end 'high' followed by a mid-week low. Addiction 92:821–831, 1997

Dyer JE, Roth B: In reply (letter). Ann Emerg Med 38:606, 2001

Dyer JE, Roth B, Hyma BA: Gamma-hydroxybutyrate withdrawal syndrome. Ann Emerg Med 37:147–53, 2001

Fadda F, Columbo G, Mosca E, et al: Suppression by gamma-hydroxybutyric acid of ethanol withdrawal syndrome in rats. Alcohol Alcohol 24:447–451, 1989

Fine J, Finestone SC. Sensory disturbances following ketamine anesthesia: recurrent hallucinations. Anesth Analg 52:428–430, 1973

Freese TE, Miotto K, Reback CJ: The effects and consequences of selected club drugs. J Subst Abuse Treat 23:151–156, 2002

Friedman J, Westlake R, Furman M: 'Grievous bodily harm': gamma hydroxybutyrate abuse leading to Wernicke-Korsakoff syndrome. Neurology 46:469–471, 1996

Gallimberti L, Ferri M, Ferrara SD, et al: Gamma-hydroxybutyric acid in the treatment of alcohol dependence: a double-blind study. Alcohol Clin Exp Res 16:673–676, 1992

Gallimberti L, Spella MR, Soncini CA, et al: Gamma-hydroxybutyric acid in the treatment of alcohol and heroin dependence. Alcohol 20:257–262, 2000

Galloway GP, Frederick SL, Staggers FE Jr, et al: Gamma-hydroxybutyrate: an emerging drug of abuse that causes physical dependence. Addiction 92:89–96, 1997

Galloway GP, Frederick-Osborne SL, Seymour R, et al: Abuse and therapeutic potential of gamma-hydroxybutyric acid. Alcohol 20:263–269, 2000

Gerra G, Caccavari R, Fontanesi B, et al: Flumazenil effects on growth hormone response to gammahydroxybutyric acid. Int Clin Psychopharmacol 9:211–215, 1994

Gessa G, Vargiu L, Crabai F, et al: Selective increase of brain dopamine induced by gamma-hydroxybutyrate. Life Sci 5:1921–1930, 1966

Gessa GL, Agabio R, Lobina C, et al: Mechanism of the antialcohol effect of gamma-hydroxybutyric acid. Alcohol 20:271–276, 2000

Gobaille S, Schleef C, Hechler V, et al: Gamma-hydroxybutyrate increases tryptophan availability and potentiates serotonin turnover in rat brain. Life Sci 70:2101–2112, 2002

Godschalk M, Dzoljic M, Bonta I: Slow wave sleep and a state resembling absence epilepsy induced in the rat by gamma-hydroxybutyrate. Eur J Pharmacol 44:105–111, 1977

Gouzoulis-Mayfrank E, Daumann J, Tuchtenhagen F, et al: Impaired cognitive performance in drug free users of recreational ecstasy (MDMA). J Neurol Neurosurg Psychiatry 68:719–725, 2000

Hall J, Maxwell J: Patterns and Trends of GHB, GBL, and 1,4BD Abuse. Austin, TX, Texas Commission on Drug and Alcohol Abuse, 2000. Avalable at: http://www.tcada.state.tx.us/research/presentation/Patterns_trends_GHB/sld001.htm. Accessed March 20, 2003.

Harries DP, De Silva R: "Ecstasy" and intracerebral haemorrhage. Scott Med J 37:150–152, 1992

Hatzidimitriou G, McCann UD, Ricaurte GA: Altered serotonin innervation patterns in the forebrain of monkeys treated with (+/–)3,4-methylenedioxymethamphetamine seven years previously: factors influencing abnormal recovery. J Neurosci 19:169–172, 1999

Hernandez M, McDaniel CH, Costanza CD, et al: GHB-induced delirium: a case report and review of the literature of gamma hydroxybutyric acid. Am J Drug Alcohol Abuse 24:179–183, 1998

Hodges B, Everett J: Acute toxicity from home-brewed gamma hydroxybutyrate. J Am Board Fam Prac 11:154–157, 1998

Howard SG, Feigenbaum JJ: Effect of gamma-hydroxybutyrate on central dopamine release in vivo: a microdialysis study in awake and anesthetized animals. Biochem Pharmacol 53:103–110, 1997

Itzhak Y, Ali SF: Repeated administration of gamma-hydroxybutyric acid (GHB) to mice: assessment of the sedative and rewarding effects of GHB. Ann N Y Acad Sci 965:451–60, 2002

Jerrard DA: "Designer drugs": a current perspective. J Emerg Med 8:733–741, 1990

Johnston LD, O'Malley PM, Bachman JG: Monitoring the Future National Results on Adolescent Drug Use: Overview of Key Findings, 2001 (NIH Publ No 02-5105). Bethesda, MD, National Institute on Drug Abuse, 2002

Jonas MM, Graeme-Cook FM: Case 6–2001: a 17-year-old girl with marked jaundice and weight loss. N Engl J Med 344:591–599, 2001

Kemmel V, Taleb O, Andriamampandry C, et al: Gamma-hydroxybutyrate receptor function determined stimulation of rubidium and calcium movements from NCB-20 neurons. Neuroscience 116:1021–1031, 2003

Kissin W, Ball J: The DAWN Report: Club Drugs, 2001 Update. Rockville, MD, Substance Abuse and Mental Health Services Administration, Oct 2002. Available at: http://www.oas.samhsa.gov/2k2/DAWN/clubdrugs2k1.pdf. Accessed April 11, 2003.

Koesters SC, Rogers PD, Rajasingham CR: MDMA ("ecstasy") and other "club drugs": the new epidemic. Pediatr Clin N Am 49:415–433, 2002

Krystal JH, Karper LP, Siebyl JP, et al: Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans: psychotmimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry 51:199–214, 1994

Lahti AC, Koffel B, LaPorte D, et al: Subanesthetic doses of ketamine stimulate psychosis in schizophrenia. Neuropsychopharmacology 13:9–19, 1995

Lammers GJ, Arends J, Declerck AC, et al: Gammahydroxybutyrate and narcolepsy: a double-blind placebo-controlled study. Sleep 16:216–220, 1993

Lester SJ, Baggott M, Welm S, et al: Cardiovascular effects of 3,4-methylenedioxymethamphetamine: a double-blind, placebo-controlled trial. Ann Intern Med 113:969–973, 2000

Levy MI, Davis BM, Mohs RC, et al: Gamma-hydroxybutyrate in the treatment of schizophrenia. Psychiatry Res 9:1–8, 1983

Li J, Stokes SA, Woeckener A: A tale of novel intoxication: seven cases of gamma-hydroxybutyric acid overdose. Ann Emerg Med 31:723–728, 1998a

Li J, Stokes SA, Woeckener A: A tale of novel intoxication: a review of the effects of gamma-hydroxybutyric acid with recommendations for management. Ann Emerg Med 31:729–736, 1998b

Lo JN, Cumming JF: Interaction between sedative premedicants and ketamine in man in isolated perfused rat livers. Anesthesiology 43:307–312, 1975

Maitre M: The gamma-hydroxybutyrate signaling system in brain: organization and functional implications. Prog Neurobiol 51:337–361, 1997

Maitre M, Andriamampandry C, Kemmel V, et al: Gamma-hydroxybutyric acid as a signaling molecule in brain. Alcohol 20:277–283, 2000

Mamelak M: Gamma-hydroxybutyrate: an endogenous regulator of energy metabolism. Neurosci Biobehav Rev 13:187–198, 1989

McCann UD, Szabo Z, Scheffel U, et al: Positron emission tomographic evidence of toxic effect of MDMA ("ecstasy") on brain serotonin neurons in human beings. Lancet 352:1433–1437, 1998

McCann UD, Eligulashvili V, Ricaurte GA: +/− 3,4-Methylenedioxymethamphetamine ('ecstasy')–induced serotonin neurotoxicity: clinical studies. Neuropsychobiology 42:11–16, 2000

McDaniel CH, Miotto KA: Gamma hydroxybutyrate (GHB) and gamma butyrolactone (GBL) withdrawal: five case studies. J Psychoactive Drugs 33:143–149, 2001

McGuire PK, Cope H, Fahy TA: Diversity of Psychopathology associated with use of 3,4-methylenedioxymethamphetamine ('Ecstasy'). Br J Psychiatry 165:391–395, 1994

Miotto K, Roth B: GHB Withdrawal. Austin, TX, Texas Commission on Alcohol and Drug Abuse, 2001. Available at: http://www.tcada.state.tx.us/research/populations/GHB_Withdrawal.pdf. Accessed February 28, 2003.

Miotto K, Darakjian J, Basch J, et al: Gamma-hydroxybutyric acid: patterns of use, effects and withdrawal. Am J Addict 10:232–241, 2001

Moncini M, Masini E, Gambassi F, et al: Gamma-hydroxybutyric acid and alcohol-related syndromes. Alcohol 20:285–291, 2000

Morgan MJ: Memory deficits associated with recreational use of "ecstasy" (MDMA). Psychopharmacology (Berl) 141:30–36, 1999

Mullins ME, Fitzmaurice SC: Lack of efficacy of benzodiazepines in treating gamma hydroxybutyrate withdrawal. J Emerg Med 20:418–420, 2001

Mycyk MB, Wilemon C, Aks SE: Two cases of withdrawal from 1,4-butanediol use. Ann Emerg Med 38:345–346, 2001

National Institute on Drug Abuse: All About GBH Report. Rockville, MD, National Institute on Drug Abuse, 2000. Available at: http://www.drugabuse.gov/whatsnew/meetings/GHB/default.html. Accessed March 12, 2003.

Nelson T, Kaufman E, Kline J, et al: The extraneuronal distribution of gamma-hydroxybutyrate. J Neurochem 37:1345–1348, 1981

Nicholson KL, Balster RL GHB: a new and novel drug of abuse. Drug Alcohol Depend 63:1–22, 2001

Nimmerrichter AA, Walter H, Gutierrez-Lobos KE, et al: Double-blind controlled trial of gamma-hydroxybutyrate and clomethiazole in the treatment of alcohol withdrawal. Alcohol 37:67–73, 2002

Olivera AA, Kiefer MW, Manley NK: Tardive dyskinesia in psychiatric patients with substance abuse disorders. Am J Drug Alcohol Abuse 16:57–66, 1990

Palatini P, Tedeschi L, Frison G, et al: Dose-dependent absorption and elimination of gamma-hydroxybutyric acid in healthy volunteers. Eur J Clin Pharmacol 45:353–356, 1993

Parrott AC, Lasky J: Ecstasy (MDMA) effects upon mood and cognition: before, during and after a Saturday night dance. Psychopharmacology (Berl) 139:261–268, 1998

Pederson W, Skrondal A: Ecstasy and new patterns of drug use: a normal population study. Addiction 94:1695–1706, 1999

Reich DL, Silvay G: Ketamine: an update on the first twenty-five years of clinical experience. Can J Anaesth 36:186–197, 1989

Ricaurte GA, Forno LS, Wilson MA, et al: (+/-)3,4-Methylenedioxymethamphetamine selectively damages central serotonergic neurons in nonhuman primates. JAMA 260:51–55, 1988

Ricaurte GA, Yuan J, McCann UD: +/− 3,4-Methylenedioxymethamphetamine ('ecstasy')-induced serotonin neurotoxicity: studies in animals. Neuropsychobiology 42:5–10, 2000

Rodgers J: Cognitive performance amongst recreational users of "ecstasy." Psychopharmacology (Berl) 151:19–24, 2000

Ross T: Gamma hydroxybutyrate overdose: two cases illustrate the unique aspects of this dangerous recreational drug. J Emerg Nurs 21:374–376, 1995

Roth RH, Giarman NJ: Gamma-butyrolactone and gamma-hydroxybutyric acid, I: distribution and metabolism. Biochem Pharmacol 15:1333–1348, 1966

Roth RH, Giarman NJ: Evidence that central nervous system depression by 1,4-butanediol is mediated through a metabolite, gamma-hydroxybutyrate. Biochem Pharmacol 17:735–739, 1968

Scharf MB, Lai AA, Branigan B, et al: Pharmacokinetics of gammahydroxybutyrate (GHB) in narcoleptic patients. Sleep 21:507–514, 1998

Schwartz RH, Miller NS: MDMA (ecstasy) and the rave: a review. Pediatrics 100:705–708, 1997

Scrima L, Hartman PG, Johnson FH, et al: The effects of gamma-hydroxybutyrate on the sleep of narcolepsy patients: a double blind study. Sleep 13:479–490, 1990

Sériès F, Sériès I, Cormier Y: Effects of enhancing slow-wave sleep by gamma-hydroxybutyrate on obstructive sleep apnea. Am Rev Respir Dis 145:1378–1383, 1992

Shannon M: Methylenedioxymethamphetamine (MDMA, "ecstasy"). Pediatr Emerg Care 16:377–380, 2000

Sharma AN, Lombardi MH, Illuzzi FA, et al: Management of gamma-hydroxybutyrate withdrawal. Ann Emerg Med 38:605–607, 2001

Sherlock K, Wolff K, Hay AW, et al: Analysis of illicit ecstasy tablets: implications for clinical management in the accident and emergency department. Emerg Med J 16:194–197, 1999

Sivilotti ML, Burns MJ, Aaron CK, et al: Pentobarbital for severe gamma-butyrolactone withdrawal. Ann Emerg Med 38:660–665, 2001

Snead OC 3rd, Furner R, Liu CC: In vivo conversion of gamma-aminobutyric acid and 1,4-butanediol to gamma-hydroxybutyric acid in rat brain: studies using stable isotopes. Biochem Pharmacol 38:4375–4380, 1989

Solhkhah R, Wilens TE: Pharmacotherapy of adolescent alcohol and other drug use. Alcohol Health Res World 22:122–125, 1998

Solhkhah R, Finkel J, Hird S: Possible risperidone-induced visual hallucinations. J Am Acad Child Adolesc Psychiatry 39:1074–1075, 2000

Solhkhah R, Wilens TE, Prince JB, et al: Bupropion sustained release for substance abuse, ADHD, and mood disorders in adolescents (NR31), in New Research Abstracts, Annual Meeting of the American Psychiatric Association. Washington, DC, American Psychiatric Association, 2001

Sprague JE, Everman SL, Nichols DE: An integrated hypothesis for the serotonergic axonal loss induced by 3,4-methylenedioxymethamphetamine. Neurotoxicology 19:427–441, 1998

Substance Abuse and Mental Health Services Administration: Emergency Department Trends From the Drug Abuse Warning Network, Final Estimates 1994–2001, DAWN Series D-21 (DHHS Publ No SMA 02–3635). Rockville, MD, Substance Abuse and Mental Health Service Administration, 2002

Takahara J, Yunoki S, Yakushiji W, et al: Stimulatory effects of gamma-hydroxybutyric acid on growth hormone and prolactin release in humans. J Clin Endocrinol Metab 44:1014–1017, 1977

Tucker GT, Lennard MS, Ellis SW, et al: The demethylation of methylenedioxymethamphetamine ("ecstasy") by debrisoquine hydroxylase (CYP2D6). Biochem Pharmacol 47:1151–1156, 1994

Verkes RJ, Gilsman HJ, Pieters MS, et al: Cognitive performance and serotonergic function in users of ecstasy. Psychopharmacology (Berl) 153:196–202, 2001

Weiner AL, Vieira L, McKay CA, et al: Ketamine abusers presenting to the emergency department: a case series. J Emerg Med 18:447–451, 2000

Weir E: Raves: a review of the culture, the drugs and the prevention of harm. CMAJ 162: 1843–1848, 2000

White PF, Way WL, Trevor AJ: Ketamine: its pharmacology and therapeutic uses. Anesthesiology 56:119–136, 1982

Williams H, Dratcu L, Taylor R, et al: "Saturday night fever:" ecstasy related problems in a London accident and emergency department. Emerg Med J 15:322–326, 1998

Winters WD, Kott KS: Continuum of sedation, activation and hypnosis or hallucinosis: a comparison of low dose effects of pentobarbital, diazepam or gamma-hydroxybutyrate in the cat. Neuropharmacology 18:877–884, 1979

Zvosec DL, Smith SW, McCutcheon JR, et al: Adverse events, including death, associated with use of 1,4-butanediol. N Engl J Med 344:87–94, 2001

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8

Inhalants

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Historical Aspects

Evidence of the use of inhalants to experience their psychotropic effects can be found in the ancient Greek world (Carroll 1977). Preble and Laury (1967, p. 271) described an example of this use as follows:

> At Delphi, the Pythia sat on a tripod above a cleft in the rocks and inhaled cold vapors emanating from inside the earth, which induced in her an ecstatic alteration of mind. In this altered state, she uttered mystical observations in the presence of the Delphi Prophet, who translated them into oracular pronouncements.

Nonetheless, it was not until 1793 that the English scientist and clergyman Joseph Priestley discovered the first modern inhalant compound, the anesthetic gas nitrous oxide. This gas was widely used for recreational purposes by the English aristocracy in private parties, and traveling charlatans expanded

its use by offering it to the general public (Sharp 1992). Because of its euphorigenic effects, this compound acquired the popular name of "laughing gas" (Sharp 1992).

The discovery of ether and chloroform increased the number of anesthetics that were susceptible to abuse by inhalation. Although the anesthetic properties of ether were not discovered until 1841, beginning at the end of the eighteenth century, it became known that this compound was capable of inducing euphoria and hallucinations (Bird 1881; Delteil et al. 1974; Follin and Rousselot 1980). In 1885, a detailed description of the clinical picture of ether intoxication was provided; three phases were identified: overexcitement, aggressiveness, and sleepiness (Delteil et al. 1974; Deniker et al. 1972; Follin and Rousselot 1980). At the end of the nineteenth century and the beginning of the twentieth century, ether was frequently inhaled and/or ingested by people with alcoholism as an alternative to more expensive alcoholic beverages (Deniker et al. 1972; von Keyserlingk 1947). Similarly, the addictive properties of chloroform have been known for many years (Payne 1998). During the nineteenth century, chloroform was frequently inhaled for its pleasurable effects, as well as to heighten sexual pleasure and sexual performance. Unfortunately, the dangers of the drug were not well known, and death or severe adverse effects such as liver damage were common outcomes among those who abused this substance (Payne 1998).

In 1867, Thomas Lauder Brunton discovered amyl nitrite, a drug with vasodilatory properties that, although used for the treatment of symptoms of acute coronary occlusion, was also thought to enhance sexual performance. More recently, nitrites have been widely used for recreational purposes, particularly by homosexuals during the period of the 1950s to 1970s (Haverkos et al. 1994). Despite the fact that products containing butyl nitrite, propyl nitrite, and related compounds were outlawed in 1991, products containing a variety of other nitrites continue to be widely available in the United States.

It has been suggested that the current period of widespread abuse of inhalants began in the 1920s as a consequence of the rapid growth of industrial society and the wide availability of substances that can be inhaled, such as gasoline, glues, solvents, and nitrites. Subsequently, inhalant abuse increased after World War II, with workers in industries with high occupational exposure to inhalants being the first group to be at high risk to develop these problems (Sharp 1992).

Epidemiology

The abuse of inhalants is currently a widespread problem, particularly among adolescents and children. Approximately 3.0% of U.S. children have used inhalants by the time they reach fourth grade (Johnston et al. 2003). In 2002, 10.5% of adolescents in the United States reported lifetime use of inhalants, with younger children having used these substances more frequently than their older counterparts (Johnston et al. 2003). The prevalence of inhalant use reaches a peak among eighth graders, who report the highest rate of use. Rates of inhalant use are higher for girls than for boys in grade 8. However, in grades 10 through 12 and after high school, boys again show a higher rate of inhalant abuse (Johnston et al. 2003). Despite the fact that inhalant use disorders typically affect the young, these problems can become chronic and can extend into adulthood.

People who abuse inhalants are found in both urban and rural settings. Adverse socioeconomic conditions, rather than racial or cultural factors per se, account for most reported ethnic differences in rates of inhalant abuse. Native American youths living on reservations typically have higher rates of inhalant abuse than youths both in the general population and among Native Americans who do not live on reservations (Substance Abuse and Mental Health Services Administration 1996).

According to the Monitoring the Future study (Johnston et al. 2003), inhalant abuse among U.S. tenth and twelfth graders declined in 2003, continuing an apparent gradual decline that began in 1996. However, despite this decline, past-year inhalant use among eighth graders increased between 2000 and 2003 (Johnston et al. 2003). Furthermore, from 2003 to 2004, lifetime use of inhalants in this age group jumped from 15.8 to 17.3%, and for the first time in recent years, lifetime use of inhalants also increased among children in grades 9 and 10 (Johnston et al. 2004). This increase appears to be explained by the fact that the number of young people who believed that the use of inhalants is dangerous declined. Epidemiological studies also have suggested that nitrite abuse is an independent risk factor for HIV seropositivity and for Kaposi's sarcoma (Haverkos et al. 1985), the most frequent form of cancer found among patients with AIDS. However, the mechanism by which chronic nitrite inhalation contributes to these diseases is not known.

Types of Inhalants

The range of inhalants abused by humans includes a broad and pharmacologically heterogeneous group of substances that are easily available to the general population and that commonly exist in household and industrial solvents, glues, propellants, lighters, and art and office supplies (see Table 8–1). These substances share a common route of self-administration by inhalation, in contrast to other drugs of abuse (e.g., nicotine, cocaine, heroin) (Sharp 1992). Inhalants can be classified as volatile solvents, nitrites, and anesthetics.

Volatile Solvents

Volatile solvents are fluids or gases contained in a wide variety of products (e.g., gasoline, paint thinner, butane gas) that have significant concentrations of aliphatic, aromatic, or halogenated hydrocarbons, which vaporize at room temperature. Because of their rapid absorption in the lungs, volatile solvents exert a rapid intoxicating effect.

Efforts to identify the specific compounds responsible for the psychotropic effects of volatile solvents are complicated by the fact that many of these products contain more than one potentially psychoactive ingredient. Another factor obscuring the identity of the psychoactive ingredients of these agents is that patients addicted to these compounds frequently seek the effects not of the product's primary ingredient but of a secondary ingredient such as the propellant gas (e.g., nitrous oxide). To date, the best-studied psychoactive compounds identified in volatile solvents include toluene, 1,1,1-trichloroethane, and trichloroethylene. However, other less well studied compounds, such as benzene, acetone, and methanol, also appear to have significant psychoactive effects.

Nitrites

Nitrite compounds are often known as "poppers" because of the popping noise produced when the capsules containing them are crushed between the fingers. Both amyl nitrite and butyl nitrite are yellowish liquids that evaporate at room temperature. These compounds are distributed under variety of names and are contained in a range of products, such as air fresheners. Isoamyl nitrite is also available in the United States by prescription. Currently, the primary indication for isoamyl nitrite is for the treatment of cyanide poi-

Table 8–1. Products that may be used as inhalants

Volatile solvents	Nitrites	Anesthetics
Solvents and gases	**Amyl, butyl, alkyl nitrites**	**Nitrous oxide**
Paint thinner/remover	Air fresheners	Dessert topping sprays[a]
Typing correction fluid	Fuel-injection fluid	Balloons
Lighter fluid	Nitrite products sold by sex shops and on the Internet[b]	High-pressured containers
Gasoline		
Fuel gas	Prescription drug[c]	
Nail polish remover		**Other anesthetics**
		Ether
Adhesives		Chloroform
Glue		Halothane
Rubber and PVC cement		
Cleaning solvents		
Degreaser		
Spot remover		
Dry cleaning fluid		

Note. PVC=polyvinylchloride.
[a]Whipped cream or "whippets."
[b]For example, "Liquid Gold," "Ram," "Thrust," "poppers," "rush."
[c]Isoamyl nitrite.

soning and for the diagnostic evaluation of mitral regurgitation and ventricular septal defects; occasionally, this compound is also prescribed for the treatment of angina pectoris.

Anesthetics

Within the category of anesthetics, the most frequently abused substance is nitrous oxide, a colorless and nearly odorless gas. It is a dissociative anesthetic and the only inhalational anesthetic agent that is a true gas, not a vapor. Nitrous oxide can produce a relatively shallow anesthesia, useful in dentistry and during childbirth, but it can also induce a deeper level of narcosis when used in combination with other anesthetics during general surgery. Nitrous oxide is also known as laughing gas because it produces a state of euphoria, giggling, and laughter.

Other anesthetics susceptible to abuse, such as ether and chloroform, have received far less attention, because they are considered to be less commonly abused substances. Nonetheless, when inhaled, ether and chloroform are also rapidly absorbed and distributed in the central nervous system (CNS), inducing a rapid euphoria. Ether and chloroform inhalation is facilitated by the fact that they have a low boiling point (i.e., approximately 34°C) (Delteil et al. 1974).

Pharmacokinetics

Volatile Solvents

Because of their high lipid solubility, the active compounds in volatile solvents readily pass through cellular membranes and are rapidly distributed into all fatty tissues. From a pharmacokinetic perspective, toluene is the best-characterized active compound in volatile solvents. When inhaled, toluene is rapidly absorbed by the lungs, with approximately 50% of toluene vapor mixed with air being taken up through the alveoli (Lof et al. 1993). With continuous exposure, toluene saturates the blood and brain in about 60 minutes (Benignus et al. 1981, 1984). Four hours after inhalation, approximately 65% of the toluene that is absorbed is excreted in urine as hippuric acid; 20 hours later, the cumulative excretion of toluene in urine can be 80% (Lof et al. 1993). Although the concentration of toluene in blood appears to reflect its concentration in the air that is breathed, the toluene level in peripheral blood may not accurately reflect its concentration within the CNS, where levels tend to be higher. This difference may be explained by toluene's high affinity for lipids and, in consequence, its tendency to concentrate and be distributed predominantly in the abundant cerebral lipids of white matter (Gerasimov et al. 2002).

Positron emission tomography studies using ^{11}C-toluene in nonhuman primates and mice showed a rapid uptake of radioactivity into striatal and frontal brain regions (Gerasimov et al. 2002). Maximal uptake of the radiotracer by these structures occurred 1–4 minutes after intravenous administration. Subsequently, clearance of the radiotracer from the striatal and frontal areas occurred rapidly, with a clearance half-life from peak uptake of 10–20 minutes. Radiotracer clearance from white matter appears to be slower

than that from the striatum and frontal regions, a finding that is consistent with toluene's high affinity for lipids and the high lipid content of white matter. These findings suggest that white matter is more susceptible to the toxic effects of toluene as a consequence of longer exposure times. Concurrent findings in rodents showed similar radiotracer kinetics of toluene, with predominant renal and hepatic excretion (Gerasimov et al. 2002).

Nitrites

Little is known regarding the pharmacokinetic properties of volatile nitrites in humans, particularly isobutyl nitrite and its primary metabolite, isobutyl alcohol. In rodents, after an intravenous infusion of isobutyl nitrite, blood concentrations peaked rapidly and then declined, with a half-life of 1.4 minutes and blood clearance rate of 2.9 L/min/kg (Kielbasa and Fung 2000). Approximately 98% of isobutyl nitrite is metabolized rapidly to isobutyl alcohol, concentrations of which also decline rapidly, with a half-life of 5.3 minutes. Bioavailability of inhaled isobutyl nitrite at a concentration of 300–900 ppm is estimated to be 43%.

Anesthetics

Nitrous oxide is rapidly absorbed through inhalation, and it is distributed predominantly in blood with a blood/gas partition coefficient of 0.5 (Stenqvist 1994). It is rapidly eliminated through the lungs, with small amounts being eliminated through the skin (Stenqvist 1994).

Following inhalation, ether and chloroform are also rapidly absorbed into the bloodstream and rapidly transferred to fatty tissues and the CNS (Baselt 1997; Harbison 1998; Reynolds 1982). Ether undergoes limited metabolism in humans (Haggart 1924), with carbon dioxide (CO_2) and acetaldehyde believed to be minor metabolites (Aune et al. 1978; Price and Dripps 1975). Approximately 90% of ether is eliminated unchanged in expired air (Haggart 1924), with the rest excreted in urine and perspiration (Haggart 1924). Similarly, chloroform is eliminated primarily by the lungs (Schroeder 1965), with approximately 43% exhaled unchanged (Baselt 1997) and 4%–5% exhaled as CO_2 (Arena and Drew 1986). Only 2% of inhaled chloroform is excreted in urine (Arena and Drew 1986). The average elimination half-life of chloroform is 1.5 hours, and one of its main metabolites is diglutathionyl dithiocar-

bonate, a compound that is associated with glutathione depletion in the liver and kidneys. This reaction is believed to result in severe hepatic and renal necrosis (Laurenzi et al. 1987).

Summary

Toluene, volatile nitrites, and anesthetics, like other substances of abuse such as cocaine, nicotine, and heroin, are characterized by rapid absorption, rapid entry into the brain, high bioavailability, a short half-life, and a rapid rate of metabolism and clearance (Gerasimov et al. 2002; Pontieri et al. 1996, 1998). Because these pharmacokinetic parameters are associated with the ability of addictive substances to induce positive reinforcing effects, it appears that the pharmacokinetic features of inhalants contribute to their high abuse liability among susceptible individuals.

Behavioral Pharmacology of Inhalants in Animals and Humans

Reinforcing Effects

Like other substances of abuse, inhalants are readily self-administered by humans and laboratory animals (Yanagita et al. 1970). When implanted with a nasal catheter through which a volume of solvent vapors (i.e., lacquer thinner, ether, and chloroform) was delivered after lever pressing, rhesus monkeys initiated and maintained self-administration in excess of 100 deliveries during a 14- to 25-day period (Yanagita et al. 1970). In these monkeys, the frequency of self-administration of toluene was positively associated with toluene vapor concentrations, with the highest frequency of self-administration occurring at the highest concentration of toluene vapors (i.e., 1%). Similarly, frequent self-administration by monkeys of other inhalants, such as nitrous oxide, has also been reported (Wood et al. 1977).

In humans, a comparative examination of the positive reinforcing effects of solvents showed that among inhalant-dependent subjects, solvents induced a more intense sensation of pleasant feelings than that induced by alcohol and nicotine in subjects addicted to these substances (Kono et al. 2001). Solvent-dependent subjects reported pleasant feelings comparable to those reported by stimulant-dependent subjects after use of methamphetamine. However,

negative reinforcing effects, measured by reports of feelings of relief after inhalant use, were comparable in intensity to those reported by alcoholic subjects after drinking alcohol (Kono et al. 2001).

Although not systematically studied, the reinforcing effects of nitrite inhalation in humans appear to be significant and to be associated with feelings of euphoria. In a study involving 173 adolescents and young adults enrolled in a substance abuse treatment program, 13% of the subjects reported having used isobutyl nitrite 10 or more times and 4% had used the substance 50 or more times (Schwartz and Peary 1986). On the other hand, 44% of the subjects in this sample reported having used isobutyl nitrite only once, finding the experience unpleasant. These findings suggest that there is a subset of individuals who are particularly susceptible to the reinforcing effects of nitrite inhalation.

Similarly, inhalation of general anesthetics such as nitrous oxide, ether, and chloroform appears to exert significant reinforcing effects in humans (Delteil et al. 1974; Deniker et al. 1972; Dohrn et al. 1993). In a double-blind, placebo-controlled study of healthy volunteers that compared subjective effects of nitrous oxide and 100% oxygen in a free-choice procedure, individuals who preferred nitrous oxide reported greater ratings of drug liking and wanting to inhale the drug again (Walker and Zacny 2002). Subjects' ratings of the peak effect of nitrous oxide were dose related, although there was variation in the degree to which individuals liked nitrous oxide. In a study examining the extent to which individuals like nitrous oxide, 75% ($n=12$) reported liking the 40% concentration, whereas 25% were neutral ($n=1$) or did not like it ($n=3$) (Dohrn et al. 1992). In summary, nitrous oxide has robust effects on mood, with variability in the extent to which subjects like the drug's effects (Dohrn et al. 1992). In addition, there is some evidence that the reinforcing effects of nitrous oxide are modulated by history of alcohol drinking. Individuals with a history of moderate drinking appear to have a greater preference for nitrous oxide inhalation than do individuals with a history of light or no drinking (Cho et al. 1997).

Effects on Motor Activity

Similar to alcohol and other CNS depressants, toluene has a biphasic dose-effect curve for the motor activity of rodents (Hinman 1987; Riegel and

French 1999). At low concentrations (i.e., 2,000–3,000 ppm), toluene increases spontaneous locomotor activity. At higher concentrations (i.e., 10,000–15,000 ppm), toluene decreases locomotor activity and produces ataxia and loss of the righting reflex (Bushnell et al. 1985; Hinman 1987; Saito and Wada 1993; Yavich and Zvartau 1994). Repeated exposure produces sensitization to toluene-induced enhancement of motor activity (Himnan 1984; Moser and Balster 1981). It is interesting to note that repeated exposure to toluene also enhances cocaine-induced increases in the locomotor activity of rodents, suggesting that behavioral and neurochemical cross-sensitization exists between these two drugs (Beyer et al. 2001). A biphasic dose-response curve for motor activity has also been described with the experimental administration of trichloroethane, amyl nitrite, and nitrous oxide (Balon et al. 2003b; Bowen and Balster 1998). The biphasic dose-response curve for motor activity has not yet been described in humans. However, in a study examining the level of motor activity after solvent inhalation, inhalant-dependent subjects reported hyperactivity comparable to that reported by alcohol-dependent subjects after alcohol ingestion but not of the magnitude described by stimulant-dependent subjects after methamphetamine use (Kono et al. 2001).

Tolerance

Tolerance is characterized by reduced responsiveness to the initial effects of a drug after repeated exposure or reduced responsiveness to a related compound (i.e., cross-tolerance). Animal studies have not provided conclusive evidence of tolerance to the effects of the centrally active compounds in toluene or trichloroethane (Moser and Balster 1981; Moser et al. 1985). Observations in humans, on the other hand, have documented pronounced tolerance among subjects who chronically inhale substances with high concentrations of toluene (Glaser and Massengale 1962; Press and Done 1967) and butane (Evans and Raistrick 1987). Kono et al. (2001) showed that tolerance to the reinforcing effects of solvents is comparable to that conditioned by nicotine but less intense than that reported with alcohol or methamphetamine use.

No systematic studies of tolerance to the reinforcing effects of inhaled nitrites have been reported. However, anecdotal observations in workers with high exposure to nitrites have suggested that tolerance to the subjective effects of this compound occurs after a few days of exposure (Marsh and Marsh

2000). On the other hand, clinical and laboratory studies in humans have demonstrated the development of tolerance to the amnestic and analgesic effects of nitrous oxide and isoflurane (see Arnold et al. 1993; Avramov et al. 1990; Rupreht et al. 1985; Whitwam et al. 1976) and, in the case of ether or chloroform, to its reinforcing effects (Krenz et al. 2003). No studies have shown the development of tolerance to the reinforcing effects of nitrous oxide.

Withdrawal

Withdrawal symptoms, including nausea, tremor, diaphoresis, insomnia, body aches, anxiety, irritability, and agitation, have been described among chronic solvent abusers (Evans and Raistrick 1987; Knox and Nelson 1966). Subjective symptoms experienced during solvent withdrawal, such as craving, anxiety, and restlessness, appear to be similar to those reported during nicotine withdrawal but less severe than those reported during alcohol or methamphetamine withdrawal (Kono et al. 2001). Although there are anecdotal reports of severe confusion resembling delirium during the early withdrawal phase from solvents (Merry and Zachariadis 1962; Nylander 1962), it is unclear the degree to which this clinical presentation was secondary to withdrawal from other substances, such as alcohol or sedatives.

Research in rodents has provided evidence of solvent withdrawal. Continuous exposure to toluene for 4 days and subsequent cessation produced an increase in handling-induced convulsions for at least 2 hours after cessation (Wiley et al. 2003). A similar pattern of trichloroethane administration to rodents produced pronounced withdrawal, which was worsened by the administration of the proconvulsant drug pentylenetetrazole and attenuated by reexposure to 2,000 ppm of toluene or the administration of alcohol, pentobarbital, or midazolam (Evans and Balster 1993).

Severe withdrawal symptoms, including insomnia, irritability, agitation, withdrawal seizures, and delirium, have been described in both mice and humans chronically exposed to the anesthetics nitrous oxide, ether, and isoflurane (Arnold et al. 1993; Delteil et al. 1974; Deniker et al. 1972; Harper et al. 1980; Smith et al. 1979; Tobias 2000). These symptoms were controlled with the administration of γ-aminobutyric acid (GABA)–ergic agents such as pentobarbital, midazolam, and diazepam (Arnold et al. 1993; Hughes et al. 1993).

No systematic studies have been conducted to examine withdrawal symptoms resulting from continuous exposure to nitrites. However, there are anecdotal reports that workers, after continuous exposure to these compounds, experienced a recurrent, generalized malaise called "Monday disease" when they returned to work after weekends during which they were not exposed (Nickerson 1970). Workers with this condition found relief by rubbing these substances on their skin or wearing work clothes impregnated with these substances (Schwartz 1946). In its worst form, this condition was also accompanied by coronary artery spasm leading to nonexertional ischemic cardiac pain and sudden death ("Sunday heart attack"), even among individuals with no demonstrable coronary artery disease (Needleman and Johnson 1980).

Summary

Despite the paucity of systematic studies in humans, the available evidence suggests that, like drugs such as alcohol, sedatives, and stimulants, inhalant drugs (i.e., solvents, general anesthetics, and nitrites) exert reinforcing effects and increase motor activity. Furthermore, with continuous use, these drugs appear to induce both tolerance and symptoms of withdrawal.

Effects of Inhalants on Specific Neurotransmitter Systems

Dopaminergic Effects

Evidence that dopaminergic neurotransmission mediates the reinforcing effects of toluene is provided by studies showing that the acute instillation of toluene in the striatum of rodents by microdialysis increases dopamine concentrations (Rea et al. 1984; Stengard et al. 1994). Similar to other drugs of abuse (DiChiara and Imperato 1988; French et al. 1997; Gessa et al. 1985), inhaled toluene initially stimulated and subsequently attenuated dopaminergic neuronal firing in the ventral tegmental area (VTA) (Riegel and French 1999). Low doses of toluene administered subchronically or chronically reduced dopamine turnover (Fuxe et al. 1982) and produced a persistent increase in D_2 receptor binding in the rat neostriatal complex (Hillefors-Berglund et al. 1993; von Euler et al. 1993). Administration of 6-hydroxydopamine to the nucleus accumbens (NAC), producing lesions in dopaminergic neurons, signif-

icantly attenuated toluene's locomotor stimulatory effects (Riegel et al. 2003). Consistent with this finding, pretreatment with remoxi-pride, a D_2 receptor antagonist that appears to bind preferentially to receptors in the NAC, significantly reduced toluene-induced hyperactivity by 57% (Riegel and French 1999).

There are few reports on the effects of nitrous oxide on dopaminergic neurotransmission. A study in mice showed that nitrous oxide inhalation produced a significant increase in locomotor activity that was antagonized in a dose-dependent fashion by the dopamine synthesis inhibitor α-methyl-*p*-tyrosine (Hynes and Berkowitz 1983). Moreover, administration of the D_2 antagonist haloperidol also reduced the locomotor activity induced by nitrous oxide (Hynes and Berkowitz 1983). These results suggest that excitatory effects induced by nitrous oxide may be also mediated by dopaminergic neurotransmission. However, other studies have reported that exposure to nitrous oxide resulted in decreased dopamine release by neurons in the striatum (Balon et al. 2002; Turle et al. 1998).

Finally, to our knowledge, no studies have examined the effects of nitrite inhalation on dopaminergic neurotransmission. However, some evidence suggests that nitric oxide (NO), the potent compound that mediates the vasodilatory effects of nitrites, also has important neuromodulatory effects in the CNS (Bredt and Snyder 1992). If NO is released in the CNS by nitrite inhalation, it is plausible that NO could mediate the euphorigenic and motor effects of nitrites by potently inhibiting dopamine uptake and enhancing dopaminergic neurotransmission in the mesolimbic reward circuit (Lonart and Johnson 1994). This mechanism has been shown to mediate some of the reinforcing effects of other drugs of abuse, such as cocaine (Collins and Kantak 2002; Pudiak and Bozarth 2002) and nicotine (Vleeming et al. 2002).

In summary, the reinforcing effects of toluene, nitrous oxide, and nitrites appear to be mediated by activation of the mesolimbic dopaminergic pathway, particularly in the VTA and the NAC. Acute and repeated administration of the majority of drugs susceptible to being abused activates the mesolimbic dopaminergic structures (Koob 1992). Increased locomotor activity in animal models of alcohol and drug addiction has been correlated with the increased dopamine activity in this circuit (Robinson and Berridge 1993; Wise and Bozarth 1987). These findings suggest that inhalants share with the majority of drugs of abuse a final common dopaminergic pathway mediating their abuse liability.

Glutamate/*N*-Methyl-D-Aspartate Receptor Effects

The glutamatergic neurotransmitter system may also mediate toluene's reinforcing effects by indirectly activating the mesolimbic dopaminergic reward pathway. It is been suggested that the effects of toluene on dopamine cell activity are similar to those of phencyclidine (PCP), a potent antagonist of *N*-methyl-D-aspartate (NMDA)–type glutamate receptors that has important hallucinatory and stimulant properties (Balster and Willetts 1996). Cruz et al. (1998) demonstrated that toluene abolishes NMDA receptor-stimulated currents in *Xenopus* oocytes, in a subunit-specific manner. However, toluene was not effective in altering kainate-type glutamate receptor-induced currents.

Other abused solvents, including trichloroethane (Cruz et al.1998), and nitrous oxide (Jevtovic-Todorovic et al. 1998; Mennerick et al. 1998) appear to be effective inhibitors of the NMDA receptor. Nitrous oxide also has neurotoxic effects similar to other NMDA receptor antagonists, such as PCP, ketamine, and MK801. Nitrous oxide inhibited ionic influx mediated by NMDA receptors in cultured rat hippocampal neurons (Jevtovic-Todorovic et al. 1998; Mennerick et al. 1998). In addition, nitrous oxide reversed the increase in striatal dopamine release induced by NMDA-receptor activation in the substantia nigra (Balon et al. 2003a). It has been hypothesized that blockade by toluene or nitrous oxide of NMDA receptors on GABA interneurons in the VTA, and the consequent removal of the inhibitory action of these neurons on dopaminergic neurons, may lead to enhanced dopamine cell firing in the VTA and subsequent activation of the dopaminergic reward pathway (Wang and French 1995).

Although, to our knowledge, the effects of inhalation of amyl nitrite or butyl nitrite on glutamatergic neurotransmission have not been studied, NO, the potent compound that mediates the peripheral effects of nitrites in blood vessels, if released in the CNS when nitrites are inhaled, may potentially affect the glutamatergic system. NO has been reported to act directly on the postsynaptic NMDA receptor, where it can increase or decrease NMDA-mediated currents and subsequent calcium influx (Aizenman et al. 1990; Dingledine et al. 1999; Manzoni et al. 1992).

Effects on Ligand-Gated Ion Channels

Inhalants appear to have significant effects on a superfamily of ligand-gated ion channels, including the $GABA_A$ receptor, the glycine receptor, the nico-

tinic acetylcholine receptor, and the serotonin 3 (5-HT_3) receptor. These receptor complexes are composed of five protein subunits surrounding a central ion pore. Each subunit has four transmembrane spanning domains and distinct binding sites for a variety of ligands (Ortells and Lunt 1995; Smith and Olsen 1995).

$GABA_A$ Effects

There are similarities between the biological actions of inhalants and those of alcohol and barbiturates (Bowen et al. 1996b). For example, acute administration of inhalants affects motor coordination (Moser and Balster 1981) and induces anxiolysis, whereas chronic administration is associated with physical dependence and withdrawal (Bowen et al. 1996a; Evans and Balster 1991, 1993). In addition, some inhalant drugs have anticonvulsant properties (Wood et al. 1984). Like other CNS-depressant agents, inhalants have biphasic effects on spontaneous locomotor activity in rodents, with increased activity seen at lower doses and diminished locomotion seen at higher doses (Gause et al. 1985; Kjellstrand et al. 1985).

The similar effects produced by administration of alcohol, sedatives, and inhaled drugs of abuse suggest that these compounds may have overlapping mechanisms of action. Previous work has established that neurotransmitter-activated ion channels, particularly the $GABA_A$ receptor, are primary sites of action of alcohol and volatile anesthetic agents. For example, as with alcohol (Mihic 1999), pharmacological concentrations of volatile anesthetic agents potentiate $GABA_A$-mediated currents (Franks and Lieb 1994). Similarly, it is known that toluene treatment alters extracellular concentrations of GABA in the cerebellum, hippocampus (Ikeuchi et al. 1993), and globus pallidus (Stengard and O'Connor 1994). Consistent with the hypothesis that inhalants affect $GABA_A$ receptor function, toluene and trichloroethane enhanced bicuculline-sensitive GABA-mediated synaptic currents in rat CA1 hippocampal neurons (Beckstead et al. 2000; Weiner et al. 1997). Toluene, trichloroethylene, and trichloroethane also increased ligand-gated currents in $GABA_A$ α_1–β_1 receptors expressed in *Xenopus laevis* oocytes (Beckstead et al. 2000) at concentrations that have been reported to occur in vivo (Kishi et al. 1988; Naalsund 1986; You et al. 1994). Because no currents were elicited in the absence of GABA, it appears that inhalants act as allosteric modulators at these ligand-gated ion channels.

In contrast, nitrous oxide appears to have a different, but overlapping, pattern of action on $GABA_A$ receptors, compared with alcohol. Nitrous oxide only weakly potentiated $GABA_A$ receptor activity (Yamakura and Harris 2000). However, similar to volatile anesthetics and alcohol, nitrous oxide inhibited ρ_1 $GABA_C$ receptors, suggesting that nitrous oxide has a differential effect on these homologous receptor subunits (Yamakura and Harris 2000). Therefore, although the sensitivity differs between nitrous oxide and volatile anesthetics and alcohol, some mechanisms of action of nitrous oxide on GABA receptors appear to be shared among these substances.

To our knowledge no studies have examined the effects of nitrites on GABA neurotransmission. However, when NO, the major mediator of the peripheral effects of nitrites, was administered within the paraventricular nucleus, it caused an increase in GABA concentrations (Horn et al. 1994).

Glycine Receptors

Glycine receptors are responsible for the majority of inhibitory neurotransmission in the brain stem and spinal cord. Inhalants, volatile anesthetics, and alcohol may share a common binding site on this ligand-gated ion channel (Beckstead et al. 2000, 2001, 2002). Active compounds in toluene, trichloroethane, and trichloroethylene appear to potentiate glycine receptor–mediated currents (Beckstead et al. 2000). Mutations in glycine receptors resulted in enhancement of glycine receptor function when these compounds were present, despite the fact that some of these mutants were insensitive to the effects of alcohol and enflurane. These findings suggest that solvents affect glycine receptor function and that, although they differ, the molecular sites of action overlap with those of alcohol and volatile anesthetics (Beckstead et al. 2000).

Nicotinic Acetylcholine Receptors

The nicotinic acetylcholine (nACh) receptor also displays sensitivity to inhalants (Bale et al. 2002). To varying degrees, toluene appeared to antagonize the function of nACh receptors that comprise different subunits. At concentrations of 50 μM to 10 mM, toluene produced a reversible, concentration-dependent inhibition of acetylcholine-induced current in *Xenopus* oocytes expressing various nicotinic receptor subtypes, with the α_4–β_2 and α_3–β_2 subunit combinations being more sensitive to inhibition than other receptor

subtypes. At these same concentrations, toluene dose-dependently inhibited acetylcholine-mediated responses in the hippocampus. These results suggest that nACh receptors, like NMDA receptors, show a subunit-dependent sensitivity to toluene and may represent an important site of action for some of the neurobehavioral effects of this volatile solvent (Bale et al. 2002).

5-HT Receptors

Similar to alcohol (Lovinger and White 1991) and volatile anesthetics (Machu and Harris 1994), trichoroethane, trichloroethylene, and toluene enhance 5-HT_3 receptor function. All three inhalants significantly and reversibly potentiated, in a dose-dependent manner, 5-HT-activated currents, mediated by mouse 5-HT_{3A} receptors expressed in *Xenopus* oocytes. Another feature common to these drugs is that the acute use of inhalants, as well as alcohol and volatile anesthetics, can produce nausea and vomiting (Meredith et al. 1989). It is believed that 5-HT_3 receptors located in the area postrema mediate this action of alcohol and the volatile anesthetics (Aapro 1991).

Opioid Receptors

Exposure to nitrous oxide has been shown to induce opioid peptide release in the periaqueductal gray area of the midbrain and increases opioid receptor density in the brain stem (Fujinaga and Maze 2002; Saracibar et al. 2001). This increase leads to activation of the descending inhibitory pathways that modulate pain/nociceptive processing in the spinal cord. Thus, the opioid receptor system is implicated in the analgesic properties of nitrous oxide, and these effects on opioid receptor function may represent a mechanism for explaining the reinforcing effects of nitrous oxide. However, there is no evidence implicating opioidergic neurotransmission in the addictive properties of solvents or nitrites.

Phenomenology and Variations in the Presentation of Inhalant Use Disorders

According to DSM-IV-TR (American Psychiatric Association 2000), inhalant use disorders include inhalant abuse and inhalant dependence. The DSM-IV-TR criteria for these conditions apply only to the use of volatile solvents, and

abuse or dependence on anesthetics or nitrites are classified separately as other (or unknown) substance-related disorders. Despite the diagnostic distinction, the generic DSM-IV-TR diagnostic criteria for substance use disorders apply across the three groups of inhalants (solvents, anesthetics, and nitrites).

Diagnostic criteria for inhalant use disorders in DSM-IV-TR are similar to those in the *International Classification of Diseases,* Tenth Revision (ICD-10) (World Health Organization 1992). These criteria include biological, cognitive, and behavioral dimensions. The DSM-IV-TR diagnosis of inhalant dependence is given when three or more of the seven criteria are present (see Table 8–2). The first criteria to be considered here are tolerance and withdrawal. These phenomena are considered to be forms of adaptation to chronic administration of these compounds and were discussed extensively earlier in this chapter.

The remaining DSM-IV-TR criteria encompass the behavioral and cognitive dimensions of inhalant dependence. These criteria include 1) impaired control (i.e., inhalants are consumed in larger amounts or over a longer period of time than was intended; there is a persistent desire or unsuccessful efforts to cut down or control inhalant use; the individual continues using inhalants despite knowledge of a persistent or recurrent physical or psychological problem) and 2) increased salience of inhalant use (i.e., a great deal of time spent using or recovering from the effects of inhalants; important social, occupational, or recreational activities are given up or reduced due to inhalant use).

Kono et al. (2001) described and compared the phenomenology of inhalant dependence with that of other substance dependence diagnoses. Although inhalant-dependent (i.e., solvent-dependent) subjects reported lower levels of drug-seeking behavior than individuals dependent on methamphetamine, alcohol, or nicotine, inhalant-dependent subjects endorsed a greater sacrifice value associated with inhalant use. Inhalant-dependent subjects were comparable to those dependent on these other substances in terms of the number of attempts to quit substance use. However, quitting attempts among inhalant-dependent subjects were briefer than among the other groups of substance-dependent subjects. Inhalant-dependent subjects reported the greatest levels of ignored obligations, legal problems, and substance use despite problems.

Clearly, more studies are needed to delineate more precisely the phenomenology of inhalant use disorders, including the phenomenology of anesthetic

Table 8–2. Diagnostic criteria for inhalant dependence

A maladaptive pattern of inhalant use as manifested by three or more of the following during a 12-month period:

1) Tolerance:
   a) A need for significantly more inhalant use to achieve intoxication
   b) Significantly diminished effect despite continued use of the same amount of inhalant
2) Withdrawal:
   a) Two or more signs or symptoms (tremor, diaphoresis, insomnia, nausea or vomiting, fleeting illusions, psychomotor agitation, anxiety, and perhaps grand mal seizures) within several hours of stopping or reducing heavy, prolonged inhalant use
   b) Using inhalants to relieve or avoid withdrawal symptoms
3) Inhalants are often used in larger amounts or over a longer period than was intended.
4) There is a persistent desire to cut down or control inhalant use.
5) A great deal of time is spent consuming inhalants or recovering from their effects.
6) Important social, occupational, or recreational activities are given up or reduced because of inhalant use.
7) Inhalant use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by inhalants.

Source. Adapted from American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders,* 4th Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000. Used with permission.

and nitrite abuse and dependence. More reliable and valid information on demographic and clinical correlates of these disorders is also needed.

Patterns of Inhalant Use in Humans

Clinical and epidemiological observations suggest that inhalant use in humans occurs along a continuum, with considerable variability in usage patterns among individuals as a function of age, gender, socioeconomic status, ethnicity, availability and type of inhalant, and other clinical variables. As a general rule, it is expected that as inhalant consumption and frequency of intoxication increase, the incidence and severity of medical and psychosocial problems will increase.

Volatile Solvent Use

The primary objective of inhaling volatile solvents is the rapid delivery of a high concentration of the substance to the lungs and, thereby, to the brain. Inhalation is typically achieved through "sniffing," "bagging," or "huffing." *Sniffing* involves the inhalation of vapors directly from an open container or a heated pan. *Bagging* refers to inhalation of vapors from a plastic or paper bag containing the substance. *Huffing* is the inhalation of vapors by holding a piece of cloth that has been soaked in the volatile substance against the nose and mouth. In some instances, abusers may spray aerosol compounds directly into the mouth. Habitual abusers generally begin with sniffing and progress to huffing and then bagging to increase the concentration of the inhalant and intensify or prolong the desired euphoria.

Rosenberg and Sharp (National Inhalant Prevention Coalition 2003) identified four patterns of solvent use:

1. Transient social use, characterized by a short history of use in social situations, occurring mainly among individuals of average intelligence who are age 10–16 years
2. Chronic social use, characterized by daily social use for 5 or more years, which usually occurs among individuals with poor social skills and limited education who are age 20–30 years and who may also have evidence of brain damage and minor legal problems
3. Transient isolated use, characterized by a short history of solo use among individuals age 10–16 years
4. Chronic isolated use, characterized by a history of continuous solo use for 5 or more years among individuals age 20–29 years with poor social skills, limited education, and significant involvement in legal problems; evidence of brain damage may be common in this group.

Nitrite Use

Although nitrite use was initially described among homosexual men who used nitrites in the context of sexual activity, more recently their use has expanded to include heterosexuals. Currently, in addition to being used as sexual enhancers, nitrites are frequently used in combination with amphetamines and ecstasy to accompany "high energy" dance and music among young

individuals attending clubs and parties (i.e., "raves"). Nitrite users buy these drugs with relatively few restrictions in sex shops and on the Internet. They are dispensed in small screw-top bottles under brand names such as Liquid Gold, Ram, or Thrust.

Anesthetic Use

Besides being known as laughing gas, the anesthetic nitrous oxide is also known as "whippets," particularly among children and adolescents, who frequently inhale this gas from a whipping cream charger or store-bought whipped cream dispenser. Nitrous oxide is also frequently inhaled from balloons by teenagers and young adults at raves and parties and during outdoor events such as rock concerts. However, the drug is often used in isolation at home or in school.

Owing to the intense pressure of the gas, inhaling nitrous oxide from a device that does not allow the user to control the flow rate can cause injury to the tissues of the mouth, throat, or lungs. Because the gas frequently freezes when propelled from its container, frostbite is a common injury among nitrous oxide users. In addition, because nitrous oxide displaces oxygen in breathed air, lungs, and the bloodstream, hypoxia can occur if nitrous oxide is inhaled in high concentrations. Similar to what can occur with the abuse of other inhalant drugs, nitrous oxide users may be rendered unconscious, with a balloon, bag, or mask used to inhale the compound still covering the mouth and nose, and at risk of death because of asphyxiation.

Inhalation of other general anesthetics susceptible to abuse, such as ether and chloroform, appears to be limited to health professionals who have easy access to these compounds and who tend to use these drugs in isolation. Recreational and social use of these substances has been somewhat limited by their high flammability and by frequent and intense undesirable adverse effects at moderate doses. It has been suggested that the abuse of ether or chloroform alone is a rare phenomenon (Delteil et al. 1974; Deniker et al. 1972), occurring usually in the context of dependence on other substances, particularly alcohol (Krenz et al. 2003).

Phenomenology of Inhalant-Induced Disorders

DSM-IV-TR (American Psychiatric Association 2000) recognizes six inhalant-induced disorders: inhalant intoxication, inhalant intoxication delirium,

inhalant-induced persisting dementia, inhalant-induced psychotic disorder, inhalant-induced mood disorder, and inhalant-induced anxiety disorder. However, because of the paucity of systematic studies in the literature documenting other inhalant-related disorders, DSM-IV-TR does not consider inhalant withdrawal, inhalant withdrawal delirium, inhalant amnestic disorder, or inhalant sexual or sleep disorders. In this section, in addition to describing inhalant-induced disorders from solvents and related products, we provide anecdotal descriptions of disorders resulting from the inhalation of general anesthetics and nitrites.

Inhalant Intoxication

Solvent intoxication is characterized in DSM-IV-TR by the presence of clinically significant maladaptive behavioral or psychological changes that develop during the intentional short-term, high-dose exposure to volatile solvents. Symptoms of solvent intoxication can include apathy (or, alternatively, excitation, belligerence, and assaultiveness), light-headedness, impaired judgment, impaired social and occupational functioning, visual disturbances such as blurred vision and nystagmus, incoordination, dysarthria, and unsteady gait. Visual and tactile hallucinations and delusions are also common. Following high doses of inhalants, severe hyporeflexia, stupor, and death caused by cardiac arrhythmia may occur. Lethargy, generalized muscle weakness, and headaches remain a few hours after cessation of solvent inhalation.

Studies of the intoxicating effects of toluene showed that the inhalation of its vapor at a concentration of 200 ppm was associated with the development of mild-to-moderate intoxication, characterized by sedation, paresthesias, and hyporeflexia. Toluene vapor concentrations of 600–800 ppm induced a confusional state, whereas greater concentrations produced an intense euphoria (Benignus 1981; Press and Done 1967). In humans, plasma concentrations of toluene of 10–100 μM have been reported to be intoxicating; these concentrations are close to the intoxicating concentrations of alcohol and inhalational anesthetics (Miller 1985).

Intoxication with amyl nitrite or butyl nitrite (i.e., poppers) is characterized by euphoria, warm feelings, change in perception of time, a sense of fullness in the head, relaxation of smooth muscle, vasodilatation, increased heart rate, and decreased systolic blood pressure. An increase in sexual drive and intensification of orgasm, poor judgment, and a reduction in inhibitions are

also associated with nitrite intoxication. These symptoms have been associated with a failure to use condoms and with other high-risk behaviors that increase the likelihood of HIV infection or other sexually transmitted diseases (Haverkos et al. 1994). In addition, nitrite intoxication suppresses natural killer cell function, which increases vulnerability to infectious agents, produces sustained alterations in the immune system, and appears to be a Kaposi's sarcoma cofactor (Haverkos et al. 1985).

The clinical presentation of intoxication with anesthetics varies as a function of the anesthetic agent used. An examination of effects of nitrous oxide at subanesthetic doses on mood and psychomotor performance in 12 healthy individuals showed that intoxicating effects were observed following the inhalation of concentrations of 20% and 40% (but not 10%) (Dohrn et al. 1992). Subjects became confused, high, stimulated, dysphoric, and subsequently sedated during inhalation of nitrous oxide. Fatigue, depression, and anxiety increased after cessation of inhalation. Subjects' cognitive performance and reaction times were significantly impaired during inhalation of the gas but recovered soon after inhalation stopped. Intoxication with other general anesthetics such as ether and chloroform is characterized by euphoria, overexcitement, aggressiveness, hallucinations, and sleepiness. Severe nausea and emesis may also occur (Bird 1881; Delteil et al. 1974; Deniker et al. 1972; Follin and Rousselot 1980).

Inhalant Intoxication Delirium

Intoxication delirium may occur with solvents, nitrous oxide (Sterman and Coyle 1983), ether, or other general anesthetics (Delteil et al. 1974). However, to our knowledge, there are no reports describing delirium associated with nitrite intoxication. The description of delirium presented here derives mainly from what has been observed during solvent intoxication.

The main disturbance in inhalant intoxication delirium is a reversible decrease in the level of consciousness and awareness of the environment, which includes an inability to focus, sustain, or shift attention. The intoxicated person is confused and easily distracted by irrelevant stimuli and difficult to engage in a meaningful conversation. He or she may also exhibit prominent disorientation, short- and long-term memory deficits, language disturbances, and perceptual disturbances that may include illusions and hallucinations. Other prominent features associated with inhalant intoxication delirium are

disturbance in the sleep-wake cycle, increased motor activity or agitation, paranoid and grandiose delusions, anxiety, depression, irritability, anger, euphoria, and/or apathy.

Inhalant intoxication delirium can occur as a consequence of disturbances in dopaminergic, glutamatergic, and GABAergic neurotransmission secondary to acute, high-level exposure to psychoactive ingredients in solvents such as toluene, trichloroethane, and trichloroethylene. Systemic effects of solvent inhalation such as cerebral hypoxia and/or metabolic acidosis may also be involved (Rosenberg 1982). Under these circumstances, inhalant intoxication delirium develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day. Usually, the delirium resolves as the intoxication ends or within a few hours after cessation of use.

Inhalant intoxication delirium can also occur in the context of chronic low-level exposures to solvents as a part of two slowly developing but reversible neurological syndromes: a solvent-induced encephalopathy and a peripheral neuropathy. Less commonly, a cerebellar ataxic syndrome, parkinsonism, and myopathy can occur alone or in combination with any of these neurological syndromes. Frequently, the encephalopathy induced by solvents rich in toluene can also present with nystagmus, seizures, and coma (King et al. 1981; Lazar et al. 1983; Malm and Lying-Tunell 1980). The diagnosis of inhalant intoxication delirium is made more difficult by the existence of a syndrome of irreversible cognitive deterioration (i.e., dementia) induced by chronic inhalation of solvents.

Inhalant-Induced Persisting Dementia

Chronic high-level exposure to solvents, particularly those rich in toluene (Filley et al. 1990; Fornazzari et al. 1983; Lazar et al. 1983), is associated with progressive and gradual development of irreversible cognitive deficits characterized by memory impairment, aphasia, apraxia, agnosia, and disturbances in executive functioning. These symptoms persist beyond the intoxication period, and there is significant impairment in social and occupational functioning, including a decline from a previous level of functioning. Evidence from the patient's history, physical examination, and laboratory test results should strongly suggest that these deficits are etiologically related to the toxic effects of inhalant use. Inhalation of toluene-rich solvents has been shown to cause cortical atrophy and widespread cerebellar damage, with the length and in-

tensity of toluene exposure correlating with the degree of damage to cerebral white matter and the level of impairment (Boor and Hurtig 1977; Filley et al. 1990; Hormes et al. 1986; Schikler et al. 1982). Other abnormalities frequently seen with inhalant-induced persisting dementia are cranial nerve damage manifested by opsoclonus, optic atrophy, cranial neuropathy, tinnitus and sensorineural hearing loss, spasticity, and autonomic dysfunction (Fornazzari et al. 1983; Hormes et al. 1986; Lazar et al. 1983; Lolin 1989; Morata et al. 1994; Pryor 1990). In the United States, before lead was removed from gasoline, lead poisoning and dementia may have also resulted from gasoline sniffing, a practice that has historically been most problematic in Native American adolescents (Boeckx et al. 1977).

Inhalant-Induced Psychotic Disorder

Inhalent-induced psychotic disorder is characterized by prominent hallucinations or delusions that are judged by the clinician to be due to the direct physiological effects of inhalants, rather than to a primary psychotic disorder. On the basis of the predominant symptom, there are two subtypes: inhalant-induced psychotic disorder with hallucinations and inhalant-induced psychotic disorder with delusions. Although the diagnosis should not be made if the psychotic symptoms are limited to a period of delirium, inhalant-induced psychotic symptoms frequently persist during periods of abstinence, making it difficult to differentiate them from a primary psychotic disorder. A temporal association between a history of severe inhalant abuse and development of psychotic symptoms is useful in differential diagnosis. In general, inhalant-induced psychotic disorder occurs after several months or years of inhalant dependence, and the psychotic symptoms are accompanied by cognitive impairment and other complications of inhalant abuse, including polyneuropathy (Hernandez-Avila et al. 1998). Evidence that hallucinations and/or delusions are not better accounted for by a primary psychotic disorder include atypical or late age at onset of psychotic symptoms, onset of inhalant abuse preceding onset of psychotic symptoms, and remission of psychotic episodes during extended periods of abstinence. In contrast, factors that suggest that the psychotic symptoms are better accounted for by a primary psychotic disorder include persistence of psychotic symptoms for a substantial period of time (i.e., 1 month or longer) after discontinuation of inhalant intoxication or withdrawal, development of symptoms that are substantially in excess of

what would be expected given the amount of inhalant used or the duration of use, or a history of primary psychotic disorder.

Inhalant-Induced Mood Disorder and Inhalant-Induced Anxiety Disorder

Chronic inhalation of solvents can induce anhedonia; elevated, expansive, or irritable mood; or anxiety symptoms. Although the clinical presentation may resemble that of a major depressive, manic, mixed, or hypomanic episode, or of any anxiety disorder, it does not generally meet the full criteria for these disorders. Nonetheless, the inhalant-induced disorder causes significant distress and impairment of social and occupational functioning. The diagnosis of an inhalant-induced mood or anxiety disorder should be made instead of a diagnosis of inhalant intoxication only when the mood and/or anxiety symptoms are in excess of those usually associated with intoxication and when the mood and/or anxiety symptoms are severe enough to warrant independent clinical attention. Evidence suggesting a primary mood or anxiety disorder includes the onset of mood and/or anxiety symptoms preceding the onset of inhalant abuse and/or persistence of symptoms after inhalant use or during extended periods of abstinence. Although these disorders are described in anecdotal reports, there are no systematic studies of the phenomenology and correlates of inhalant-induced mood or anxiety symptoms.

Clinical Evaluation of Patients With Inhalant Use Disorders

Accurate diagnosis of patients with inhalant use disorders may require a variety of methods, including psychiatric history and mental status examination, physical examination and laboratory testing, neuropsychological testing, and neurophysiological testing.

Psychiatric History and Examination

Given that cognitive and behavioral disturbances are commonly associated with inhalant use disorders, diagnostic assessment of individuals with such disorders is probably best done by using a standardized interview schedule, such as the Composite International Diagnostic Interview (CIDI) (Robins et

al. 1989) or the Structured Clinical Interview for DSM-IV (SCID) (First et al. 1997). The number of DSM-IV-TR inhalant use disorder symptoms endorsed by the patient can be used as a measure of severity. In addition, the composite score from the drug dependence section of the Addiction Severity Index (ASI; McLellan et al. 1992) may provide another useful measure of severity of the addiction to inhalants. This score, however, will not be as specific a measure of inhalant use disorder severity as that obtained using the CIDI or SCID.

Assessment of psychological function should focus on measures of cognitive functioning, psychotic symptoms, depressive and anxiety symptoms, and global psychological distress. Instruments that are generally reliable, valid, and acceptable for evaluation of these areas include the Brief Psychiatric Rating Scale (Overall and Gorham 1962), the Beck Depression Inventory (Beck et al. 1961), and the Symptom Checklist–90—Revised (Derogatis 1992). The psychiatric severity subscale of the ASI assesses overall psychiatric severity, including the number of inpatient and outpatient treatment episodes, medication status, and lifetime and current symptoms (McLellan et al. 1992).

Physical Examination and Laboratory Findings

Medical complications are common among patients with inhalant use disorders. Because these problems are manifested in most organ systems, a thorough physical examination is indicated for any patient with an inhalant use disorder diagnosis. The physical examination provides essential information about the presence and extent of organ damage and should be focused on the systems most vulnerable to developing inhalant-related pathology, including the central and peripheral nervous systems, the kidneys, the hematopoietic system, the cardiovascular system, the gastrointestinal system, the respiratory system, and the immune system. The physician should also be alert to other acute inhalant-related signs, including inhalant intoxication or withdrawal, intoxication or withdrawal from other drugs, and the acute presentation of psychiatric symptoms. Other systemic health problems associated with inhalant use disorder include malnutrition, muscle wasting, infectious diseases (such as tuberculosis, dermatitis, pediculosis, and hepatitis), and physical trauma.

Laboratory tests can help in assessing the effects of inhalant use. Laboratory tests that measure hepatic function, renal function, and hematopoietic

function (i.e., serum levels of hepatic aminotransferases, bilirubin, urea nitrogen, and creatinine, as well as a complete blood count) can be useful to clinicians. Although there are no specific diagnostic laboratory markers of the abuse of nitrites or nitrous oxide, urinary concentrations of hippuric acid and orthocresol appear to be good indicators of inhalation of substances rich in toluene, such as glue and solvents (De Rosa et al. 1987). Correlations between urinary concentrations of hippuric acid and of ortho-cresol and toluene concentrations in inhaled air when examined within 17 hours of inhalation were reported to be 0.88 and 0.63, respectively (De Rosa et al. 1987). Laboratory testing can also assist the clinician in providing objective, nonjudgmental feedback to inhalant-abusing patients on the adverse physical consequences of their substance use. When possible, laboratory results should be graphically presented to the patient in an easy to comprehend format that includes normal values as a comparison. The goal of this effort is to enhance the patient's motivation to initiate abstinence from inhalants. Ongoing monitoring reinforces the patient's abstinence as the laboratory test values decline and eventually normalize. Because patients may not acknowledge problems with other drugs, a urine toxicology screen is also recommended in patients with an inhalant use disorder. The screen should include opioids, cocaine, cannabis, benzodiazepines, and hallucinogens. Laboratory tests for syphilis, HIV, and other sexually transmitted diseases, and for women, serum pregnancy testing, should also be performed.

Neuropsychological Testing

Given that a variety of neuropsychological deficits occur among inhalant abusers, neuropsychological testing can assist in the clinical evaluation of patients with inhalant use disorder. Tsushima and Towne (1977) compared 20 adolescent paint-sniffers to matched control subjects and found deficits on tests of motor speed, memory, auditory discrimination, and visuomotor function. These investigators also found a correlation between these deficits and the duration of paint sniffing. Allison and Jerrom (1984) reported similar findings in 10 delinquent solvent inhalers. These subjects demonstrated impairments in memory, attention, concentration, and nonverbal intelligence. A correlation has also been observed between exposure to solvents and impairment on tests of auditory memory and visual abstraction (Moen et al. 1990).

Neurophysiological Testing

Neurophysiological testing may also assist the clinician in identifying and assessing the severity of inhalant dependence. Visual and auditory evoked potentials may serve as markers of inhalant dependence and early neurological damage in children. In a study of 15 children (ages 9–17 years) with a significant history of inhalant abuse but without clinical evidence of neurological abnormalities, eight of the children showed abnormal visual or auditory evoked potentials (Tenenbein and Pillay 1993). Consistent with the evidence in humans, similar abnormalities in evoked potentials have been observed in animal models of inhalant abuse (Rebert et al. 1989; Stewart et al. 1972). More recently, Kucuk et al. (2000) evaluated brain perfusion in long-term abusers of toluene, acetone, benzene, and their derivatives. Ten patients (ages 16–18 years) who had been inhalant dependent for a mean period of approximately 4 years but who had stopped using inhalants for an average of 5.4 months (range = 1–11 months) and ten age-matched control subjects were included in the study. Brain single photon emission computed tomography was performed by using Tc-99m-HMPAO. The inhalant-dependent subjects exhibited serious abnormalities, including hypoperfusion foci and nonhomogeneous uptake of the radiopharmaceutical.

Treatment

Once an individual has received a diagnosis of an inhalant use disorder, the initial decisions involve determining the most appropriate setting for treatment and deciding on the intensity of treatment required. Continuous inhalant users may require inpatient treatment. Intermittent users without evidence of serious comorbid psychopathology or acute adverse effects of inhalant use can be managed on an ambulatory basis through psychosocial and pharmacological approaches. Despite the relatively high prevalence of inhalant abuse and dependence, especially among children and adolescents, there is a paucity of studies examining treatment intervention in this population. The vast majority of substance abuse treatment programs employ treatment approaches that were developed to treat other substance use disorders and are unprepared to treat patients with inhalant use disorders. Because of the severe cognitive deterioration and comorbid psychopathology associated with inhal-

ant use disorders, the treatment of these patients can be challenging, even to the most experienced clinicians. Clinicians treating patients with these disorders should be prepared to work with these patients for extended periods of assessment and supportive care.

Psychosocial Treatment

Although to our knowledge there are no controlled studies examining specific psychosocial interventions in the treatment of inhalant abuse or dependence, some general guidelines have been developed to address the specific needs of this population (National Inhalant Prevention Coalition 2003). First, given the significant neurotoxic effects of inhalants, it is critical to identify the presence of any cognitive deficits or disruptive behaviors that may interfere with psychosocial treatment. As discussed earlier, neuropsychological testing, a developmental history, and examination of school performance may help in achieving this goal. Second, given that family involvement appears to be highly important in the recovery efforts of inhalant abusers, a comprehensive evaluation of the family structure and dynamics is recommended, and family therapy addressing drug education and parenting and social skills training must be considered in treating these patients (National Inhalant Prevention Coalition 2003). Third, given that inhalant use frequently occurs in groups, examination of peer group dynamics is warranted and should be aimed at assisting the patient to break negative peer bonds and substitute positive ones. For these reasons treatment should be social in nature, although individual counseling should be also available. Fourth, it is recommended that initial therapeutic interventions with inhalant abuse patients be brief, informal, and concrete, with the aim of developing rapport and enhancing motivation for treatment. In this population, more formal individual or group substance abuse therapy appears to be ineffective, and confrontational approaches appear to be detrimental (National Inhalant Prevention Coalition 2003).

Pharmacotherapy

Management of Inhalant Withdrawal

The objective in treating inhalant withdrawal is the relief of discomfort, prevention or treatment of complications, reduction of urges to use inhalants, and preparation for rehabilitation. Successful management of inhalant with-

drawal should provide a basis for subsequent efforts at rehabilitation. Pharmacological management may potentially assist clinicians and patients in achieving these goals.

Signs and symptoms of inhalant withdrawal, specifically those related to solvents and anesthetics, resemble those of alcohol and sedative withdrawal. It is likely that the majority of inhalant-dependent patients may be safely managed by using social detoxification similar to that used to treat alcohol withdrawal (Naranjo et al. 1983; Sellers et al. 1983). This nonpharmacological approach has been shown to be effective in the treatment of mild-to-moderate alcohol withdrawal. It consists of frequent reassurance, reality orientation, monitoring of vital signs, personal attention, and general medical and nursing care (Naranjo and Sellers 1986). Social detoxification of inhalant-dependent subjects may have to be maintained for longer periods of time than with alcohol- or sedative-dependent subjects because of the psychopathology that is often associated with inhalant dependence. Among severely affected inhalant-dependent patients, especially among those dependent on solvents with a high toluene content, pronounced withdrawal symptoms characterized by intense craving, autonomic hyperactivity, seizures, and/or delirium can occur. The inhalant withdrawal clinical picture may also be complicated by intoxication or withdrawal symptoms caused by other substances of abuse, especially alcohol and/or sedatives. In consideration of these problems, Brouette and Anton (2001) recommended closely monitoring these patients as if they were being treated for alcohol withdrawal. If symptoms develop—particularly signs of autonomic hyperactivity such as tachycardia, elevated blood pressure, and diaphoresis—benzodiazepines are generally the first-line drugs to treat this condition (Mayo-Smith 1997). Nonetheless, because of the potential for abuse of these medications and their potential to detrimentally affect cognitive functioning, they should be prescribed with caution. The apparent commonalities between the effects of chronic consumption of alcohol and inhalants on GABAergic neurotransmission suggest that pharmacological agents that enhance GABAergic function, such as the anticonvulsants carbamazepine, valproate, gabapentin, vigabatrin, and tiagabine, may ameliorate inhalant withdrawal symptoms without the potential risks associated with the prescription of benzodiazepines. Clinical trials provided evidence of beneficial effects of carbamazepine in the treatment of alcohol withdrawal; case series have supported the potential utility of some of the other agents for this

application (Gentry et al. 2002). Potential adverse reactions with and disadvantages to the use of these medications include the possibility of liver and bone marrow toxicity, which necessitates blood monitoring with carbamazepine or valproate treatment. Although excessive sedation and drowsiness are common problems with the use of gabapentin, vigabatrin, and tiagabine, this effect can be advantageous in treating the sleep disturbances and anxiety that are frequently associated with inhalant withdrawal. Controlled clinical trials examining the safety and efficacy of these medications for treatment of inhalant withdrawal are needed.

Relapse Prevention

Despite recent advances in understanding the neuropharmacological basis of inhalant dependence, there are no published studies examining the effects of potentially efficacious medications in the treatment of this condition. In the following sections, we discuss psychopharmacological agents that, because of their known effects on the neurotransmitter systems that mediate inhalants' reinforcing effects, may assist inhalant abusers achieve abstinence.

Atypical antipsychotics. Atypical antipsychotics, including clozapine, risperidone, olanzapine, and quetiapine, have been shown to reduce substance use in animals and among patients with schizophrenia or schizoaffective disorders (Brown et al. 2002; Mechanic et al. 2003; Smelson et al. 2002; Zimmett et al. 2000). In contrast to the typical antipsychotics, which generally are antagonists of the D_2 receptor subtype, atypical antipsychotics have a higher affinity for other dopamine receptor subtypes such as the D_3 and D_4 receptors. In addition, atypical antipsychotics have a high affinity for the 5-HT_2 receptor subtype (Bymaster et al. 1996). This broad receptor binding profile has been implicated in many of the atypical antipsychotics' clinical characteristics and suggests that dopamine receptor antagonism can be achieved at the two dopamine receptor subtypes believed to be responsible for drug reward (i.e., D_1 and D_2 in NAC) (Arnold et al. 1977). Anecdotal reports by clinicians who have used atypical antipsychotics to treat patients with dual diagnoses (e.g., patients with schizophrenia and cocaine abuse) (Littrell et al. 2001; Zimmet et al. 2000) and several controlled studies (Brown et al. 2002; Smelson et al. 2002) showed that these medications re-

duce craving for cocaine and other stimulants. Given the stimulant-like effects of inhalants on mesolimbic dopaminergic reward circuitry and the cross-sensitization of stimulant effects with toluene or trichloroethane effects, it is plausible that atypical antipsychotics may reduce inhalant use by dampening inhalant reward. Controlled examination of this hypothesis is warranted.

Anticonvulsants. In addition to their potential utility in the treatment of inhalant withdrawal, anticonvulsant medications such as valproate, topiramate, gabapentin, vigabatrin, and tiagabine may have a role in the rehabilitation of inhalant dependence. These compounds could antagonize the rewarding effects of inhalants by inhibiting mesocorticolimbic dopamine release through the facilitation of GABA activity. Topiramate produces a similar effect by inhibition of glutamatergic activity and has been shown in a placebo-controlled clinical trial to reduce alcohol drinking in a sample of alcohol-dependent subjects (Johnson et al. 2003). Given the similarities between the effects on GABAergic neurotransmission of alcohol and inhalants, it is plausible that anticonvulsants with significant effects on this neurotransmitter system may help to reduce inhalant use among inhalant abusers.

Acamprosate. Acamprosate, an amino acid derivative, affects both GABAergic and glutamatergic neurotransmission. Clinical studies involving more than 4,000 patients in Europe have provided consistent evidence of the efficacy of acamprosate in alcoholism rehabilitation (Kranzler and Van Kirk 2001). Acamprosate's effects on both GABAergic and glutamatergic neurotransmission, together with a benign side effect profile, make this compound a potentially useful one for the treatment of inhalant dependence. Furthermore, on the basis of experiments in rodents suggesting that this agent may have a protective effect against NMDA-mediated neurotoxicity (Koob et al. 2002), this medication may be of utility in preventing the neurotoxicity associated with inhalant use.

5-HT_3 antagonists. Given that the 5-HT_{3A} receptor may also be involved in the reinforcing effects of inhalants (Lovinger and White 1991), it is plausible that medications that antagonize this receptor complex may reduce or dampen the reward produced by inhalant use. Two medications that selectively block 5-HT_{3A} receptors have been used for their psychopharmacologic effects: the anti-emetic ondansetron and the antidepressant mirtazapine. Ondansetron

has been shown to reduce alcohol consumption among alcoholic patients with early onset of problem drinking (i.e., before age 25 years) (Johnson et al. 2000). Mirtazapine is efficacious in the treatment of major depression (see Benkert et al. 2000), but it has not been evaluated in controlled trials for the treatment of substance dependence. Studies examining the effects of these compounds in the treatment of inhalant use disorders may be warranted.

Pharmacological Treatment of Comorbid Psychiatric Conditions

Comorbid psychiatric disorders have been shown to contribute to the development or maintenance of a variety of substance use disorders (Hasin et al. 2004). Effective treatment of the comorbid disorders may have beneficial effects on substance abuse outcomes. Although no systematic studies have been conducted among inhalant abusers, these patients often manifest persistent anxiety symptoms, insomnia, depression, delusions and hallucinations, cognitive impairment, and general distress. These symptoms may last for weeks or months and are difficult to differentiate from the emergence of diagnosable psychiatric disorders. Irrespective of their etiology, negative emotional states and distress, including frustration, anger, anxiety, depression, and boredom, have been shown to contribute to relapse in addictive disorders (Marlatt 1985).

Despite the high prevalence and clinical significance of comorbid disorders among inhalant abusers, to our knowledge there is only one published study of the treatment of comorbid psychiatric problems among inhalant-dependent patients (Hernandez Avila et al. 1998). This double-blind study of the safety and efficacy of pharmacotherapy compared carbamazepine with haloperidol in the treatment of inhalant-induced psychotic symptoms. Forty male patients were randomly assigned to receive 5 weeks of treatment with carbamazepine or haloperidol. Both treatment groups improved significantly over time, with approximately one-half of the patients in each group considered treatment responders at the end of the study. Adverse effects, especially extrapyramidal symptoms, were significantly more common and more severe in the haloperidol group. Additional studies are needed to address the effects of pharmacotherapy on mood, anxiety, and cognitive symptoms occurring in the context of inhalant abuse.

Conclusion

Inhalant use is a widespread problem, especially among children and adolescents. Acutely, this heterogeneous group of substances (i.e., solvents, nitrites, general anesthetics) exerts significant reinforcing effects, and continuous use of these drugs appears to induce tolerance and withdrawal symptoms. In addition to rapid absorption, rapid entry into the brain, and high bioavailability, inhalants' effects on dopaminergic, glutamatergic, and GABAergic neurotransmission appear to contribute to their abuse liability. Medications that modulate these systems in conjunction with psychosocial interventions may assist in reducing inhalant use in addicted patients. Further research on the treatment of inhalant use disorders is warranted.

References

Aapro MS: 5-HT3 receptor antagonists: an overview of their present status and future potential in cancer therapy-induced emesis. Drugs 42:551–568, 1991

Aizenman E, Hartnett KA, Reynolds IJ: Oxygen free radicals regulate NMDA receptor function via a redox modulatory site. Neuron 5:841–846, 1990

Allison WM, Jerrom DW: Glue sniffing: a pilot study of the cognitive effects of long-term use. Int J Addict 19:453–458, 1984

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000

Arena JM, Drew RH: Poisoning, 5th ed. Springfield, IL, Charles C Thomas, 1986, pp 258–259

Arnold EB, Molinoff PB, Rutledge CO: The release of endogenous norepinephrine and dopamine from cerebral cortex by amphetamine. J Pharmacol Exp Ther 202:544–557, 1977

Arnold JH, Truog RD, Rice SA: Prolonged administration of isoflurane to pediatric patients during mechanical ventilation. Anesth Analg 76:520–526, 1993

Aune H, Renck H, Bessen A: Metabolism of diethyl ether to acetaldehyde in man (letter). Lancet 2:97, 1978

Avramov MN, Shingu K, Mori K: Progressive changes in electroencephalographic responses to nitrous oxide in humans: a possible acute drug tolerance. Anesth Analg 70:369–374, 1990

Bale AS, Smothers CT, Woodward JJ: Inhibition of neuronal nicotinic acetylcholine receptors by the abused solvent, toluene. Br J Pharmacol 137:375–383, 2002

Balon N, Kriem B, Dousset E, et al: Opposing effects of narcotic gases and pressure on the striatal dopamine release in rats. Brain Res 947:218–224, 2002

Balon N, Dupenloup L, Blanc F, et al: Nitrous oxide reverses the increase in striatal dopamine release produced by N-methyl-D-aspartate infusion in the substantia nigra pars compacta in rats. Neurosci Lett 343:147–149, 2003a

Balon N, Risso JJ, Blanc F, et al: Striatal dopamine release and biphasic pattern of locomotor and motor activity under gas narcosis. Life Sci 72:2731–2740, 2003b

Balster RL, Willetts J: Phencyclidine: a drug of abuse and a tool for neuroscience research, in Pharmacological Aspects of Drug Dependence: Towards an Integrated Neurobehavioral Approach (Handbook of Experimental Pharmacology, Vol 118). Edited by Schuster CR, Kuhar MJ. Berlin, Germany, Springer-Verlag, 1996, pp 233–262

Baselt RC: Biological Monitoring Methods for Industrial Chemicals, 3rd ed. Littleton, MA, PSG Publishing, 1997

Beck AT, Ward CH, Mendelson M, et al: An inventory for measuring depression. Arch Gen Psychiatry 4:461–471, 1961

Beckstead MJ, Weiner JL, Eger EI 2nd, et al: Glycine and gamma-aminobutyric acid(A) receptor function is enhanced by inhaled drugs of abuse. Mol Pharmacol 57:1199–1205, 2000

Beckstead MJ, Phelan R, Mihic SJ: Antagonism of inhalant and volatile anesthetic enhancement of glycine receptor function. J Biol Chem 276:24959–24964, 2001

Beckstead MJ, Phelan R, Trudell JR, et al: Anesthetic and ethanol effects on spontaneously opening glycine receptor channels. J Neurochem 82:1343–1351, 2002

Benignus VA: Health effects of toluene: a review. Neurotoxicology 2:567–588, 1981

Benignus VA, Muller KE, Barton CN, et al: Toluene levels in blood and brain of rats during and after respiratory exposure. Toxicol Appl Pharmacol 61:326–334, 1981

Benignus VA, Muller KE, Graham JA, et al: Toluene levels in blood and brain of rats as a function of toluene level in inspired air. Environ Res 33:39–46, 1984

Benkert O, Szegedi A, Kohnen R: Mirtazapine compared with paroxetine in major depression. J Clin Psychiatry 61:656–663, 2000

Beyer CE, Stafford D, LeSage MG, et al: Repeated exposure to inhaled toluene induces behavioral and neurochemical cross-sensitization to cocaine in rats. Psychopharmacology (Berl) 154:198–204, 2001

Bird T: Revelations under ether. Lancet 118:9, 1881

Boeckx RL, Postl B, Coodin FJ: Gasoline sniffing and tetraethyl lead poisoning in children. Pediatrics 60:140–145, 1977

Boor JW, Hurtig HI: Persistent cerebellar ataxia after exposure to toluene. Ann Neurol 2:440–442, 1977

Bowen SE, Balster RL: A direct comparison of inhalant effects on locomotor activity and schedule-controlled behavior in mice. Exp Clin Psychopharmacol 6:235–247, 1998

Bowen SE, Wiley JL, Balster RL: The effects of abused inhalants on mouse behavior in an elevated plus-maze. Eur J Pharmacol 312:131–136, 1996a

Bowen SE, Wiley JL, Evans EB, et al: Functional observational battery comparing effects of ethanol, 1,1,1-trichloroethane, ether, and flurothyl. Neurotoxicol Teratol 18:577–585, 1996b

Bredt DS, Snyder SH: Nitric oxide, a novel neuronal messenger. Neuron 8:3–11, 1992

Brouette T, Anton R: Clinical review of inhalants. Am J Addict 10:79–94, 2001

Brown ES, Nejtek VA, Perantie DC, et al: Quetiapine in bipolar disorder and cocaine dependence. Bipolar Disord 4:406–411, 2002

Bushnell PJ, Evans HL, Palmes ED: Effects of toluene inhalation on carbon dioxide production and locomotor activity in mice. Fundam Appl Toxicol 5:971–977, 1985

Bymaster FP, Hemrick-Luecke SK, Perry KW, et al: Neurochemical evidence for antagonism by olanzapine of dopamine, serotonin, alpha 1-adrenergic and muscarinic receptors in vivo in rats. Psychopharmacology (Berl) 124:87–94, 1996

Carroll E: Notes on the epidemiology of inhalants. NIDA Res Monogr 15:14–24, 1977

Cho AM, Coalson DW, Klock PA, et al: The effects of alcohol history on the reinforcing, subjective and psychomotor effects of nitrous oxide in healthy volunteers. Drug Alcohol Depend 45:63–70, 1997

Collins SL, Kantak KM: Neuronal nitric oxide synthase inhibition decreases cocaine self-administration behavior in rats. Psychopharmacology (Berl) 159:361–369, 2002

Cruz SL, Mirshahi T, Thomas B, et al: Effects of the abused solvent toluene on recombinant N-methyl-D-aspartate and non-N-methyl-D-aspartate receptors expressed in Xenopus oocytes. J Pharmacol Exp Ther 286:334–340, 1998

De Rosa E, Bartolucci GB, Sigon M, et al: Hippuric acid and ortho-cresol as biological indicators of occupational exposure to toluene. Am J Ind Med 11:529–537, 1987

Delteil P, Stoesser F, Stoesser R: L'étheromanie. Ann Med Psychol (Paris) 1:329–340, 1974

Deniker P, Cottereau MJ, Loo H, et al: L'usage de l'éther dans les toxicomanies actuelles. Ann Med Psychol (Paris) 1:674–683, 1972

Derogatis LR: The Symptom Checklist-90-Revised. Minneapolis, MN, NCS Assessments, 1992

Di Chiara G, Imperato A: Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc Natl Acad Sci U S A 85:5274–5278, 1988

Dingledine R, Borges K, Bowie D, et al: The glutamate receptor ion channels. Pharmacol Rev 51:7–61, 1999

Dohrn CS, Lichtor JL, Finn RS, et al: Subjective and psychomotor effects of nitrous oxide in healthy volunteers. Behav Pharmacol 3:19–30, 1992

Dohrn CS, Lichtor JL, Coalson DW, et al: Reinforcing effects of extended inhalation of nitrous oxide in humans. Drug Alcohol Depend 31:265–280, 1993

Evans AC, Raistrick D: Phenomenology of intoxication with toluene-based adhesives and butane gas. Br J Psychiatry 150:769–773, 1987

Evans EB, Balster RL: CNS depressant effects of volatile organic solvents. Neurosci Biobehav Rev 15:233–241, 1991

Evans EB, Balster RL: Inhaled 1,1,1-trichloroethane-produced physical dependence in mice: effects of drugs and vapors on withdrawal. J Pharmacol Exp Ther 264: 726–733, 1993

Filley CM, Heaton RK, Rosenberg NL: White matter dementia in chronic toluene abuse. Neurology 40:532–534, 1990

First MB, Spitzer RL, Gibbon M, et al: Structured Clinical Interview for DSM-IV Axis I Disorders, Research Version, Patient Edition With Psychotic Screen (SCID-I/P W/ PSY SCREEN) New York, New York State Psychiatric Institute, Biometrics Research, 1997

Follin S, Rousselot Y: Analyse de la conduite étheromaniaque d'un schizophrène. Ann Med Psychol (Paris) 138:405–419, 1980

Fornazzari L, Wilkinson DA, Kapur BM, et al: Cerebellar, cortical and functional impairment in toluene abusers. Acta Neurol Scand 67:319–329, 1983

Franks NP, Lieb WR: Molecular and cellular mechanisms of general anaesthesia. Nature 367:607–614, 1994

French ED, Dillon K, Wu X: Cannabinoids excite dopamine neurons in the ventral tegmentum and substantia nigra. Neuroreport 8:649–652, 1997

Fujinaga M, Maze M: Neurobiology of nitrous oxide-induced antinociceptive effects. Mol Neurobiol 25:167–189, 2002

Fuxe K, Andersson K, Nilsen OG, et al: Toluene and telencephalic dopamine: selective reduction of amine turnover in discrete DA nerve terminal systems of the anterior caudate nucleus by low concentrations of toluene. Toxicol Lett 12:115–123, 1982

Gause EM, Mendez V, Geller I: Exploratory studies of a rodent model for inhalant abuse. Neurobehav Toxicol Teratol 7:143–148, 1985

Gentry JR, Hill C, Malcolm R: New anticonvulsants: a review of applications for the management of substance abuse disorders. Ann Clin Psychiatry 14:233–245, 2002

Gerasimov MR, Ferrieri RA, Schiffer WK, et al: Study of brain uptake and biodistribution of [11C]toluene in non-human primates and mice. Life Sci 70:2811–2828, 2002

Gessa GL, Muntoni F, Collu M, et al: Low doses of ethanol activate dopaminergic neurons in the ventral tegmental area. Brain Res 348:201–203, 1985

Glaser HH, Massengale ON: Glue-sniffing in children: deliberate inhalation of vaporized plastic cements. JAMA 181:300–303, 1962

Haggart HW: The absorption, distribution and elimination of ethyl ether. J Biol Chem 59:737–802, 1924

Harbison RM: Hamilton and Hardy's Industrial Toxicology, 5th ed. St. Louis, MO, Mosby, 1998

Harper MH, Winter PM, Johnson BH, et al: Withdrawal convulsions in mice following nitrous oxide. Anesth Analg 59:19–21, 1980

Hasin D, Nunes E, Meydan J: Comorbidity of alcohol, drug, and psychiatric disorders: epidemiology, in Dual Diagnosis and Psychiatric Treatment: Substance Abuse and Comorbid Disorders, 2nd Edition. Edited by Kranzler HR, Tinsley JA. New York, Marcel Dekker, 2004, pp 1–34

Haverkos HW, Pinsky PF, Drotman DP, et al: Disease manifestation among homosexual men with acquired immunodeficiency syndrome: a possible role of nitrites in Kaposi's sarcoma. Sex Transm Dis 12:203–208, 1985

Haverkos HW, Kopstein AN, Wilson H, et al: Nitrite inhalants: history, epidemiology, and possible links to AIDS. Environ Health Perspect 102:858–861, 1994

Hernandez-Avila CA, Ortega-Soto HA, Jasso A, et al: Treatment of inhalant-induced psychotic disorder with carbamazepine versus haloperidol. Psychiatr Serv 49:812–815, 1998

Hillefors-Berglund M, Liu Y, von Euler G: Persistent, specific and dose-dependent effects of toluene exposure on dopamine D2 agonist binding in the rat caudate-putamen. Toxicology 77:223–232, 1993

Himnan DJ: Tolerance and reverse tolerance to toluene inhalation: effects on open-field behavior. Pharmacol Biochem Behav 21:625–631, 1984

Hinman DJ: Biphasic dose-response relationship for effects of toluene inhalation on locomotor activity. Pharmacol Biochem Behav 26:65–69, 1987

Hormes JT, Filley CM, Rosenberg NL: Neurologic sequelae of chronic solvent vapor abuse. Neurology 36:698–702, 1986

Horn T, Smith PM, McLaughlin BE, et al: Nitric oxide actions in paraventricular nucleus: cardiovascular and neurochemical implications. Am J Physiol 266:R306–R313, 1994

Hughes J, Leach HJ, Choonara I: Hallucinations on withdrawal of isoflurane used as sedation. Acta Paediatr 82:885–886, 1993

Hynes MD, Berkowitz BA: Catecholamine mechanisms in the stimulation of mouse locomotor activity by nitrous oxide and morphine. Eur J Pharmacol 90:109–114, 1983

Ikeuchi Y, Hirai H, Okada Y, et al: Excitatory and inhibitory effects of toluene on neural activity in guinea pig hippocampal slices. Neurosci Lett 158:63–66, 1993

Jevtovic-Todorovic V, Todorovic SM, Mennerick S, et al: Nitrous oxide (laughing gas) is an NMDA antagonist, neuroprotectant and neurotoxin. Nat Med 4:460–463, 1998

Johnson BA, Roache JD, Javors MA, et al: Ondansetron for reduction of drinking among biologically predisposed alcoholic patients: a randomized controlled trial. JAMA 284:963–971, 2000

Johnson BA, Ait-Daoud N, Bowden CL, et al: Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. Lancet 361(9370):1677–1685, 2003

Johnston LD, O'Malley PM, Bachman JG: Monitoring the Future National Survey Results on Drug Use, 1975–2002. Vol 2. College Students and Adults Ages 19–40 (NIH Publ No 03–5376). Bethesda, MD, National Institute on Drug Abuse, 2003, p 253

Johnston LD, O'Malley PM, Bachman JG, et al: Overall teen drug use continues gradual decline; but use of inhalants rises, December 21, 2004. University of Michigan News and Information Services: Ann Arbor, MI . Available at: www.monitoringthefuture.org. Accessed April 12, 2005.

Kielbasa W, Fung HL: Pharmacokinetics of a model organic nitrite inhalant and its alcohol metabolite in rats. Drug Metab Dispos 28:386–391, 2000

King MD, Day RE, Oliver JS, et al: Solvent encephalopathy. Br Med J 283:663–665, 1981

Kishi R, Harabuchi I, Ikeda T, et al: Neurobehavioural effects and pharmacokinetics of toluene in rats and their relevance to man. Br J Ind Med 45:396–408, 1988

Kjellstrand P, Holmquist B, Jonsson I, et al: Effects of organic solvents on motor activity in mice. Toxicology 35:35–46, 1985

Kranzler HR, Van Kirk J: Efficacy of naltrexone and acamprosate for alcoholism treatment: a meta-analysis. Alcohol Clin Exp Res 25:1335–1341, 2001

Knox JW, Nelson JR: Permanent encephalopathy from toluene inhalation. N Engl J Med 275:1494–1496, 1966

Kono J, Miyata H, Ushijima S, et al: Nicotine, alcohol, methamphetamine, and inhalant dependence: a comparison of clinical features with the use of a new clinical evaluation form. Alcohol 24:99–106, 2001

Koob GF: Neural mechanisms of drug reinforcement. Ann N Y Acad Sci 654:171–191, 1992

Koob GF, Mason BJ, De Witte P, et al: Potential neuroprotective effects of acamprosate. Alcohol Clin Exp Res 26:586–592, 2002

Krenz S, Zimmermann G, Kolly S, et al: Ether: a forgotten addiction. Addiction 98:1167–1168, 2003

Kucuk NO, Kilic EO, Ibis E, et al: Brain SPECT findings in long-term inhalant abuse. Nucl Med Commun 21:769–773, 2000

Laurenzi RG, Locatelli C, Brucato A: N-Acetylcysteine: a proposal for therapy in acute poisoning due to highly hepatotoxic organic solvents. Vet Human Toxicol 29:95, 1987

Lazar RB, Ho SU, Melen O, et al: Multifocal central nervous system damage caused by toluene abuse. Neurology 33:1337–1340, 1983

Littrell KH, Petty RG, Hilligoss NM, et al: Olanzapine treatment for patients with schizophrenia and substance abuse. J Subst Abuse Treat 21:217–221, 2001

Lof A, Wigaeus Hjelm E, Colmsjo A, et al: Toxicokinetics of toluene and urinary excretion of hippuric acid after human exposure to 2H8-toluene. Br J Ind Med 50:55–59, 1993

Lolin Y: Chronic neurological toxicity associated with exposure to volatile substances. Hum Toxicol 8:293–300, 1989

Lonart G, Johnson KM: Inhibitory effects of nitric oxide on the uptake of [3H]dopamine and [3H]glutamate by striatal synaptosomes. J Neurochem 63:2108–2117, 1994

Lovinger DM, White G: Ethanol potentiation of 5-hydroxytryptamine3 receptor-mediated ion current in neuroblastoma cells and isolated adult mammalian neurons. Mol Pharmacol 40:263–270, 1991

Machu TK, Harris RA: Alcohols and anesthetics enhance the function of 5-hydroxytryptamine$_3$ receptors expressed in Xenopus laevis oocytes. J Pharmacol Exp Ther 271:898–905, 1994

Malm G, Lying-Tunell U: Cerebellar dysfunction related to toluene sniffing. Acta Neurol Scand 62:188–190, 1980

Manzoni O, Prezeau L, Marin P, et al: Nitric oxide-induced blockade of NMDA receptors. Neuron 8:653–662, 1992

Marlatt GA: Relapse prevention: theoretical rationale and overview of the model, in Relapse Prevention: Maintenance Strategies in the Treatment of Addictive Behaviors. Edited by Marlatt GA, Gordon JR. New York, Guilford, 1985, pp 3–70

Marsh N, Marsh A: A short history of nitroglycerine and nitric oxide in pharmacology and physiology. Clin Exp Pharmacol Physiol 27:313–319, 2000

Mayo-Smith MF: Pharmacological management of alcohol withdrawal: a meta-analysis and evidence-based practice guideline. American Society of Addiction Medicine Working Group on Pharmacological Management of Alcohol Withdrawal. JAMA 278:144–151, 1997

McLellan AT, Kushner H, Metzger D, et al: The fifth edition of the Addiction Severity Index. J Subst Abuse Treat 9:199–213, 1992

Mechanic JA, Maynard BT, Holloway FA: Treatment with the atypical antipsychotic, olanzapine, prevents the expression of amphetamine-induced place conditioning in the rat. Prog Neuropsychopharmacol Biol Psychiatry 27:43–54, 2003

Mennerick S, Jevtovic-Todorovic V, Todorovic SM, et al: Effect of nitrous oxide on excitatory and inhibitory synaptic transmission in hippocampal cultures. J Neurosci 18:9716–9726, 1998

Meredith TJ, Ruprah M, Liddle A, et al: Diagnosis and treatment of acute poisoning with volatile substances. Hum Toxicol 8:277–286, 1989

Merry J, Zachariadis N: Addiction to glue sniffing. Br Med J 5317:1448, 1962

Mihic SJ: Acute effects of ethanol on GABAA and glycine receptor function. Neurochem Int 35:115–123, 1999

Miller KW: The nature of the site of general anesthesia. Int Rev Neurobiol 27:1–61, 1985

Moen BE, Riise T, Haga EM, et al: Reduced performance in tests of memory and visual abstraction in seamen exposed to industrial solvents. Acta Psychiatr Scand 81:114–119, 1990

Morata TC, Dunn DE, Sieber WK: Occupational exposure to noise and ototoxic organic solvents. Arch Environ Health 49:359–365, 1994

Moser VC, Balster RL: The effects of acute and repeated toluene exposure on operant behavior in mice. Neurobehav Toxicol Teratol 3:471–475, 1981

Moser VC, Scimeca JA, Balster RL: Minimal tolerance to the effects of 1,1,1-trichloroethane on fixed-ratio responding in mice. Neurotoxicology 6:35–42, 1985

Naalsund LU: Hippocampal EEG in rats after chronic toluene inhalation. Acta Pharmacol Toxicol (Copenh) 59:325–331, 1986

Naranjo CA, Sellers EM: Clinical assessment and pharmacotherapy of the alcohol withdrawal syndrome, in Recent Developments in Alcoholism, Vol 4. Edited by Galanter M. New York, Plenum, 1986, pp 265–281

Naranjo CA, Sellers EM, Chater K, et al: Nonpharmacologic interventions in acute alcohol withdrawal. Clin Pharmacol Ther 34:214–219, 1983

National Inhalant Prevention Coalition: Inhalant Treatment Guidelines. Austin, TX, National Inhalant Prevention Coalition, 2003

Needleman P, Johnson EM: Vasodilator drugs and the treatment of angina, in Goodman and Gilman's The Pharmacological Basis of Therapeutics, 6th Edition. Edited by Goodman GA, Goodman LS, Gilman A. New York, Macmillan, 1980, pp 819–833

Nickerson M: Vasodilator drugs, in The Pharmacological Basis of Therapeutics, 4th Edition. Edited by Goodman LS, Gilman A. New York, Macmillan, 1970, pp 745–763

Nylander I: "Thinner" addiction in children and adolescents. Acta Paedopsychiatr 29: 273–283, 1962

Ortells MO, Lunt GG: Evolutionary history of the ligand-gated ion-channel superfamily of receptors. Trends Neurosci 18:121–127, 1995

Overall JE, Gorham DR: The Brief Psychiatric Rating Scale. Psychol Rep 10:799–812, 1962

Payne JP: The criminal use of chloroform. Anaesthesia 53:685–690, 1998

Pontieri FE, Tanda G, Orzi F, et al: Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs. Nature 382:255–257, 1996

Pontieri FE, Zocchi A, Orzi F: Mapping of functional changes associated with administration of substances of abuse in the rat. Funct Neurol 13:311–326, 1998

Preble E, Laury GV: Plastic cement: the ten cent hallucinogen. Int J Addict 2:271–272, 1967

Press E, Done AK: Solvent sniffing: physiologic effects and community control measures for intoxication from the intentional inhalation of organic solvents, I. Pediatrics 39:451–461, 1967

Price HL, Dripps RD: General anesthetics, in The Pharmacological Basis of Therapeutics, 5th Edition. Edited by Goodman LS, Gilman A. New York, Macmillan, 1975, pp 88–96

Pryor GT: Persisting neurotoxic consequences of solvent abuse: a developing animal model for toluene-induced neurotoxicity. NIDA Res Monogr 101:156–166, 1990

Pudiak CM, Bozarth MA: The effect of nitric oxide synthesis inhibition on intravenous cocaine self-administration. Prog Neuropsychopharmacol Biol Psychiatry 26:189–196, 2002

Rea TM, Nash JF, Zabik JE, et al: Effects of toluene inhalation on brain biogenic amines in the rat. Toxicology 31:143–1450, 1984

Rebert CS, Matteucci MJ, Pryor GT: Acute electrophysiologic effects of inhaled toluene on adult male Long-Evans rats. Pharmacol Biochem Behav 33:157–165, 1989

Reynolds JEF: Martindale: The Extra Pharmacopoeia, 28th Edition. London, Pharmaceutical Press, 1982, pp 745–746

Riegel AC, French ED: Acute toluene induces biphasic changes in rat spontaneous locomotor activity which are blocked by remoxipride. Pharmacol Biochem Behav 62:399–402, 1999

Riegel AC, Ali SF, French ED: Toluene-induced locomotor activity is blocked by 6-hydroxydopamine lesions of the nucleus accumbens and the mGluR2/3 agonist LY379268. Neuropsychopharmacology 28:1440–1447, 2003

Robins LN, Wing J, Wittchen HU, et al: The Composite International Diagnostic Interview: an epidemiological instrument suitable for use in conjunction with different diagnostic systems and in different cultures. Arch Gen Psychiatry 45: 1069–1077, 1989

Robinson TE, Berridge KC: The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Brain Res Rev 18:247–291, 1993

Rosenberg J: Brain damage and epilepsy in a sailor on a ship with chemicals. Tidsskr Nor Laegeforen 102:576–577, 1982

Rupreht J, Dworacek B, Bonke B, et al: Tolerance to nitrous oxide in volunteers. Acta Anaesthesiol Scand 29:635–638, 1985

Saito K, Wada H: Behavioral approaches to toluene intoxication. Environ Res 62:53–62, 1993

Saracibar G, Hernandez ML, Echevarria E, et al: Toluene alters mu-opioid receptor expression in the rat brainstem. Ind Health 39:231–234, 2001

Schikler KN, Seitz K, Rice JF, et al: Solvent abuse associated cortical atrophy. J Adolesc Health Care 3:37–39, 1982

Schroeder HG: Acute and delayed chloroform poisoning. Br J Anaeseth 37:972–975, 1965

Schwartz AM: The cause, relief and prevention of headaches arising from contact with dynamite. N Engl J Med 235:541–544, 1946

Schwartz RH, Peary P: Abuse of isobutyl nitrite inhalation (rush) by adolescents. Clin Pediatr 25:308–310, 1986

Sellers EM, Naranjo CA, Harrison M, et al: Diazepam loading: simplified treatment of alcohol withdrawal. Clin Pharmacol Ther 34:822–826, 1983

Sharp CW: Introduction to inhalant Abuse, in Inhalant Abuse: A Volatile Research Agenda (NIDA Research Monograph 129). Edited by Sharp CW, Beuvais F, Spence R. Rockville, MD, National Institute on Drug Abuse, 1992, pp 1–10

Smelson DA, Losonczy MF, Davis CW, et al: Risperidone decreases craving and relapses in individuals with schizophrenia and cocaine dependence. Can J Psychiatry 47: 671–675, 2002

Smith GB, Olsen RW: Functional domains of $GABA_A$ receptors. Trends Pharmacol Sci 16:162–168, 1995

Smith RA, Winter PM, Smith M, et al: Convulsions in mice after anesthesia. Anesthesiology 50:501–504, 1979

Stengard K, O'Connor WT: Acute toluene exposure decreases extracellular gamma-aminobutyric acid in the globus pallidus but not in striatum: a microdialysis study in awake, freely moving rats. Eur J Pharmacol 292:43–46, 1994

Stengard K, Hoglund G, Ungerstedt U: Extracellular dopamine levels within the striatum increase during inhalation exposure to toluene: a microdialysis study in awake, freely moving rats. Toxicol Lett 71:245–255, 1994

Stenqvist O: Nitrous oxide kinetics. Acta Anaesthesiol Scand 38:757–760, 1994

Sterman AB, Coyle PK: Subacute toxic delirium following nitrous oxide abuse. Arch Neurol 40:446–447, 1983

Stewart RD, Fisher TN, Hosko MJ, et al: Experimental human exposure to methylene chloride. Arch Environ Health 25:342–348, 1972

Substance Abuse and Mental Health Services Administration: Preliminary Estimates from the 1995 National Household Survey on Drug Abuse. Rockville, MD, U.S. Department of Health and Human Services, 1996

Tenenbein M, Pillay N: Sensory evoked potentials in inhalant (volatile solvent) abuse. J Paediatr Child Health 29: 206–208, 1993

Tobias JD: Tolerance, withdrawal, and physical dependency after long-term sedation and analgesia of children in the pediatric intensive care unit. Crit Care Med 28: 2122–2132, 2000

Tsushima WT, Towne WS: Effects of paint sniffing on neuropsychological test performance. J Abnorm Psychol 86:402–407, 1977

Turle N, Saget A, Zouani B, et al: Neurochemical studies of narcosis: a comparison between the effects of nitrous oxide and hyperbaric nitrogen on the dopaminergic nigro-striatal pathway. Neurochem Res 23:997–1003, 1998

Vleeming W, Rambali B, Opperhuizen A: The role of nitric oxide in cigarette smoking and nicotine addiction. Nicotine Tob Res 4:341–348, 2002

von Euler G, Ogren SO, Li XM, et al: Persistent effects of subchronic toluene exposure on spatial learning and memory, dopamine-mediated locomotor activity and dopamine D2 agonist binding in the rat. Toxicology 77:223–232, 1993

Von Keyserlingk H: Die Äthersucht. Der Nervenarzt 18:450–453, 1947

Walker DJ, Zacny JP: Analysis of the reinforcing and subjective effects of different doses of nitrous oxide using a free-choice procedure. Drug Alcohol Depend 66:93–103, 2002

Wang T, French ED: NMDA, kainate, and AMPA depolarize nondopamine neurons in the rat ventral tegmentum. Brain Res Bull 36:39–43, 1995

Weiner JL, Gu C, Dunwiddie TV: Differential ethanol sensitivity of subpopulations of GABAA synapses onto rat hippocampal CA1 pyramidal neurons. J Neurophysiol 77:1306–1312, 1997

Whitwam JG, Morgan M, Hall GM, et al: Pain during continuous nitrous oxide administration. Br J Anaesth 48:425–429, 1976

Wiley JL, Bale AS, Balster RL: Evaluation of toluene dependence and cross-sensitization to diazepam. Life Sci 72:3023–3033, 2003

Wise RA, Bozarth MA: A psychomotor stimulant theory of addiction. Psychol Rev 94: 469–492, 1987

Wood RW: Stimulus properties of inhaled substances. Environ Health Perspect 26:69–76, 1978

Wood RW, Grubman J, Weiss B: Nitrous oxide self-administration by the squirrel monkey. J Pharmacol Exp Ther 202:491–499, 1977

Wood RW, Coleman JB, Schuler R, et al: Anticonvulsant and antipunishment effects of toluene. J Pharmacol Exp Ther 230:407–412, 1984

World Health Organization: The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines. Geneva, World Health Organization, 1992

Yamakura T, Harris RA: Effects of gaseous anesthetics nitrous oxide and xenon on ligand-gated ion channels: comparison with isoflurane and ethanol. Anesthesiology 93:1095–1101, 2000

Yanagita T, Takahashi S, Ishida K, et al: Voluntary inhalation of volatile anesthetics and organic solvents by monkeys. Jpn J Clin Pharmacol 1:13–16, 1970

Yavich L, Zvartau E: A comparison of the effects of individual organic solvents and their mixture on brain stimulation reward. Pharmacol Biochem Behav 48:661–664, 1994

You L, Muralidhara S, Dallas CE: Comparisons between operant response and 1,1,1-trichloroethane toxicokinetics in mouse blood and brain. Toxicology 93:151–163, 1994

Zimmet SV, Strous RD, Burgess ES, et al: Effects of clozapine on substance use in patients with schizophrenia and schizoaffective disorder: a retrospective survey. J Clin Psychopharmacol 20:94–98, 2000

9

Tobacco

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Comprehensive treatment of tobacco addiction is necessary because of the addictive nature of nicotine and the serious health consequences of tobacco dependence (Fiore et al. 2000). Approximately one-third of individuals who experiment with cigarettes become regular smokers (see Henningfield 1995). Once dependence develops, tobacco addiction can become a chronic relapsing disorder with dire medical consequences. Indeed, cigarette smoking is responsible for approximately 430,000 deaths each year in the United States (Giovino 2002).

Fortunately, effective smoking treatments (both behavioral and pharmacological) are now available (George and O'Malley 2004). Although behavioral interventions are an integral part of smoking treatment, our review will

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cover only pharmacotherapies that aid in smoking cessation (see George and O'Malley 2004). A variety of recent publications discuss the behavioral treatment of tobacco dependence (Fiore et al. 1996). Specifically, we discuss here the phenonomenology of nicotine addiction and clinical aspects of tobacco dependence and withdrawal, nicotine replacement therapy (NRT) products, and other medications that may enhance smoking cessation rates and/or reduce smoking relapse. We also briefly review nicotine dependence pharmacotherapies for persons with psychiatric and medical comorbidity.

Phenomenology of Nicotine Addiction and Clinical Aspects of Withdrawal

The primary addictive substance in cigarette smoke is nicotine. Cigarette smoking is a very efficient nicotine delivery system because nicotine is aerosolized and subsequently absorbed through the extensive pulmonary vasculature. Consequently, smoking produces high arterial nicotine concentrations (i.e., compared with venous concentrations) (Henningfield 1995). These high arterial concentrations deliver a bolus of 1–3 mg of nicotine rapidly to the brain (i.e., within seconds after the onset of smoking) (Henningfield 1995). A number of neurotransmitters are released with nicotinic receptor activation, including dopamine, norepinephrine, serotonin, and endogenous opioids. The immediate positive reinforcing effects of smoking include a reduction in anxiety and increased alertness and concentration.

Nicotine's half-life is 2 hours, so repeated administration is needed throughout the day for continued effects. Consequently, daily smokers usually smoke at frequent intervals to maintain a narrow range of nicotine levels. Parodoxically, chronic administration of nicotine results in an increase in the number of nicotinic receptors, presumably resulting from chronic nicotinic receptor desensitization and inactivation. An increased number of receptors may play a role in the withdrawal symptoms many smokers experience with prolonged cigarette abstinence (Dani and De Biasi 2001). Withdrawal symptoms include dysphoria or depressed mood, insomnia, irritability, anxiety, frustration, difficulty in concentration, and increased appetite and weight gain. Withdrawal symptoms typically peak within 24–36 hours after cessation and usually diminish after 1 week of abstinence, but prolonged withdrawal may occur in some

individuals. Thus, some individuals may continue smoking cigarettes to avoid the negative symptoms of withdrawal (i.e., negative reinforcement of smoking behavior) (Henningfield 1995). It seems probable that both the primary, positively reinforcing effects of smoking and the avoidance of withdrawal symptoms sustain tobacco use in most smokers.

Pharmacological Treatments for Tobacco Dependence

Nicotine Replacement Therapies

Nicotine replacement therapies (NRTs) were designed to enhance efficacy rates during smoking cessation by replacing some of the nicotine usually delivered by smoking (Henningfield 1995). The U.S. Food and Drug Administration (FDA)–approved NRTs for smoking cessation include 2- and 4-mg nicotine polacrilex gum and nicotine lozenge, transdermal nicotine, nicotine nasal spray, and nicotine inhaler. All replacement therapies have been shown to significantly increase smoking cessation success rates. The choice of NRT for an individual patient depends on the patient's preference, the side effects of the NRT, the presence of other medical conditions, and previous success or failure with a certain type of NRT. All NRTs yield an approximate doubling of the smoking quit rates, relative to placebo, in clinical trials. A review of NRTs, which are considered first-line treatment for smoking cessation, follows.

Nicotine Gum

Nicotine polacrilex gum was the first NRT marketed for smoking cessation. Two- and 4-mg doses are available in a variety of flavors (i.e., original, mint, and orange) for over-the-counter purchase. Nicotine gum contains nicotine bound to an ion exchange resin. The nicotine in nicotine gum is released slowly into the mouth and absorbed through the buccal mucosa. Nicotine gum is most beneficial with concurrent behavioral therapy and when used on a fixed schedule (i.e., chewing one piece every 1–2 hours) rather than ad lib dosing. The recommended treatment duration for nicotine gum is 1–3 months; however, benefits may occur with a longer duration of treatment (Fiore et al. 2000).

The gum should be chewed slowly, with intermittent parking of the gum at the side of the mouth, to avoid adverse effects (e.g., hiccups, heartburn, stomach upset). Only 50% of the nicotine in a piece of gum is systemically

absorbed. Nicotine concentrations peak approximately 30 minutes after the onset of chewing (Henningfield 1995). The starting dose for individuals who smoke fewer than 20 cigarettes per day is 2 mg, whereas the 4-mg dose is recommended for heavier smokers (Henningfield 1995). This recommendation comes in part from studies that show a higher dose of gum is more beneficial for heavier smokers. The gum should probably not be prescribed to persons with temporomandibular joint disease or those who have dental or oral problems that could be exacerbated by gum chewing.

Nicotine Lozenge

The nicotine lozenge contains nicotine bound to a polacrilex ion-exchange resin (similar to the nicotine gum). It is available for over-the-counter purchase in 2- and 4-mg dosage forms. Because the lozenge does not require chewing, it may be preferable to the gum for patients with dental problems and for patients who find chewing gum objectionable. The lozenge formulations release 25% more nicotine, compared to an equal dose of the gum (Shiffman et al. 2002). In a large randomized trial, low-dependence smokers (i.e., those who waited longer than 30 minutes upon awakening to have their first cigarette) were randomly assigned to receive the 2-mg lozenge or a matching placebo and highly dependent smokers (i.e., those who had their first cigarette within 30 minutes upon awakening) were randomly assigned to receive the 4-mg lozenge or placebo for at least 24 weeks (Shiffman et al. 2002). Participants in the active lozenge group had a significantly higher 28-day abstinence rate at 6 weeks, compared to the placebo group, for both the 2-mg (46% vs. 29.7%; $P<0.001$) and 4-mg doses (48.7% vs. 20.8%; $P<0.001$). Efficacy of the drug was sustained through a 1-year follow-up.

Patients who use the lozenge for smoking cessation should use one lozenge every 1–2 hours for the first 2–4 weeks, decreasing the interval to every 2–4 hours thereafter. Adverse effects that are common with the nicotine lozenge include heartburn, hiccups, and nausea (Shiffman et al. 2002). Because the product contains phenylalanine, the lozenge should not be used for smoking cessation by individuals with phenylketonuria.

Transdermal Nicotine

Transdermal nicotine (i.e., the nicotine patch) is also available over the counter for smoking cessation. This form of nicotine delivery may be espe-

cially useful for smoking cessation because a constant delivery of nicotine may aid in patients' adherence to NRT. Eight weeks of treatment are generally sufficient for smoking cessation (Fiore et al. 1994). Compared with other NRTs, transdermal nicotine probably has the lowest abuse potential, because there are few or no withdrawal symptoms after treatment has ended and the patient does not have control over nicotine delivery.

Transdermal nicotine is available in a variety of formulations and dosing schedules (e.g., 15 mg/16 hours; 7, 14, and 21 mg/24 hours; and 11 and 22 mg/24 hours) (Cinciprinni and McClure 1998). Peak nicotine concentrations for the various systems are reached 2–6 hours after application, and steady state conditions occur 2–3 days after continued patch use (Henningfield 1995). The highest-dose patch (i.e., 21 or 22 mg/24 hours or 15 mg/16 hours) delivers approximately 0.9 mg of nicotine per hour transdermally (Henningfield 1995).

The transdermal system is applied in the morning and removed either before bedtime or the next morning. Among individuals smoking 10 or more cigarettes per day, the highest dose patch should be used to start; an intermediate dose can be used if the patient smokes fewer than 10 cigarettes per day (Henningfield 1995). Although dosage reduction is usually recommended after 2–4 weeks with most formulations to ease smokers off NRT because of clinical concerns about nicotine withdrawal from transdermal nicotine, no benefit of dosage reduction on patch efficacy was found in one meta-analysis (Fiore et al. 1994), and, in fact, there is little evidence for a clinically significant nicotine withdrawal syndrome after transdermal nicotine discontinuation. Transdermal nicotine should not be used for patients that have skin conditions that could be exacerbated by the patch.

Nicotine Nasal Spray

Nicotine nasal spray delivers nicotine through the nasal mucosa. One advantage of nicotine nasal spray is that it relieves tobacco cravings quickly. One study found that nicotine nasal spray was 2.6 times more likely to produce smoking cessation, compared with placebo, at 1 year (Sutherland et al. 1992). The active spray was also the most beneficial among highly dependent smokers (Sutherland et al. 1992).

The nasal spray is available only by prescription. One spray to each nostril constitutes a dose. Although one dose delivers approximately 1 mg of nicotine,

only 0.5 mg of nicotine is systemically absorbed. Patients should initially use one or two doses per hour but should not exceed more than five doses per hour or 40 doses/day (Sutherland et al. 1992). The nasal spray delivers nicotine rapidly, with venous nicotine concentrations peaking at 5–10 minutes after administration (Sutherland et al 1992). Compared with other nicotine delivery systems, nicotine nasal spray, most closely approximates the pharmacokinetic profile of nicotine following smoking. Given that this form of NRT is administered nasally, patients with rhinitis, nasal polyps, or sinusitis should probably not use nicotine nasal spray for smoking cessation. The nasal spray produces some initial irritation of the nasal mucosa at the dosage formulation (10 mg/mL) that is available commercially, but this effect subsides with repeated dosing.

Nicotine Inhaler

Nicotine (vapor) inhalers, which are used by puffing through a cartridge inhaler, may be useful for smoking cessation in some patients because its use is similar to the smoking ritual (i.e., holding the device, with repeated hand-to-mouth activity and puffing on the device, replicates many of the sensory and motoric aspects of smoking) and it delivers nicotine rapidly (although not as rapidly as the nasal spray). In one placebo-controlled study, in which subjects were allowed to use an inhaler for up to 6 months, quit rates at 1 year remained higher in the nicotine inhaler group than in the placebo inhaler group (28% and 18%, respectively; $P=0.046$) (Hjalmarson et al. 1997).

This product is also only available by prescription. The recommended treatment period is up to 24 weeks (McNeil Consumer Products 1997). Using the inhaler by puffing 80 deep inhalations over 20 minutes results in a systemic absorption through the buccal mucosa of 2 mg of nicotine, with maximal nicotine concentrations occurring 15 minutes after the end of inhalation. When the product is used as directed, the patient will likely use 6–16 inhalers per day. This form of NRT is relatively contraindicated in patients with asthma because, although most of the nicotine is absorbed through the buccal mucosa and it is not delivered to the lungs (McNeil Consumer Products 1997), nicotine by inhalation may produce bronchial constriction.

Combined NRT Formulations

As previously discussed, currently available NRT products typically double the rate of smoking cessation, relative to placebo. It has been suggested that one

way to improve efficacy further would be to combine a passive and continuous nicotine delivery system (i.e., the patch) with an active and intermittent delivery system (e.g., the gum, inhaler, or spray) (Fiore et al. 2000; American Psychiatric Association, in press). The rationale for combined treatment is that smokers may need a constant delivery of nicotine to alleviate withdrawal symptoms as well as an ad-lib nicotine medication that can be used to control smoking urges and further relieve withdrawal symptoms (Sweeney et al. 2001). Moreover, two nicotine replacement products may provide a higher degree of nicotine substitution, compared to monotherapy. Findings from three studies have suggested that combination regimens may increase efficacy.

One study comparing active patch (15 mg/16 hours for 12 weeks, 10 mg/16 hours for 6 weeks, and 5 mg/16 hours for 6 weeks) and 2-mg nicotine gum (for 6 months) to active patch and placebo gum found that the combined treatment had greater efficacy at 24 weeks (34% for the combined treatment vs. 23% for active patch and placebo gum; $P=0.027$) (Kornitzer et al. 1995). However, efficacy was not sustained at 1 year. Another study compared "combination treatment" consisting of an active patch (15mg/16 hours for 12 weeks with a 6-week taper) and active gum (2-mg nicotine gum for 6 months, at which time withdrawal was encouraged) to "gum only" (placebo patch and active gum) and found greater efficacy at 3 months for the combination treatment (39% vs. 28%; $P=0.038$), but the results were not sustained at 1 year (Puska et al. 1995). A third study showed that active patch and nasal spray was superior to active patch and placebo spray for smoking cessation (Blondal et al. 1999a). Subjects used the patch for 5 months and the spray for up to 1 year. At 1 year, smoking cessation rates were 27% in the combination group versus 11% in the patch-only group ($P=0.001$). These studies suggested that the combined use of a constant and an intermittent delivery system may improve smoking cessation rates over those observed with a single agent, but more research is needed in this area before definitive recommendations can be made (Sweeney et al. 2001). It is noteworthy that no significant adverse events related to nicotine toxicity were noted in any of these trials; however, combining NRT products is not an FDA-approved treatment for smoking cessation.

Nonnicotine Pharmacotherapies

Given that not all smokers respond well to NRT, and because many smokers have comorbid symptoms that suggest that mechanisms independent of the

nicotinic receptor may increase vulnerability to nicotine dependence, there has been considerable interest in nonnicotine medications to treat nicotine dependence, either alone or in combination with NRTs. The observations that the antidepressant bupropion has potential as a treatment for smoking cessation and that other antidepressants (e.g., tricyclic antidepressants and selective serotonin reuptake inhibitors [SSRIs]) may modify smoking behaviors have catalyzed intensive research into agents that act directly on dopamine, norepinephrine, serotonin, glutamate, γ-aminobutyric acid (GABA), nicotinic, cannabinoid, or opioid receptors. We review here data on the safety and efficacy of bupropion and other nonnicotine therapies. Of the nonnicotine medications for smoking cessation, only sustained-release bupropion is currently considered a first-line treatment for cigarette smokers.

Sustained-Release Bupropion

The phenylaminoketone atypical antidepressant agent bupropion (amfebutamone) as a sustained-release (SR) formulation (Zyban) is considered a first-line pharmacological treatment for nicotine-dependent smokers who want to quit smoking. The mechanism of action of this antidepressant in the treatment of nicotine dependence likely involves blockade of dopamine and norepinephrine reuptake (Ascher et al. 1995), as well as antagonism of high-affinity nicotinic acetylcholine receptors (Slemmer et al. 2000). The goals of bupropion therapy for nicotine dependence are 1) cessation of smoking behavior and 2) reduction of nicotine withdrawal symptoms. In addition, bupropion SR may delay cessation-induced weight gain.

Efficacy. A pivotal study by Hurt et al. (1997) established the efficacy and safety of bupropion SR for treatment of nicotine dependence, which led to its approval for this indication by the FDA in 1998. This study was a 7-week, double-blind, placebo-controlled, multicenter trial of three doses of bupropion SR (100 mg/day, 150 mg/day, or 300 mg/day in twice daily dosing). Patients were 615 cigarette smokers who smoked at least 15 cigarettes/day. The medication was administered in combination with weekly individual cessation counseling. End-of-trial 7-day point prevalence cessation rates were 19.0% for placebo and 28.8%, 38.6%, and 44.2% for the 100 mg/day, 150 mg/day, and 300 mg/day bupropion doses, respectively. At 1-year follow-up, cessation rates were 12.4% for placebo and 19.6%, 22.9%, and 23.1% for the 100 mg/day,

150 mg/day, and 300 mg/day bupropion doses, respectively. Bupropion treatment dose-dependently reduced weight gain associated with smoking cessation and significantly reduced nicotine withdrawal symptoms at the 150mg/day and 300 mg/day doses. In this study, the major side effects associated with bupropion, compared with placebo, were insomnia and dry mouth. Accordingly, the target dosage for bupropion treatment of smoking cessation that was recommended was 150 mg daily for 3–4 days, with a subsequent increase to 150 mg twice daily. The "target quit date" is typically set on the eighth day of bupropion treatment, when bupropion levels are at steady state concentrations.

The combination of bupropion SR with the nicotine transdermal patch was evaluated in a double-blind, double placebo-controlled, randomized multicenter trial (Jorenby et al. 1999). A total of 893 cigarette smokers who smoked at least 15 cigarettes/day were randomly assigned to one of four groups: 1) placebo bupropion (0 mg/day) plus placebo patch, 2) bupropion (300 mg/day) plus placebo patch, 3) placebo bupropion plus nicotine patch (21 mg/day for 4 weeks, followed by 2 weeks of 14 mg/day and 2 weeks of 7 mg/day), and 4) bupropion (300 mg/day) plus nicotine patch (21 mg/day for 4 weeks, followed by 2 weeks of 14 mg/day and 2 weeks of 7 mg/day). Bupropion was administered 1 week before the target quit date (day 15), at which time patch treatment was initiated for a total of 8 weeks. All subjects received weekly individual smoking cessation counseling. Cessation rates at the 1-year follow-up assessment were 15.6% for placebo, 16.4% for active nicotine transdermal patch alone, 30.3% for bupropion alone, and 35.5% for the combination of patch and bupropion. The rates for both the group receiving bupropion plus the patch and the bupropion-only group were significantly better than those for the placebo group and the patch-only group, but the rate for the combination was not significantly better than that for bupropion only. Weight suppression after cessation was most robust in the combination therapy group. Side effects were consistent with the profiles of both the patch and bupropion, and the combination was well tolerated. It is noteworthy that patch-only treatment was significantly different from placebo at the end of the trial but not at the follow-up assessments. In this trial, 6.1% of the subjects who were randomly assigned to receive combination treatment with the nicotine patch and bupropion developed hypertension. Most of the subjects who developed hypertension had preexisting hypertension; however, patients

who are using NRT and bupropion together for smoking cessation should have their blood pressure monitored.

Use in smoking cessation in psychiatric or substance abuse populations. Some studies have suggested that bupropion SR may be useful for smoking cessation/reduction in psychiatric patients who smoke or in substance-misusing smokers. Hayford et al. (1999), in a secondary analysis of data from the study by Hurt et al. (1997), found that bupropion SR was equally efficacious for smoking cessation in smokers irrespective of a history of major depression or alcoholism. However, no prospective studies of the use of bupropion in recovering alcoholic patients or in substance abusers have been published. As for psychiatric patients, Chengappa et al. (2001) studied open-label bupropion for smoking cessation in a group of 25 patients with major depression and nicotine dependence who were being treated with an SSRI. These investigators found that eight of 25 patients (32%) had quit smoking by the end of the 9-week trial.

Bupropion SR has been evaluated in three trials involving patients with schizophrenia, including an open-label trial of 300 mg/day (Weiner et al. 2001) and placebo-controlled trials of 150 mg/day (Evins et al. 2001) and 300 mg/day (George et al. 2002). Weiner et al. (2001) conducted a 26-week trial of open-label bupropion SR (300 mg/day), with 14 weeks of initial cognitive-behavioral group therapy in a group of eight schizophrenic patients who smoked. The overall reduction in expired carbon monoxide (CO) levels was about 40%, compared with levels before starting therapy, and one of the eight subjects achieved smoking cessation by the end of the trial. Negative symptoms of schizophrenia were reduced by bupropion during the trial. Similarly, in a double-blind trial of 12 weeks' duration, Evins et al. (2001) found that among 18 schizophrenic patients who were smokers, bupropion (150 mg/day) led to a 40%–50% reduction in CO levels, compared with placebo. One of nine subjects in the bupropion group versus none of nine in the placebo group had achieved smoking cessation by the end of the trial. During this trial, bupropion reduced both positive and negative symptoms of schizophrenia. In the third study, George et al. (2002) conducted a double-blind, placebo-controlled 10-week trial of bupropion SR (300 mg/day) in a sample of 32 nicotine-dependent smokers with schizophrenia or schizoaffective disorder. All subjects received weekly group therapy emphasizing motivational

enhancement, relapse prevention, and social skills training. Trial endpoint cessation rates (confirmed by a CO level <10 ppm) were 8 of 16 (50%) in the bupropion group and 2 of 16 (12.5%) in the placebo group ($P<0.05$). Positive symptoms of schizophrenia were not affected, but negative symptom scores were reduced by approximately 15% in the bupropion group. In addition, treatment with atypical antipsychotic (versus neuroleptic) drugs strongly predicted success in smoking cessation in schizophrenic patients. Accordingly, results from these preliminary studies suggest that 1) smoking reduction or cessation is possible in patients with schizophrenia (with endpoint cessation rates ranging from 11% to 50%); 2) exacerbation of psychotic symptoms is unlikely and negative symptoms of schizophrenia may be reduced; and 3) the drug's efficacy for smoking cessation may be greater at higher doses in this population.

Side effects. The primary side effects reported with bupropion administration in cigarette smokers are headache, dry mouth, nausea and vomiting, insomnia, and activation. Although most of these adverse effects occur during the first week of treatment, insomnia can persist. Seizures are of exceedingly low occurrence (<0.5%) at doses of 300 mg daily or less, but a prior history of seizures or a seizure disorder contraindicate its use.

Other Nonnicotine Pharmacotherapies

Findings from studies of several non-FDA-approved nonnicotine pharmacotherapies for nicotine dependence are summarized in the following sections.

Nortriptyline. Nortriptyline, a tricyclic antidepressant, has been shown in double-blind, placebo-controlled randomized trials to be superior to placebo for smoking cessation (Prochazka et al. 1998). Nortriptyline appears to have efficacy comparable to that of bupropion for smoking cessation (Hall et al. 2002). The efficacy of this agent may be improved with more intensive behavioral therapies (Hall et al. 1998). Nortriptyline's mechanism of action is thought to relate to its noradrenergic and serotonergic reuptake blockade, because these two neurotransmitters have been implicated in the neurobiology of nicotine dependence. Side effects of nortiptyline are typical of tricyclic antidepressants and include dry mouth, blurred vision, constipation, and orthostatic hypotension. Nortriptyline appears to have some utility for smokers with a past history of major depression, and it can be recommended as a second-

line agent after NRTs and bupropion, although more study of nortriptyline is needed.

Mecamylamine. Mecamylamine, a noncompetitive blocker at the ion channel site of both high-affinity central nervous system and peripheral nicotinic receptors, may decrease some of the positive subjective effects of cigarette smoking (Clarke 1991; Stolerman et al. 1973). When mecamylamine was given to smokers who were not trying to stop smoking, they initially increased their smoking in an attempt to overcome the blockade produced by the drug (Clarke 1991; Stolerman et al. 1973). Mecamylamine does not precipitate withdrawal in humans, perhaps because it is a noncompetitive antagonist of high-affinity nicotinic receptors that does not bind to the nicotine binding site (Clarke 1991; Stolerman et al. 1973). The initial studies provided limited evidence of short-term efficacy with mecamylamine, but the high doses used produced significant dropout rates due to side effects (Clarke 1991; Stolerman et al. 1973). Side effects included abdominal cramps, constipation, dry mouth, and headaches. On the basis of a theory that combined blockade and agonist therapy might be beneficial (Rose and Levin 1991), two randomized, controlled trials were conducted comparing mecamylamine in combination with nicotine patch with placebo and nicotine patch (Rose et al. 1998, 1994). The rationale for the study design was that mecamylamine would reduce the rewarding effects of nicotine, and the nicotine patch would reduce nicotine withdrawal symptoms. The study provided evidence of the efficacy of the combination therapy, and trials of the combination of transdermal mecamylamine and nicotine patch for smoking cessation are in progress. Overall, however, mecamylamine lacks sufficient evidence to be recommended for smoking cessation, but it is considered a promising approach.

Clonidine. Clonidine dampens sympathetic activity originating at the locus coeruleus by stimulation of presynaptic α_2-adrenergic receptors in the sympathetic chain (Covey and Glassman 1991; Hughes 1994). It appears to have some efficacy for alcohol and opioid withdrawal and thus was evaluated for treatment of nicotine withdrawal as well (Covey and Glassman 1991; Hughes 1994). Several clinical trials used oral or transdermal clonidine in doses of 0.1–0.4 mg/day for 2–6 weeks with or without behavior therapy. Three meta-analytic reviews reported that clonidine improved quit rates (Covey and Glassman 1991; Gourlay and Benowitz 1995; Law and Tang 1995).

The most common side effects of clonidine are dry mouth, sedation, and constipation (Gourlay and Benowitz 1995). Postural hypotension, rebound hypertension, and depression were rare with use of clonidine for smoking cessation (Gourlay and Benowitz 1995). Several studies have suggested that clonidine is more effective in women than in men; however, other studies have failed to find this association (Gourlay and Benowitz 1995). In general, the effects of clonidine have not proven to be as robust as those of NRTs, but this agent should be considered as a second-line therapy for smokers for whom initial treatment with NRTs or bupropion failed.

Naltrexone. Naltrexone hydrochloride is a long-acting form of the opioid antagonist naloxone. The rationale for using naltrexone for smoking cessation is that the performance-enhancing and other positive effects of nicotine may be mediated by opioid receptors (Pomerleau and Pomerleau 1984). Most, but not all, studies have found that naltrexone increases smoking (interpreted again as an attempt to overcome blockade) (Hughes 1994; Sutherland et al. 1995), although a recent trial in recovering alcoholic patients suggested that naltrexone may reduce smoking consumption by about five cigarettes per day, even though it appears to have little utility in smoking cessation (Rohsenow et al. 2003). The side effects of naltrexone include elevated liver enzyme values, nausea, and blockade of analgesia from narcotic pain relievers (Hughes 1994). There is little evidence to support the efficacy of naltrexone hydrochloride alone for smoking cessation (Sutherland et al. 1995), and results are conflicting as to whether adding it to the nicotine patch enhances efficacy (Covey et al. 1999; Krishnan-Sarin et al. 2004).

Buspirone. Buspirone is a 5-HT_{1A} receptor partial agonist that acts as an anxiolytic but produces minimal, if any, sedation and has no apparent abuse potential or risk of physical dependence. Side effects of buspirone include headache, nausea, dizziness, and muscle tension. Some short-term trials reported that buspirone appeared to reduce nicotine withdrawal, but others failed to support this finding (Hughes 1994). Buspirone improved short-term smoking cessation rates in unselected smokers and improved abstinence in smokers with high levels of anxiety (Hughes 1994). Schneider et al. (1996) conducted a double-blind, placebo-controlled, randomized trial of buspirone (60 mg/day) for 6 weeks in 100 cigarette smokers. At the end of the trial, cessation rates were no different between the drug and placebo groups (20% and

25%, respectively). There were also no group differences at 1-year follow-up. Anxiety levels before cessation were not predictive of outcome, and the agent did not reduce nicotine withdrawal symptoms or craving. Because of its favorable side effect profile and some evidence of efficacy, buspirone is classed as a promising therapy, but at this time it cannot be recommended for treatment of nicotine dependence.

SSRIs. The available evidence provides little support for the use of SSRIs to assist in smoking cessation, either alone (Niaura et al. 2002) or in combination with NRTs. Placebo-controlled trials of fluoxetine combined with the nicotine inhaler (Blondal et al. 1999b) and paroxetine combined with the nicotine patch (Killen et al. 2000) failed to show that either of these combinations augments smoking cessation rates, relative to the effects of the NRT plus placebo. Thus, the use of SSRIs for smoking cessation is not recommended. However, there may be some utility to the use of SSRIs in smokers with a history of depression.

Monoamine oxidase (MAO) inhibitors. Drugs that produce inhibition of MAO-A and MAO-B theoretically could be helpful for smoking cessation, because they result in blockade of the metabolism of neurotransmitters involved in the biology of nicotine dependence, such as dopamine (MAO-B inhibitors) and serotonin and norepinephrine (MAO-A inhibitors), leading to increases in their synaptic levels, which are reduced during acute tobacco withdrawal. The net effect of treatment with these agents could be to reverse the effects of withdrawal, thereby ameliorating withdrawal symptoms and the risk of a relapse to smoking. A single trial of the MAO-A inhibitor moclobemide provided evidence of a short-term increase in the rate of smoking cessation in a sample of 88 smokers (Berlin et al. 1995). Furthermore, a preliminary trial by George et al. (2003) in a group of 40 smokers provided support for the short-term efficacy of the MAO-B inhibitor selegiline hydrochloride for smoking cessation. Larger trials of these agents are warranted before firm recommendations for their use for smoking cessation can be made.

Lobeline. The alkaloid lobeline, whose mechanism of action in unclear but that appears to have dopamine reuptake blockade and nicotinic receptor antagonist properties (Dwoskin and Crooks 2002), was evaluated in a double-blind, randomized, placebo-controlled, multicenter trial involving 180 ciga-

rette smokers for a total of 6 weeks (Glover et al. 1998). Subjects took 7.5-mg sublingual tablets of lobeline ($n=90$) or placebo ($n=90$) up to nine times daily. All subjects received weekly behavioral counseling. There was no difference between the groups in trial endpoint smoking cessation rates (26% in each) in the intent-to-treat analysis; this finding was not altered when data were limited to completers or to those with documented adherence to the study medication. Thus, there is little evidence that lobeline is a useful pharmacotherapy for smoking cessation, and, consequently, it cannot be recommended.

Studies of Relapse Prevention

Although a large number of studies have examined the use of pharmacotherapy for smoking cessation, there are far fewer studies on its use in preventing smoking relapse. The paucity of reports on the extended use of NRTs for the prevention of smoking relapse may be related to concerns over the potential for abuse of NRTs with extended use (American Psychiatric Association, in press). However, it is recommended that for a patient who reports prolonged urges to smoke or reports nicotine withdrawal symptoms, the clinician should consider extending the current approved pharmacotherapy or adding an additional pharmacotherapy (Fiore et al. 2000). If a patient is concerned that weight gain may threaten relapse, continued use of bupropion SR or nicotine gum has been shown to delay weight gain (Fiore et al. 2000).

Recent studies have extended the use of bupropion for smoking cessation to the prevention of smoking relapse. Hays et al. (2001) compared the effects of bupropion with placebo for the prevention of smoking relapse in 784 cigarette smokers who achieved smoking abstinence after a 7-week open-label trial of bupropion (300 mg/day). Abstinent smokers were randomly assigned to receive bupropion (300 mg/day) or placebo for a total of 45 weeks. The majority (58.8%) of the smokers enrolled in the open-label phase of the trial quit smoking. Significantly more smokers were abstinent at the end of the 52-week treatment period in the bupropion group, compared with the placebo group (55.1 vs. 42.3%, $P<0.01$), but no difference was evident at the 1-year posttreatment follow-up assessment. In addition, the number of days to smoking relapse was greater in the bupropion group, compared with the placebo group (156 vs. 65 days, $P<0.05$). Weight gain was significantly less in the bupropion group, both at the end of treatment and at the 1-year follow-up. The results of this study support the efficacy of bupropion SR in preventing smok-

ing relapse. However, the question of how long bupropion therapy can be continued as a maintenance treatment requires further study.

Treatment of Special Populations of Smokers

Patients With Comorbid Psychiatric Disorders

Alcohol and Drug Abuse

Strong evidence exists that rates of smoking in substance abusers (60%–90%) are much higher than those in the general population and that the presence of alcohol and/or illicit drug use is a predictor of negative smoking cessation treatment outcomes (Hughes 1996). Conditioned effects of substance use with smoking, which result from the frequent concurrence of these behaviors, may be an important factor in determining the high rates of both comorbidity and smoking cessation treatment failure. Nonetheless, many alcohol and drug abusers express an interest in smoking cessation, and motivational interventions should be used for patients who do not express a current interest in quitting. There is little evidence to suggest that smoking cessation can increase the risk of relapse for alcohol and substance use disorders. There is also little evidence to guide whether smoking cessation should be attempted concurrently with efforts to accomplish abstinence from alcohol and drugs or after abstinence from these substances has been achieved, and thus this decision may best be guided by the patient's preference. In addition, studies of pharmacotherapies for smoking cessation in substance abusers are few (Kalman et al. 2001), but there is some evidence for the utility of combined NRT and behavioral approaches. Use of pharmacotherapy for alcoholism, such as disulfiram or naltrexone, may be considered in alcoholic smokers, but there are no empirical studies to support their efficacy. Despite the lack of an empirical basis to optimize smoking cessation among substance abusing patients, the substantial risk that smoking represents in this population (Hurt et al. 1996) supports the use of systematic efforts to promote smoking cessation in substance abuse treatment programs.

Depression

Persons with depressive symptoms or major depression also have high rates of smoking (40%–60% prevalence), and depression appears to be a predictor of

negative treatment outcome during smoking cessation (Covey et al. 2000; Niaura et al. 2001). Pharmacotherapies for smoking cessation have not been carefully tested in patients with major depression, but, given the efficacy of these agents in nondepressed smokers and their effects in depression, antidepressants such as bupropion and nortriptyline should be strongly considered (Fiore et al. 2000). Behavioral therapies, including cognitive-behavioral therapy, should also be considered for depressed smokers, as these patients are likely to fail at smoking cessation with interventions that are less intensive. After smoking cessation, plasma levels of antidepressants that are metabolized by the cytochrome P450 enzyme 1A2 (CYP1A2) (e.g., tricyclic antidepressants) may increase, necessitating close monitoring of antidepressant levels and side effects.

Schizophrenia

As in patients with depression and substance use disorders, rates of smoking in schizophrenic patients are much higher (58%–88%) than in the general population (George and Vessicchio 2001). Motivation to quit smoking is often poor in these patients, and thus motivational interventions may be useful as initial treatments. Rates of smoking cessation for these patients are very low (Lasser et al. 2000), suggesting that more intensive interventions are needed. Such interventions would appear to be of paramount importance, because it has been shown that schizophrenic patients have higher rates of lung cancer and cardiovascular disease, compared to the general population (Lichtermann et al. 2001).

There have been several preliminary controlled cessation trials of combinations of higher intensity behavioral support and pharmacotherapies (NRT or bupropion) for patients with schizophrenia that have had modest short-term cessation rates (Addington et al. 1998; Evins et al. 2001; George et al. 2000; George et al. 2002; Ziedonis and George 1997). Concurrent alcohol and drug abuse occurs with a high rate in these patients and can complicate cessation efforts. Most studies have attempted to promote smoking cessation in schizophrenic patients with dual diagnoses whose drug abuse is in recovery and who are psychiatrically stable. Plasma levels of antipsychotic medications that are metabolized by the CYP1A2 system may be increased within 3–6 weeks of smoking cessation, necessitating regular monitoring of antipsychotic plasma levels and side effects. There is some evidence that, among smokers with schizophrenia, prescription of atypical antipsychotic agents (e.g., clozapine)

can either reduce smoking among patients who are not attempting to quit smoking or facilitate smoking cessation among patients who attempt smoking cessation with the nicotine patch (George et al. 2000) or bupropion (George et al. 2002). However studies of this effect are needed in larger samples.

Other Psychiatric Disorders

Rates of smoking among patients with bipolar disorders and anxiety disorders (e.g., posttraumatic stress disorder, panic disorder) are also higher than those in the general population (Lasser et al. 2000), but there has been little study of the factors associated with motivation to quit smoking or of smoking cessation interventions in these patient groups.

Smokers With Comorbid Medical Problems

General precautions for each medication that has been used for smoking cessation are listed in the sections describing each medication. All FDA-approved first-line medications for smoking cessation have a relatively good safety profile. Consensus opinions on the safety of the various medications for persons with cardiovascular disease, other medical conditions, and pregnancy are beyond the scope of this chapter but can be found elsewhere (Society for Research on Nicotine and Tobacco 2003).

In general, for smokers with cardiac disease, the benefits of nicotine replacement therapy outweigh the potential risks. In a safety and efficacy study that included veterans with cardiac disease, smoking concurrently with the nicotine patch was not associated with an increase in adverse events (Joseph et al. 1996). Although bupropion SR is generally well tolerated by smokers, it has not been adequately studied in persons with cardiac disease, and definitive conclusions regarding its safety in this patient population cannot currently be made (Society for Research on Nicotine and Tobacco 2003).

Pregnant Smokers

Prescription NRTs are listed by the FDA as category D medications (i.e., producing evidence of fetal harm) that are to be used only if the potential benefits outweigh the risks. This classification is based mainly on animal studies showing that nicotine is a neurobehavioral teratogen. Over-the-counter NRT products advise pregnant smokers to ask their health professional before using the product for smoking cession. With these considerations in mind, the use

of NRT should be considered for smoking cessation if the pregnant woman is unable to quit without such measures.

Use of nicotine gum for smoking cessation can lower overall nicotine exposure, compared with smoking, as measured by salivary cotinine concentrations, and eliminate exposure of the mother and fetus to carbon monoxide and other harmful chemicals in tobacco smoke (Oncken et al. 1996). Because nicotine is a neurobehavioral teratogen that may contribute to sudden infant death syndrome, using the lowest dose of nicotine replacement that aids in smoking cessation seems prudent. Consequently, during pregnancy, use of intermittent NRTs (e.g., gum, lozenge, inhaler) may be preferable to the constant delivery of nicotine that results from the nicotine patch for smoking cessation (Fiore et al. 2000), although this approach has not been adequately studied. One study of the 15 mg/16 hours nicotine patch in pregnant smokers found no improvement in overall quit rates at 6 weeks among women randomly assigned to receive nicotine or placebo patch; however, women randomly assigned to receive the active patch delivered babies with higher birth weights than those born to women who had received placebo (Wisborg et al. 2000). Thus, transdermal nicotine may be beneficial in pregnancy, particularly for heavier smokers (i.e., those smoking at least 15 cigarettes/day). Although bupropion is listed as a category B medication in pregnancy (i.e., no evidence of risk in humans), there are no controlled studies examining its safety and efficacy in pregnant women (Briggs et al. 2002).

Conclusion

Five first-line agents are recommended for smoking cessation (transdermal nicotine, nicotine gum, inhaler, nasal spray, and bupropion SR). In addition, the nicotine lozenge has recently become commercially available and could also be considered as a promising first-line treatment. Nortriptyline is a promising second-line nonnicotine pharmacotherapy that should be considered for the treatment of smokers with comorbid depressive symptoms, major depression, or a past history of major depression. Clonidine may also have some merit as a second-line agent, possibly in female smokers, but side effects limit its safety and probably also limit patients' adherence to treatment with this medication. Other agents to be considered as third-line treatments are naltrexone, buspirone, MAO inhibitors, and the SSRIs, but their efficacy for smoking cessation has not been established.

Pharmacotherapies should be used for the treatment of tobacco dependence, with optimal results produced by the combination of medications with behavioral support. More study is needed to determine how the intensity of behavioral treatments interacts with different pharmacotherapeutic agents. Although bupropion SR and NRTs significantly increase smoking cessation rates, the majority of smokers are unable to achieve long-term abstinence and absolute 1-year quit rates remain low. Additional research is warranted to determine whether medications for smoking cessation, used as monotherapies (e.g., bupropion) or in combination (e.g., nicotine patch plus bupropion), prevent smoking relapse. New medications should be evaluated for the treatment of tobacco dependence. Well-controlled, large-scale studies are also needed to identify specific therapies that are safe and effective for smoking cessation among patients with comorbid psychiatric, substance abuse, and medical problems.

References

Addington J, el-Guebaly N, Campbell W, et al: Smoking cessation treatment for patients with schizophrenia. Am J Psychiatry 155:974–976, 1998

American Psychiatric Association: Practice Guideline for the Treatment of Patients With Substance Use Disorders, 2nd Edition. Washington, DC, American Psychiatric Association (in press)

Ascher JA, Cole JO, Colin JN, et al: Bupropion: a review of its mechanism of antidepressant activity. J Clin Psychiatry 56:395–401, 1995

Berlin I, Said S, Spreux-Varoquaux O, et al: A reversible monoamine oxidase A inhibitor (moclobemide) facilitates smoking cessation and abstinence in heavy, dependent smokers. Clin Pharmacol Ther 58:444–452, 1995

Blondal T, Gudmundsson LJ, Olafsdottir I, et al: Nicotine nasal spray with nicotine patch for smoking cessation: randomised trial with 6- year follow up. BMJ 318: 285–8, 1999a

Blondal T, Gudmundsson LJ, Tomasson K, et al: The effcts of fluoxetine combined with nicotine inhalers in smoking cessation—a randomized trial. Addiction 94: 1007–1015, 1999b

Briggs G, Freeman R, Yaffe S: Drugs in Pregnancy and Lactation: A Reference Guide to Maternal and Fetal Risk. Philadelphia, Lippincott, Williams & Wilkins, 2002

Chengappa KN, Kambhampati R, Perkins K, et al: Bupropion sustained release as a smoking cessation treatment in remitted depressed patients maintained on treatment with selective serotonin reuptake inhibitor antidepressants. J Clin Psychiatry 62:503–508, 2001

Cinciprinni PM, McClure JB: Smoking cessation: recent developments in behavioral and pharmacologic interventions. Oncology 12:249–259, 1998

Clarke PB: Nicotinic receptor blockade therapy and smoking cessation. Br J Addict 86:501–505, 1991

Covey LS, Glassman AH: A meta-analysis of double-blind placebo controlled trials of clonidine for smoking cessation. Br J Addict 86:991–998, 1991

Covey LS, Glassman AH, Stetner F: Naltrexone effects on short-term and long-term smoking cessation. J Addict Dis 18:31–40, 1999

Covey LS, Sullivan MA, Johnston A, et al: Advances in non-nicotine pharmacotherapy for smoking cessation. Drugs 59:17–31, 2000

Dani JA, De Biasi M: Cellular mechanisms of nicotine addiction. Pharmacol Biochem Behav 70:439–446, 2001

Dwoskin LP, Crooks PA: A novel mechanism of action and potential use for lobeline as a treatment for psychostimulant abuse. Biochem Pharmacol 63:89–98, 2002

Evins AE, Mays VK, Rigotti NA, et al: A pilot trial of bupropion added to cognitive behavioral therapy for smoking cessation in schizophrenia. Nicotine Tob Res 3: 397–403, 2001

Fiore MC, Smith SS, Jorenby DE, et al: The effectiveness of the nicotine patch for smoking cessation. JAMA 271:1940–1947, 1994

Fiore MC, Bailey WC, Cohen SJ, et al: Smoking Cessation. Clinical Practice Guideline No 18 (ACHPR Publ No 96-0692). Rockville, MD, U.S. Department of Health and Human Services, 1996

Fiore MC, Bailey WC, Cohen SJ, et al: Treating Tobacco Use and Dependence. Clinical Practice Guideline. Rockville, MD, U.S. Department of Health and Human Services, 2000

George TP, O'Malley SS: Current pharmacological treatments for nicotine dependence. Trends Pharmacol Sci 25:42–48, 2004

George TP, Vessicchio JC: Nicotine addiction in schizophrenia. Psychiatric Times 18(2):39–41, 2001

George TP, Ziedonis DM, Feingold A, et al: Nicotine transdermal patch and atypical antipsychotic medications for smoking cessation in schizophrenia. Am J Psychiatry 157:1835–1842, 2000

George TP, Vessicchio JC, Termine A, et al: A placebo-controlled trial of bupropion for smoking cessation in schizophrenia. Biol Psychiatry 52:53–61, 2002

George TP, Vessicchio JC, Termine A, et al: A preliminary placebo-controlled trial of selegiline hydrochloride for smoking cessation. Biol Psychiatry 53:136–143, 2003

Giovino GA: Epidemiology of tobacco use in the United States. Oncogene 21:7326–7340, 2002

Glover ED, Leischow SJ, Rennard SI, et al: A smoking cessation trial with lobeline sulfate: a pilot study. Am J Health Behav 22:62–74, 1998

Gourlay SG, Benowitz NL: Is clonidine an effective smoking cessation therapy? Drugs 50:197–207, 1995

Hall SM, Reus VI, Munoz RF, et al: Nortriptyline and cognitive-behavioral therapy in the treatment of cigarette smoking. Arch Gen Psychiatry 55:683–690, 1998

Hall SM, Humfleet GL, Reus VI, et al: Psychological intervention and antidepressant treatment in smoking cessation. Arch Gen Psychiatry 59:930–936, 2002

Hayford KE, Patten CA, Rummans TA, et al: Efficacy of bupropion for smoking cessation in smokers with a former history of major depression or alcoholism. Br J Psychiatry 174:173–178, 1999

Hays JT, Hurt RD, Rigotti NA, et al: Sustained-release bupropion for pharmacologic relapse prevention after smoking cessation. Ann Intern Med 135:423–433, 2001

Henningfield JE: Nicotine medications for smoking cessation. N Engl J Med 333: 1196–1203, 1995

Hjalmarson A, Nilsson F, Sjostrom L, et al: The nicotine inhaler in smoking cessation. Arch Intern Medicine 157:1721–1728, 1997

Hughes JR: Non-nicotine pharmacotherapies for smoking cessation. J Drug Dev 6: 197–203, 1994

Hughes JR: The future of smoking cessation therapy in the United States. Addiction 91:1797–1802, 1996

Hurt RD, Offord KP, Croghan IT, et al: Mortality following inpatient addictions treatment: role of tobacco use in a community-based cohort. JAMA 275:1097–1103, 1996

Hurt RD, Sachs DP, Glover ED, et al: A comparison of sustained-release bupropion and placebo for smoking cessation. N Engl J Med 337:1195–1202, 1997

Jorenby DE, Leischow SJ, Nides MA, et al: A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. N Eng J Med 340:685–691, 1999

Joseph AM, Norman SM, Ferry LH, et al: The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. N Engl J Med 335:1792–1798, 1996

Kalman D, Hayes K, Colby SM, et al: Concurrent versus delayed smoking cessation treatment for persons in early alcohol recovery: a pilot study. J Subst Abuse Treat 20:233–238, 2001

Killen JD, Fortmann SP, Schatzberg AF, et al: Nicotine patch and paroxetine for smoking cessation. J Consult Clin Psychol 68:883–889, 2000

Kornitzer M, Boutsen M, Dramaix M, et al: Combined use of nicotine patch and gum in smoking cessation: a placebo-controlled clinical trial. Prev Med 24:41–47, 1995

Krishnan-Sarin S, Meandzija B, O'Malley S: Naltrexone and nicotine patch for smoking cessation: a preliminary study. Nicotine Tob Res 6:631–639, 2004

Lasser K, Boyd JW, Woolhander S, et al: Smoking and mental illness: a population-based prevalence study. JAMA 284:2606–2610, 2000

Law M, Tang JL: An analysis of the effectiveness of interventions intended to help people stop smoking. Arch Intern Med 155:1933–1941, 1995

Lichtermann D, Ekelund E, Pukkala E, et al: Incidence of cancer among persons with schizophrenia and their relatives. Arch Gen Psychiatry 58:573–578, 2001

McNeil Consumer Products: Nicotrol Inhaler (nicotine inhalation system) Physician Insert. Fort Washington, PA, McNeil Consumer Products, 1997

Niaura R, Britt DM, Shadel WM, et al: Symptoms of depression and survival experience among three samples of smokers trying to quit. Psychol Addict Behav 15:13–17, 2001

Niaura R, Spring B, Borrelli B, et al: Multicenter trial of fluoxetine as an adjunct to behavioral smoking cessation treatment. J Consult Clin Psychol 70:887–896, 2002

Oncken CA, Hatsukami DK, Lupo VR, et al: Effects of short-term use of nicotine gum in pregnant smokers. Clin Pharmacol Ther 59:654–61, 1996

Pomerleau OF, Pomerleau CS: Neuroregulators and the reinforcement of smoking: towards a biobehavioral explanation. Neurosci Biobehav Rev 8:503–513, 1984

Prochazka AV, Weaver MJ, Keller RT, et al: A randomized trial of nortriptyline for smoking cessation. Arch Intern Med 158:2035–2039, 1998

Puska P, Korhonen HJ, Vartiainen E, et al: Combined use of nicotine patch and gum compared with gum alone in smoking cessation: a clinical trial in North Karelia. Tob Control 4:231–235, 1995

Rohsenow DJ, Monti PM, Colby SM, et al: Naltrexone treatment for alcoholics: effect on cigarette smoking rates. Nicotine Tob Res 5:231–236, 2003

Rose JE, Levin ED: Concurrent agonist-antagonist administration for the analysis and treatment of drug dependence. Pharmacol Biochem Behav 41:219–226, 1991

Rose JE, Behm FM, Westman EC, et al: Mecamylamine combined with nicotine skin patch facilitates smoking cessation beyond nicontine patch treatment alone. Clin Pharmacol Ther 56:86–99, 1994

Rose JE, Behm FM, Westman EC: Nicotine-mecamylamine treatment for smoking cessation: the role of pre-cessation therapy. Exp Clin Psychopharmacol 6:331–343, 1998

Schneider NG, Olmstead RE, Steinberg C, et al: Efficacy of buspirone in smoking cessation: a placebo-controlled trial. Clin Pharmacol Ther 60:568–575, 1996

Shiffman S, Dresler CM, Hajek P, et al: Efficacy of a nicotine lozenge for smoking cessation. Arch Intern Med 162:1267–76, 2002

Slemmer JE, Martin BR, Damaj MI: Bupropion is a nicotinic antagonist. J Pharmacol Exp Therap 295:321–327, 2000

Society for Research on Nicotine and Tobacco: Database and Educational Resource for the Treatment of Tobacco Dependence. Available at http://www.treatobacco.net. Accessed April 18, 2005.

Stolerman IP, Goldfarb T, Fink R, et al: Influencing cigarette smoking with nicotine antagonists. Psychopharmacologia 28:247–259, 1973

Sutherland G, Stapleton JA, Russel MA, et al: Randomised controlled trial of nasal nicotine spray in smoking cessation. Lancet 340:324–329, 1992

Sutherland G, Stapleton JA, Russell MA, et al: Naltrexone, smoking behaviour and cigarette withdrawal. Psychopharmacology (Berl) 120:418–425, 1995

Sweeney CT, Fant RV, Fagerstrom KO, et al: Combination nicotine replacement therapy for smoking cessation. CNS Drugs 15:453–467, 2001

Weiner E, Ball MP, Summerfelt A, et al: Effects of sustained-release bupropion and supportive group therapy on cigarette consumption in patients with schizophrenia. Am J Psychiatry 158:635–637, 2001

Wisborg K, Henriksen TB, Jespersen LB, et al: Nicotine patches for pregnant smokers: a randomized controlled study. Obstet Gynecol 96:967–971, 2000

Ziedonis DM, George TP: Schizophrenia and nicotine use: report of a pilot smoking cessation program and review of neurobiological and clinical issues. Schiophr Bull 23:247–254, 1997

10

Psychotherapy and Pharmacotherapy in Treatment of Substance Use Disorders

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In research and clinical treatment of substance use disorders, pharmacotherapy and psychotherapy are frequently combined. Medication is often used as a maintenance drug, to reduce cravings or intoxication, or to produce aversion to a substance, while the focus of psychotherapy may be to encourage abstinence, teach the patient new coping skills, or improve motivation to address drug or alcohol problems.

A number of psychosocial treatments for alcohol and other substance use disorders exist and are widely used. In this chapter, we discuss six of these psychotherapies as they are applied to alcohol, cocaine, and opioid dependence: brief interventions, motivational enhancement therapy, cognitive-behavioral therapy, behavioral treatments (including contingency management and community reinforcement approaches), behavioral marital therapy, and 12-step facilitation. We also describe studies that examined the efficacy of a medication in combination with one or more of the six psychotherapies. In the second section of the chapter, we highlight research that directly studied the interaction between psychosocial and pharmacological treatments.

Psychotherapies for Substance Use Disorders

Brief Interventions

Brief interventions focus on changing behavior in just a few sessions. This type of counseling strategy can range in duration from 5 minutes up to four 60-minute sessions. Fleming and Manwell (1999) described five steps common in many brief interventions: 1) provide assessment and feedback; 2) negotiate a goal with respect to abstinence or minimal use; 3) use behavior modification techniques, such as identifying high-risk situations; 4) provide bibliotherapy by making available informational materials on substance use and its consequences; and 5) ensure follow-up to check on progress.

In nondependent heavy drinkers, brief interventions have been shown to reduce alcohol use (Bien et al. 1993; Paokolainen 1999; Wilk et al. 1997). Typically, efficacy has been demonstrated for at least 1 year (Fleming and Manwell 1999), with some studies showing longer-term beneficial effects (Fleming et al. 1997; Kristenson et al. 1983). In community-based primary care clinics, the positive effects of brief interventions may also extend to reductions in alcohol-related health problems (Fleming et al. 1997; Kristenson et al. 1983). These treatments typically require little training (Ockene et al. 1999), and they also appear to be cost-effective (Fleming et al. 1997; Kristenson et al. 1983).

Brief interventions have been applied in pharmacotherapy trials with alcohol-dependent individuals as well (Bohn et al. 1994; Kranzler et al. 1997; Kranzler et al. 2003; Naranjo et al. 1995; O'Connor et al. 1997). In an open-label

study of naltrexone, O'Connor and colleagues (1997) combined naltrexone treatment (50 mg/day) with a brief intervention that extended the usual visit in duration and then was followed by seven brief follow-up visits over the subsequent 10 weeks. The treatment retention rate was good (72%), and the percentage of days abstinent increased from 37% in the pretreatment period to 89% with the intervention.

Recently, Kranzler and colleagues (2003) reported on brief (four-session) coping skills training for heavy drinkers. Patients were randomly assigned to one of four conditions: daily administration of placebo, daily administration of naltrexone, targeted administration of placebo, or targeted administration of naltrexone. Patients in the targeted conditions were taught to consume their medication during high-risk situations. Patients in both the targeted naltrexone and placebo conditions reduced their drinking as long as medication was available at least 3 days per week. Among patients randomly assigned to daily medication administration, drinking was reduced among those patients receiving active naltrexone but not among those receiving placebo. Thus, brief interventions may be useful when provided in conjunction with medications that reduce alcohol use among heavy drinkers.

Studies of brief interventions with cocaine and heroin abusing patients are less common. One open-label investigation of brief counseling in conjunction with buprenorphine (an alternative to methadone) for heroin dependence found that this combined medication and brief intervention approach, delivered in primary care physicians' offices, was useful in reducing heroin use (Fiellin et al. 2002). At baseline, 95% of urine samples were drug positive, and the rate of drug-positive samples decreased to 25% during the 13-week treatment period. Of the 14 patients enrolled in the study, 9 achieved substantial periods of opioid abstinence. Although this report demonstrated the feasibility of combining brief interventions with medication in opioid-dependent patients, it did not investigate the efficacy of the brief intervention relative to a control psychotherapy condition. Results of such comparisons in this population are of particular interest, because, given the extensive psychosocial problems in most opioid-dependent patients, the effectiveness of brief psychotherapy interventions is probably limited to a select subsample. Most work with methadone maintenance populations has suggested that more extensive psychosocial interventions may be necessary (McLellan et al. 1993).

Motivational Enhancement Therapy

Motivational enhancement therapy (MET) was developed by Miller and Rolnick (1991) and is based on the transtheoretical stages of change model (Prochaska and DiClemente 1986). The emphasis of MET is on increasing patients' motivation to reduce or abstain from substances by encouraging commitment to behavior change and on helping the patient use his/her own coping and interpersonal resources. Motivational interviewing techniques, which include expression of empathy and a nonconfrontational style, are used. The patient's ambivalence about substance use is addressed, and the therapist provides feedback about the patient's strengths and difficulties, gives direct advice, and supports the patient's self-efficacy (Miller and Rolnick 1991). MET may be particularly appealing because it is a brief therapy that can easily be used in numerous settings where patients are treated with pharmacotherapy for substance use disorders.

The efficacy of MET has been addressed in alcohol treatment. A manual-based, four-session MET program was included in the National Institute on Alcohol Abuse and Alcoholism (NIAAA) Project MATCH and compared with 12-session interventions consisting of either cognitive-behavioral therapy or 12-step facilitation (Miller et al. 1995b). The brief MET was as efficacious as the two longer treatments in improving drinking-related outcomes, and MET demonstrated greater efficacy with angry patients (Project MATCH Research Group 1997).

A small number of pharmacotherapy trials for alcohol have used MET. A four-session, modified version of MET was used in the 6-month double-blind, placebo-controlled U.S. multisite study of acamprosate treatment for alcoholism (Mason and Goodman, 2001). Patients who made abstinence their treatment goal evidenced greater medication efficacy than those who elected reduced drinking as their treatment goal. Anton and colleagues (2004) conducted a double-blind multisite study in which 270 recently abstinent alcohol-dependent patients were randomly assigned to receive placebo or 5 mg/day, 20 mg/day, or 40 mg/day dosages of nalmefene. Patients received four sessions of MET designed to reduce alcohol use and encourage medication adherence. Adherence was very good, with more than 90% of prescribed medication doses taken and 90% of patients attending their first two MET sessions. Patients in all four groups experienced fewer heavy drinking days,

more abstinent days, and decreased cravings for alcohol with treatment. However, medication group did not significantly distinguish patients on any alcohol-related variable. Kranzler et al. (2004) conducted a double-blind, randomly controlled study of a naltrexone depot formulation for treatment of alcohol dependence in which patients also received MET designed to increase medication adherence and abstinence from alcohol. Patients in this study also evidenced good adherence, with 77.8% remaining in treatment throughout the entire 12-week study period. Most of the patients in both the naltrexone (65.8%) and placebo (63.1%) groups attended all five of their scheduled MET sessions. Although MET may have contributed to greater abstinence and treatment adherence in these studies, efficacy trials of MET within the context of pharmacotherapy trials for alcohol are needed.

Fewer published reports have studied the use of MET with cocaine- and opioid-dependent patients. The efficacy of brief motivational interviewing approaches was evaluated in cocaine-dependent patients as part of the National Institute on Drug Abuse Clinical Trials Network, but the results are not yet available. One pilot study reported that a single MET session was associated with reductions in drug use and sex work among 25 primarily heroin- and cocaine-using street sex workers (Yahne et al. 2002). In another study, 105 cocaine-dependent patients participating in a 10-day cocaine detoxification program were randomly assigned to receive either standard treatment (involving daily urine samples, graphing and review of urine test results, psychoeducation, and assessment) or standard treatment plus MET (Stotts et al. 2001). The MET patients provided more cocaine-free urine samples and were more likely to use behavioral coping skills than the patients who received standard treatment. Some studies have found that MET is particularly beneficial to cocaine- and opioid-dependent patients who present to treatment with low motivation for change (Rohsenow et al. 2004). Despite this initial success, comparatively few studies have explored the efficacy of MET in illicit drug use disorders, and no current studies have focused on the efficacy of MET for opioid or cocaine dependence within a clinical trial for medication.

Cognitive-Behavioral Therapies

Cognitive-behavioral therapy (CBT) is based on the theoretical assumption that alcohol and other substance use problems are related to maladaptive so-

cial learning and adverse life situations. CBT interventions are designed to improve interpersonal and coping skills, reduce the risk of relapse, and increase self-efficacy. The patient and therapist discuss triggers that may be cues for substance use. Patients are made aware that triggers may be internal (such as feelings, thoughts, or cravings) or external (such as interactions with drug-using friends, proximity to a liquor shop, or an argument with a spouse). To cope with urges to use drugs or drink in the presence of triggers, patients are taught problem-solving and coping techniques.

A number of randomized clinical trials have demonstrated the efficacy of CBT for treating substance use disorders, compared with no-treatment control conditions (see Carroll 1996 for review). However, the superiority of CBT over other psychosocial treatments is not as clear. Although some studies have found CBT to be more effective than other treatments, others have found this method to be comparable to other treatment approaches (Carroll 1996). In Project MATCH, for instance, CBT, MET, and 12-step facilitation produced similar outcomes, with each therapy leading to substantial improvement in alcohol-related symptoms during the 12-week treatment period (Project MATCH Research Group 1997).

One benefit of CBT may be that it contributes to longer-term recovery once treatment has ended (Carroll et al. 1994b; O'Malley et al. 1996). This continued decline in symptoms is not generally seen with other therapies, in which a gradual return to baseline levels of use and associated problems is more typical. According to the theory underlying CBT, this continued improvement may result from the enhanced coping and relapse prevention skills that are acquired by the patient during treatment.

A number of pharmacotherapy trials for alcohol-dependent patients have used CBT as the platform psychotherapy (Angelone et al. 1998; Johnson et al. 1996, 2000; Kiefer 2002; Kranzler et al. 1995; Mason et al. 1999). For example, alcohol-dependent patients in a placebo-controlled clinical trial of naltrexone received 12 sessions of manual-based CBT (Anton et al. 1999). Patients taking naltrexone reported reduced drinking and longer time to relapse, compared with the placebo group during the treatment period. However, both groups demonstrated substantial engagement in the psychotherapy, as evidenced by high rates of treatment completion and attendance at sessions. Anton et al. (2001) suggested that combining naltrexone treatment with CBT offers the patient an opportunity to hone relapse prevention skills during

high-risk situations that are better managed with the anti-craving and reward reduction properties of naltrexone. This conclusion is consistent with previous findings that patients who receive CBT experience longer-term improvement in substance use (Carroll et al. 1994b; O'Malley et al. 1996).

CBT has also been studied in cocaine and opioid users who are receiving pharmacological treatment. In one study, cocaine-dependent methadone-maintained patients were randomly assigned to either 6 months of individual and group counseling sessions based on a CBT model or once weekly group counseling sessions (Rosenblum et al. 1999). Patients in both study groups reduced their cocaine use over a 48-week posttreatment period. Overall no group differences were found on cocaine use or therapy attrition; however, patients with more severe cocaine problems fared better in more intensive treatment. The general lack of differences between treatment conditions may have been related to the similarities between the two psychotherapies tested. The group counseling used some techniques—such as identification of triggers, discussion of consequences of drug use, and homework—that are common in CBT.

CBT has also been used to encourage engagement in methadone treatment and to reduce risky behaviors. Goldstein et al. (2002) used CBT to encourage reengagement of methadone patients who had dropped out of treatment. Patients were randomly assigned to one of two groups: 1) an outreach intervention that involved street-level outreach, individual counseling, and CBT groups or 2) no intervention. Eighty-seven percent of the patients in the intervention group received at least one intervention service during the 3-month study period; however, methadone treatment reentry was not significantly different between the intervention (62%) and comparison (50%) groups. Intervention subjects who participated in at least two CBT groups (72%) were significantly more likely to return to methadone treatment than were intervention subjects who participated in no or one CBT groups (53%) or comparison subjects (50%). It is important to note that there were no differences in treatment reentry as a function of level of exposure to outreach or individual counseling services. In another study, O'Neill et al. (1996) randomly assigned methadone-maintained pregnant injecting drug users to either standard methadone treatment or standard treatment plus six sessions of CBT directed at reducing HIV risk behaviors. Patients receiving CBT reported safer injecting practices (i.e., reduced frequency of sharing needles) at follow-up, compared with intake. The risk behaviors of the patients in standard treatment remained the same or increased.

Thus, although CBT may not be superior to other types of interventions in increasing abstinence during treatment, studies suggest that CBT may have other beneficial effects. CBT may have a longer-term impact on abstinence than that seen with other treatments. Further, this treatment may also be used to encourage other behaviors, such as safe needle practices or engagement in pharmacotherapy.

Behavioral Treatments

Behavioral treatments, including the community reinforcement approach (CRA) and contingency management (CM), are based on the principle that drugs induce positive effects and these effects reinforce continued substance use. To reduce drug use, the therapist rearranges the patient's environment so that drug use is less reinforcing than abstinence in CRA and CM treatments.

In CRA with alcohol-dependent patients, reinforcement of disulfiram compliance is one of the primary components of treatment, such that use of alcohol loses its reinforcing aspects and, in fact, becomes aversive. Furthermore, reinforcement from other sources is increased. Positive reinforcement for not drinking comes in the form of scheduling other recreational activities and reorganizing daily life by breaking down practical barriers. For example, the therapist may assist the patient in obtaining a telephone, a place to live, or transportation to treatment.

Strong evidence exists for the efficacy of CRA in treatment of alcohol use disorders (Miller et al. 1995a). In controlled studies conducted on both an inpatient (Azrin 1976) and outpatient basis (Azrin et al 1982; Smith et al. 1998), patients receiving CRA evidenced substantial enhancements in abstinence rates and psychosocial functioning, compared with patients receiving other treatments. A manual for this approach is available for alcohol-dependent patients (Meyers and Smith 1995) as well as cocaine-dependent patients (Budney and Higgins 1998). However, fewer studies of CRA have been undertaken of late, potentially because of concern that coordinating community resources is overly burdensome (Kadden 2001).

CM treatments are based on principles similar to those underlying CRA, but CM extends positive reinforcement for not using substances to include tangible rewards. For example, every time the patient provides a substance-negative urine specimen or ingests medication, he or she earns a reward, such as a voucher that is exchangeable for retail goods and services (Higgins et al.

1994). An extensive literature exists on the use of CM for treatment of substance use disorders. Petry et al. (2000) found that alcohol-dependent veterans who received CM for providing negative breath analysis readings in addition to standard psychosocial therapy were more likely to stay in treatment and had a longer time to first drinking episode and first heavy drinking episode than veterans who received standard treatment alone. In treatment of cocaine dependence, a series of studies demonstrated the efficacy of the CM approach in conjunction with CRA (Higgins et al. 1993, 1994, 2000, 2003). CM has also been reported to be efficacious in marijuana-dependent patients (Budney et al., 2000) and opioid-dependent patients both during maintenance treatment (e.g., Petry and Martin, 2002) and detoxification (Bickel et al. 1997; McCaul et al. 1984). Rawson and colleagues (2002) examined the efficacy of CM combined with CBT or standard treatment (consisting of twice-monthly counseling, medical appointments, and case management) in methadone-maintained cocaine-dependent patients. Patients who received CM in combination with CBT or standard care provided more cocaine-free urine samples than patients who received standard treatment only.

Studies have shown that CM can be used to directly reinforce adherence to medication treatments as well (Petry 2000). Liebson et al (1978) found that methadone-maintained alcohol-dependent patients reduced alcohol use when methadone treatment was contingent on disulfiram consumption. To date, one of the most common applications of CM techniques to pharmacotherapy has been the provision of vouchers or cash contingent upon naltrexone consumption in recently detoxified opioid-dependent patients (Carroll et al. 2001, 2002; Preston et al. 1999). These studies have generally reported significant increases in retention and reductions in opioid use among patients receiving the CM treatment, relative to other therapies.

These studies suggest that behavioral treatment strategies, such as CRA and CM, can be effective alone and as adjuncts to pharmacotherapy. Whether the emphasis is on abstinence, treatment retention, or medication compliance, the results of studies on behavioral approaches are promising.

Behavioral Couples Therapy

One common form of family therapy for alcohol dependence is behavioral couples therapy (BCT) (Epstein and McCrady 1998). This treatment, which

has its basis in social learning theory and family systems models, assumes a reciprocal connection between substance use and relationship functioning, such that substance use affects the quality and nature of a couple's relationship. In turn, aspects of the relationship can also influence substance use. BCT focuses on improving how the couple interacts, by working on communication and problem solving skills and enhancing social support.

Several studies with alcohol-dependent patients showed that BCT improves outcomes in relationship adjustment and reduces drinking (McCrady et al. 1991; O'Farrell et al. 1992). In one study, BCT was found to be more cost-effective than individual or group counseling (O'Farrell et al. 1996). However, little is known about the components of BCT that are associated with improved outcomes, and most studies have applied this therapy in groups of patients with little psychiatric comorbidity and with cooperative significant others.

Some studies have involved a spouse or significant other in observing medication ingestion. In a 6-month study, patients who consumed disulfiram (200 mg/day) under observation of a significant other significantly increased the number of abstinent days and decreased the total number of drinks, relative to patients who received placebo under observation (Chick et al. 1992).

Other studies have included BCT or other styles of family counseling as the psychotherapeutic intervention in medication trials. One study evaluated family counseling in conjunction with naltrexone treatment (Carroll et al. 2001). Opioid-dependent patients (N=127) were randomly assigned to one of three conditions: 1) standard naltrexone treatment three times weekly, 2) naltrexone treatment with CM for consuming naltrexone, and 3) naltrexone treatment with CM for consuming naltrexone plus family counseling. Forty-eight percent of the patients assigned to the third condition never attended even one of their family sessions, suggesting considerable difficulty engaging families of opioid-dependent patients in treatment. Among those who attended one or more sessions, family counseling appeared to increase retention and opioid abstinence rates, compared to the other two treatment conditions. Compared with patients in the non-family-therapy conditions, patients who attended the family therapy sessions showed decreases in family problems during the trial, suggesting treatment-specific effects.

BCT also can reduce drug use and improve psychosocial problems when combined with methadone treatment. Fals-Stewart et al. (2001) randomly as-

signed 36 men initiating methadone treatment to standard care (methadone plus twice-weekly individual drug abuse counseling) or methadone plus weekly couples therapy with their partner and once weekly individual drug abuse counseling. Patients in the couples therapy condition demonstrated reduced opioid and cocaine use during treatment and had higher levels of relationship satisfaction posttreatment, compared with subjects in standard care. In a second study by this group, Fals-Stewart and O'Farrell (2003) randomly assigned 124 opioid-dependent men receiving naltrexone treatment to either individual counseling or BCT. (Parents or siblings were included in the treatment if the patient did not have a spouse or significant other.) Patients in BCT were less likely to use opioids, cocaine, alcohol, or other drugs during treatment, compared with patients in individual treatment. BCT patients reported greater abstinence at 1-year follow-up and had more consecutive days abstinent, compared with the patients who received individual therapy.

These findings suggest that BCT may improve outcomes on a number of levels when provided along with methadone or naltrexone treatment in poly-drug-using patients. However, the Carroll et al. (2001) study also demonstrated that engaging family members in treatment may be no easy task. Thus, additional strategies to encourage family involvement may increase the effectiveness of this approach.

12-Step Therapies

Alcoholics Anonymous (AA) is a self-help organization for people whose common goal is recovery from alcoholism, and it is the most widely accessed resource for individuals with alcohol problems (McCrady and Miller 1993). The philosophy is based on the concept of alcoholism as a chronic disease that cannot be cured, but one that can be halted by means of complete abstinence. AA has described 12 principles or steps to guide those in recovery. Twelve-step facilitation, a manual-based psychotherapy to promote AA participation (Nowinski et al. 1992), was equally efficacious, compared with cognitive-behavioral and motivational enhancement therapies, in a large study of treatments for alcohol dependence (Project Match Research Group, 1997).

A common belief is that AA discourages use of treatment medications, which are considered "crutches" However, in a survey of a large sample of AA members, more then one-half of respondents reported that the use of relapse-preventing

medication either was or might be a good idea; only 12% reported that they would tell another member to stop taking it (Rychtarik et al. 2000). Given the positive outcomes of 12-step facilitation in Project MATCH and the apparent tolerance of medication usage among the majority of AA members, use of this treatment approach in combination with pharmacotherapy seems appropriate.

The Veterans Administration Cooperative Studies Group completed a multisite, placebo-controlled study of naltrexone for treatment of alcohol dependence (Krystal et al. 2001). For 13 months, participants received 12-step facilitation counseling and were encouraged to attend AA meetings. The 12-step facilitation approach was adapted to promote use of pharmacotherapy, introduce basic relapse-prevention principles, and reinforce abstinence and continued treatment. Although no differences in outcomes were noted between those receiving naltrexone and those receiving placebo, moderate to high rates of medication and counseling compliance were noted in the first 3 months, along with high rates of alcohol abstinence and a relatively low proportion of drinking days in both groups. A recent trial of sertraline for the treatment of alcohol dependence also incorporated 12-step facilitation and support group attendance, in conjunction with brief physician visits (Pettinati et al. 2001). This research suggested that 12-step-oriented interventions can be combined successfully with pharmacotherapy to engage and retain alcohol-dependent patients in treatment.

In other substance use disorders, the use of 12-step interventions is also popular, and participation in 12-step groups is correlated with better outcomes in cocaine abusers (e.g., McKay et al. 1994). However, a study of 128 cocaine abusers found that cognitive-behavioral therapy was more efficacious than 12-step facilitation in engendering cocaine abstinence (Maude-Griffin et al. 1998). Thus, the relative efficacy of 12-step approaches for drug use disorders requires further investigation. No known studies have systematically evaluated the efficacy of 12-step treatments in opioid-dependent patients, either alone or in conjunction with pharmacotherapies.

Interactions of Psychotherapy and Pharmacological Treatments

Pharmacotherapy studies typically use one of the psychotherapies reviewed earlier as a platform for evaluation of one or more pharmacotherapies. Rela-

tively few studies have simultaneously manipulated the type or dose of both medication and psychotherapy as a specific test of treatment interactions. Such interaction studies can provide information on the relative efficacy of psychotherapy and medication approaches, and they can explore how combining medication and psychotherapy may differentially affect substance use, compared with either treatment method alone, as described later in this section.

O'Malley et al. (1992) conducted a double-blind study combining naltrexone and CBT for alcoholism. Patients were randomly assigned to participate in cognitive-behavioral coping skills treatment or supportive therapy and to receive 50 mg/day of naltrexone or placebo. Naltrexone-treated patients who received supportive therapy had more continuous abstinence than the other treatment groups. However, naltrexone-treated patients who received CBT had a lower level of craving and lower risk of relapse than the other three groups. This interaction would not have been observed in a study that manipulated only psychosocial treatment or only medication.

In another study examining psychotherapy and naltrexone, O'Malley and colleagues (1998, 2001) randomly assigned patients to either CBT or brief medical management during an initial 3-month open-label naltrexone phase. CBT and medical management had comparable effects on alcohol symptoms. Treatment responders were then randomly assigned to either naltrexone or placebo in a 9-month, double-blind phase. Among the patients who received placebo, those who had received medication management evidenced a return of alcohol symptoms, although the CBT patients maintained their previous treatment gains. Thus, similar to the results of the earlier study by O'Malley et al. (1992), patients receiving CBT experienced positive effects from psychotherapy that were independent of the medication.

The COMBINE study, a multisite study sponsored by NIAAA, is another example of research that directly tests the interaction between psychosocial and pharmacological treatments for alcoholism (COMBINE Study Research Group 2003a, 2003b). Patients are randomly assigned to receive naltrexone and acamprosate, alone or in combination, and they are also randomly assigned to one of two psychosocial treatments: 1) a low-intensity condition that addresses medication adherence, monitors side effects, and provides brief intervention or 2) a high-intensity condition that includes elements of the low-intensity treatment plus counseling that is grounded in CBT, motivational, and 12-step approaches. A recent feasibility pilot study found that patients can

be recruited, assessed, treated, and retained under the current design of the study (COMBINE Study Research Group 2003b). Some results from this pilot study suggest that those in the high-intensity therapy group may be more adherent to medication treatment than those in the low-intensity group. Efficacy results from the main study have not yet been reported, but the COMBINE study has already provided models and manuals for continuing interaction trials and will likely contribute substantially to our understanding of the interactions of psychotherapy and pharmacotherapy in the treatment of alcoholism.

Some studies with cocaine and opioid abusers have also examined the interaction between pharmacotherapy and psychotherapy. Carroll et al. (1998) randomly assigned 122 patients who abused both cocaine and alcohol to one of five treatments: 1) CBT plus disulfiram, 2) 12-step facilitation plus disulfiram, 3) clinical management plus disulfiram, 4) CBT alone, or 5) 12-step facilitation alone. The patients who received disulfiram remained in treatment longer and achieved greater durations of cocaine and alcohol abstinence than those who did not receive disulfiram. Further, those who received CBT or 12-step facilitation demonstrated longer periods of abstinence from cocaine use and combined cocaine and alcohol use than those who received clinical management. These data suggest a possible additive effect of certain forms of psychotherapy in conjunction with disulfiram in the treatment of concurrent cocaine and alcohol abuse, at least in the short run. Differences between CBT, 12-step, and case management and between disulfiram and no medication were no longer statistically significant by the end of a 1-year follow-up period (Carroll et al. 2000).

Carroll et al. (2004) conducted another study examining psychotherapy and disulfiram treatment for cocaine dependence. In this randomized, double-blind, placebo-controlled study, patients (N=121) were assigned to one of four conditions: 1) disulfiram plus CBT; 2) disulfiram plus interpersonal therapy (IPT), which addressed adherence to a medical model of psychiatric problems, interpersonal functioning, and supportive therapeutic exploration; 3) placebo plus CBT; or 4) placebo plus IPT. The patients who received disulfiram reduced their cocaine use, relative to those who received placebo, and the patients who received CBT reduced their cocaine use, relative to those who received IPT. Cocaine abstinence among the patients who received CBT plus placebo was not statistically different from that of the patients who re-

ceived CBT or IPT in addition to disulfiram. These results are consistent with the findings of a prior study that demonstrated the efficacy of CBT and disulfiram for treatment of cocaine dependence (Carroll et al. 1998).

In another double-blind, placebo-controlled study of treatment for cocaine dependence, Carroll and colleagues (1994a) focused on the interaction of CBT and desipramine (an antidepressant medication). Patients ($N=121$) were randomly assigned to one of four treatment conditions: 1) case management and placebo, 2) case management and desipramine, 3) CBT and placebo, or 4) CBT and desipramine. Case management involved providing nonspecific elements of psychotherapy (i.e., therapeutic relationship, empathy, education), medication management, and a convincing therapeutic rationale. Patients in each group improved over the 12-week study period, but no overall differences in retention or cocaine abstinence were found among the four treatment groups. However, the patients with more severe baseline cocaine use benefited more when treated with CBT than when treated with case management, although low-severity patients benefited more when treated with desipramine than with placebo. Further, depressed patients benefited more from CBT than from case management. These findings demonstrate that interaction effects may be complex and difficult to detect in studies that examine only medication or only psychotherapy.

At 1-year follow-up (Carroll et al. 1994b), 80% of the patients from the original study by Carroll et al. (1994a) were reassessed. Patients in all groups had maintained cocaine use reductions. However, CBT-treated patients had had a delayed improvement, relative to the case management patients, and they reported fewer cocaine-related symptoms. Thus, the results were similar to those of other CBT studies that have found delayed positive treatment effects (O'Malley et al. 1996) but were inconsistent with the findings of Carroll et al. (2000) in a follow-up of disulfiram-treated cocaine-dependent patients, in which the long-term effects of CBT were found to be similar to those of 12-step facilitation and clinical management.

Several CM studies have explored interactions between medication and psychosocial treatments for substance use disorders. In a 12-week randomized, double-blind study of buprenorphine-maintained opioid- and cocaine-dependent patients, Kosten et al. (2003a) found that desipramine and CM together led to greater abstinence from cocaine and heroin and more consecutive weeks of abstinence than either treatment individually or placebo. A later

report on this same group of patients revealed that eliminating the escalating voucher reinforcement and replacing it with a fixed reinforcement value had a negative effect on abstinence, particularly in patients who were receiving both CM and desipramine (Kosten et al. 2003b). Therefore, reducing or changing this intervention in certain ways may have a detrimental effect on some patients, but such results need to be replicated.

In another CM study, Dallery et al. (2001) used a within-subject design to examine the effect of varying the contingency magnitude and methadone dose on treatment-resistant opiate and cocaine use in methadone patients. Baseline low-magnitude ($374) and high-magnitude ($3,369) voucher reinforcement schedules were compared in patients alternately receiving maintenance doses of 60 mg/day and 120 mg/day of methadone. Regardless of methadone dose, only 2% of urine samples were negative for both cocaine and heroin before contingencies were in place. During phase 1, when patients were maintained on 60 mg/day of methadone, 19% of the samples during low-magnitude reinforcement and 28% of the samples during high-magnitude reinforcement were negative for both opiates and cocaine. When the methadone dose was raised to 120 mg/day (phase 2), 32% of the low-magnitude samples and 46% of the high-magnitude samples were negative for both drugs. These results suggest that methadone dose and increased reinforcement value had an additive effect on drug use.

In a double-blind methadone study, Preston et al. (2000) randomly assigned 120 methadone-maintained opioid-dependent patients to one of four conditions: 1) standard methadone treatment, 2) standard treatment plus CM vouchers, 3) standard treatment plus a 20 mg/day methadone dose increase, or 4) standard treatment plus CM and a 20 mg/day methadone dose increase. Standard treatment consisted of 50 mg/day of methadone, weekly individual counseling, and noncontingent vouchers. Contingent vouchers were associated with greater abstinence from heroin, regardless of whether the patient also received a methadone dose increase. The methadone dose increase was associated with reduced self-reported opioid use and fewer cravings. In contrast to the findings of Dallery et al. (2001), combining CM and the dose increase did not improve treatment outcome beyond either treatment presented alone.

Finally, in a recent study, Schottenfeld and colleagues (2005) conducted a 24-week, double-blind medication trial in which 162 opioid- and cocaine-

dependent patients received manual-guided counseling and were randomly assigned to receive sublingual buprenorphine (12–16 mg/day) or methadone (65–85 mg/day). Patients were also randomly assigned to receive voucher-based CM or feedback on their treatment performance. The CM escalated during the first 12 weeks and was maintained at a lower nominal level for the second 12 weeks of the study. Patients treated with methadone stayed in treatment longer, evidenced longer periods of abstinence from cocaine and opioids, and had a larger proportion of drug-free urine tests than patients who received buprenorphine. Patients who received CM experienced more abstinence from cocaine and opioids during the first 12 weeks of the study (when voucher amounts escalated) than patients in the performance-feedback condition, but this difference was not significant when results from the entire 24 weeks of the study were analyzed. No interaction effects were found between medication type and treatment condition—a finding suggesting that there was no additive effect of combining methadone and buprenorphine. The authors concluded that adding CM to methadone or buprenorphine treatment may improve treatment outcomes for patients with co-occurring cocaine and opioid dependence.

Thus, some of the studies that combined psychosocial and pharmacological treatments revealed interaction or additive effects between the therapies tested. However, the interactions found were not consistent or reliable across studies, nor were many of them predicted. More research on the interactions between medication and psychosocial interventions will further inform our understanding of the most effective treatment combinations.

Conclusion

Many studies have examined the efficacy of a variety of psychosocial treatments for alcohol, cocaine, and opioid use disorders, alone and in conjunction with pharmacotherapy. However, only a handful of studies have explored how these two treatment approaches may interact. More research is needed to further explore the ways in which psychosocial interventions may be used in conjunction with pharmacotherapy to optimize outcomes for both treatments. Providing encouragement for abstinence, greater treatment retention, medication adherence, and coping with medication side effects are some potential applications of psychosocial therapies.

In some pharmacotherapy studies, psychotherapy exposure has been minimized, on the basis of concern that psychotherapy may produce a ceiling effect on improvement in drug or alcohol use, making medication effects difficult to detect. However, a recent meta-analysis revealed that psychosocial interventions, in fact, may enhance pharmacotherapeutic effects (Hopkins et al. 2002). In this review we have also noted instances where psychosocial and medication treatments have had beneficial additive effects. Minimization of psychotherapy in pharmacotherapy trials may be counterproductive, because psychosocial therapies that encourage the patient to remain engaged in treatment may positively affect patients' adherence to the medication regimen, a factor that has an effect on alcohol treatment outcomes (Chick et al. 2000; Volpicelli et al. 1997).

Patients' characteristics, such as substance use disorder typology, severity, family history, and co-occurring psychopathology, may also interact with psychosocial and pharmacological treatment, and the nature of these interactions is an additional area of future study. Kranzler and colleagues (1996), for example, found that type B alcoholic patients (characterized by early onset of alcoholism, greater premorbid psychopathology, and more severe alcohol problems) who were treated with CBT experienced poorer treatment outcomes if they also received fluoxetine, compared to placebo. Others have found that patients fitting differing typologies of substance use disorders may experience differential medication effects (Johnson et al. 2000; Pettinati 2001), suggesting that, with continued research, we may expect to find similar interactions with psychosocial interventions.

Although studies directed at measuring the interaction between diverse types of psychotherapy and different medications are complex, additional research in this area is needed. Such studies offer the methodological sophistication required to understand the complicated relationships between interventions that can substantially affect treatment outcomes.

References

Angelone SM, Bellini L, DiBella D, et al: Effects of fluvoxamine and citalopram in maintaining abstinence in a sample of Italian detoxified alcoholics. Alcohol Alcoholism 33:151–156, 1998

Anton RF, Moak DH, Waid LR, et al: Naltrexone and cognitive behavioral therapy for the treatment of outpatient alcoholics: results of a placebo-controlled trial. Am J Psychiatry 156:1758–1764, 1999

Anton RF, Moak DH, Latham PK, et al: Posttreatment results of combining naltrexone with cognitive-behavior therapy for the treatment of alcoholism. J Clin Psychopharmacol 21:72–77, 2001

Anton RF, Pettinati H, Zweben A, et al: A multi-site dose ranging study of nalmefene in the treatment of alcohol dependence. J Clin Psychopharmacol 24:421–428, 2004

Azrin NH: Improvements in the community reinforcement approach to alcoholism. Behav Res Ther 14:339–348, 1976

Azrin NH, Sisson RW, Meyers R, et al: Alcoholism treatment by disulfiram and community reinforcement therapy. J Behav Ther Exp Psy 13:105–112, 1982

Bickel WK, Amass L, Higgins ST, et al: Effects of adding behavioral treatment to opioid detoxification with buprenorphine. J Consult Clin Psychol 65:803–810, 1997

Bien TH, Miller WR, Tonigan JS: Brief interventions for alcohol problems: a review. Addiction 88:315–335, 1993

Bohn MJ, Kranzler HR, Beazoglou D, et al: Naltrexone and brief counseling to reduce heavy drinking: results of a small clinical trial. Am J Addict 3:91–99, 1994

Budney AJ, Higgins ST: A Community Reinforcement Plus Vouchers Approach: Treating Cocaine Addiction. (NIDA Publ No 98–4309). Rockville, MD, National Institute on Drug Abuse, 1998

Budney AJ, Higgins ST, Radonovich KJ, et al: Adding voucher-based incentives to coping skills and motivational enhancement improves outcomes during treatment for marijuana dependence. J Consult Clin Psychol 68:1051–1061, 2000

Carroll KM: Relapse prevention as a psychosocial treatment: a review of controlled clinical trials. Exp Clin Psychopharm 4:46–54, 1996

Carroll KM, Rounsaville BJ, Gordon LT, et al: Psychotherapy and pharmacotherapy for ambulatory cocaine abusers. Arch Gen Psychiatry 51: 177–187, 1994a

Carroll KM, Rounsaville BJ, Nich C, et al: One-year follow-up of psychotherapy and pharmacotherapy for cocaine dependence: delayed emergence of psychotherapy effects. Arch Gen Psychiatry 51: 989–997, 1994b

Carroll KM, Nich C, Ball SA, et al: Treatment of cocaine and alcohol dependence with psychotherapy and disulfiram. Addiction 93:713–728, 1998

Carroll KM, Nich C, Ball SA, et al: One-year follow-up of disulfiram and psychotherapy for cocaine-alcohol users: sustained effects of treatment. Addiction 95:1335–1349, 2000

Carroll KM, Ball SA, Nich C, et al: Targeting behavioral therapies to enhance naltrexone treatment of opioid dependence: efficacy of contingency management and significant other involvement. Arch Gen Psychiatry 58:755–761, 2001

Carroll KM, Sinha R, Nich C, et al: Contingency management to enhance naltrexone treatment of opioid dependence: a randomized clinical trial of reinforcement magnitude. Exp Clin Psychopharmacol 10:54–63, 2002

Carroll KM, Fenton LR, Ball SA, et al: Efficacy of disulfiram and cognitive behavior therapy in cocaine-dependent outpatients. Arch Gen Psychiatry 61:264–272, 2004

Chick J, Gough K, Faldowski W, et al: Disulfiram treatment of alcoholism. Br J Psychiatry 161:84–89, 1992

Chick J, Howlett H, Morgan MY, et al: United Kingdom multicentre acamprosate study (UKMAS): a 6-month prospective study of acamprosate versus placebo in preventing relaspe after withdrawal from alcohol. Alcohol Alcoholism 35:176–187, 2000

COMBINE Study Research Group: Testing combined pharmacotherapies and behavioral interventions in alcohol dependence: rationale and methods. Alcohol Clin Exp Res 27:1107–1122, 2003a

COMBINE Study Research Group: Testing combined pharmacotherapies and behavioral interventions in alcohol dependence (The COMBINE Study): a pilot feasibility study. Alcohol Clin Exp Res 27:1123–1131, 2003b

Dallery J, Silverman K, Chutuape MA, et al: Voucher-based reinforcement of opiate plus cocaine abstinence in treatment-resistant methadone patients: effects of reinforcer magnitude. Exp Clin Psychopharm 9:317–325, 2001

Epstein EE, McCrady BS: Behavioral couples treatment of alcohol and drug use disorders: current status and innovations. Clin Psychol Rev 18:689–711, 1998

Fals-Stewart W, O'Farrell TJ: Behavioral family counseling and naltrexone for male opioid-dependent patients. J Consult Clin Psychol 71:432–442, 2003

Fals-Stewart W, O'Farrell TJ, Birchler GR: Behavioral couples therapy for male methadone maintenance patients: effects of drug-using behavior and relationship adjustment. Behav Ther 32:391–411, 2001

Fiellin DA, Pantalon MV, Pakes JP, et al: Treatment of heroin dependence with buprenorphine in primary care. Am J Drug Alcohol Abuse 28: 231–241, 2002

Fleming M, Manwell LB: Brief intervention in primary care settings: a primary treatment method for at-risk, problem, and dependent drinkers. Alcohol Res Health 23:128–137, 1999

Fleming MF, Barry KL, Manwell LB, et al: Brief physician advice for problem alcohol drinkers: a randomized controlled trial in community-based primary care practices. J Am Med Assoc 277:1029–1045, 1997

Goldstein MF, Deren S, Sung-Yeon K, et al: Evaluation of an alternative program for MMTP drop-outs: impact on treatment re-entry. Drug Alcohol Depend 66:181–187, 2002

Higgins ST, Budney AJ, Bickel WK, et al: Achieving cocaine abstinence with a behavioral approach. Am J Psychiatry 150:763–769, 1993

Higgins ST, Budney AJ, Bickel WK, et al: Incentives improve outcome in outpatient behavioral treatment of cocaine-dependence. Arch Gen Psychiatry 51:568–576, 1994

Higgins ST, Wong CJ, Badger GJ, et al: Contingent reinforcement increases cocaine abstinence during outpatient treatment and 1 year of follow-up. J Consult Clin Psychol 68:64–72, 2000

Higgins ST, Sigmon SC, Wong CJ, et al: Community reinforcement therapy for cocaine-dependent outpatients. Arch Gen Psychiatry 60:1043–1052, 2003

Hopkins JS, Garbutt JC, Poole CL, et al: Naltrexone and acamprosate: meta-analysis of two medical treatments for alcoholism. Presented at the 25th annual meeting of the Research Society on Alcoholism, San Francisco, CA, June 28–July 3, 2002

Johnson A, Jasinski DR, Galloway GP, et al: Ritanserin in the treatment of alcohol dependence: a multi-center clinical trial. Psychopharmacol 128:206–215, 1996

Johnson BA, Roache JD, Javors MA, et al.: Ondansetron for reduction of drinking among biologically predisposed alcoholic patients: a randomized controlled trial. JAMA 284:963–971, 2000

Kadden RM: Behavioral and cognitive-behavioral treatments for alcoholism: research opportunities. Addict Behav 26:489–507, 2001

Kiefer F: Randomized controlled trial of naltrexone, acamprosate and the combination in the treatment of alcoholism. Presented at the 25th annual meeting of the Research Society on Alcoholism, San Francisco, CA, June 28–July 3, 2002

Kosten T, Oliveto A, Feingold A, et al: Desipramine and contingency management for cocaine and opiate dependence in buprenorphine maintained patients. Drug Alcohol Depend 70:315–325, 2003a

Kosten T, Poling J, Oliveto A: Effects of reducing contingency management values on heroin and cocaine use for buprenorphine- and desipramine-treated patients. Addiction 98:665–671, 2003b

Kranzler HR, Burleson JA, Korner P, et al: Placebo-controlled trial of fluoxetine as an adjunct to relapse prevention in alcoholics. Am J Psychiatry 152:391–397, 1995

Kranzler HR, Burleson JA, Brown J, et al: Fluoxetine treatment seems to reduce the beneficial effects of cognitive-behavioral therapy in type B alcoholics. Alcohol Clin Exp Res 20:1534–1541 1996

Kranzler HR, Tennen H, Penta C, et al: Targeted naltrexone treatment of early problem drinkers. Addict Behav 22:431–436, 1997

Kranzler HR, Armeli S, Tennen H, et al: Targeted naltrexone for early problem drinkers. J Clin Psychopharmacology 23:294–304, 2003

Kranzler HR, Wesson DR, Billot L, et al: Naltrexone depot for treatment of alcohol dependence: a multicenter, randomized, placebo-controlled clinical trial. Alcohol Clin Exp Res 28:1051–1059, 2004

Kristenson H, Ohlin H, Hulten-Nousslin M, et al: Identification and intervention of heavy drinking in middle-aged men: results and follow-up of 24–60 months of long-term study with randomized controls. Alcohol Clin Exp Res 7:203–209, 1983

Krystal JH, Cramer JA, Krol WF, et al: Naltrexone in the treatment of alcohol dependence. N Engl J Med. 345:1734–1739, 2001

Liebson IA, Tommasello A, Bigelow GE: A behavioral treatment of alcoholic methadone patients. Annals Int Med 89:342–344, 1978

Mason BJ, Goodman AM: Acamprosate treatment of alcohol dependence: results of the U.S. multicenter study (abstract). Biol Psychiatry 49(8 suppl):14S, 2001

Mason BJ, Salvato, FR, Williams LD, et al: Double-blind, placebo-controlled study of oral nalmefene for alcohol dependence. Arch Gen Psychiatry 56:719–724, 1999

Maude-Griffin PM, Hohenstein JM, Humfleet GL, et al: Superior efficacy of cognitive-behavioral therapy for urban crack cocaine abusers: main and matching effects. J Consult Clin Psychol 66:832–837, 1998

McCaul ME, Stitzer ML, Bigelow GE, et al: Contingency management interventions: effects on treatment outcome during methadone detoxification. J Appl Behav Anal 17:35–43, 1984

McCrady BS, Miller WR (eds): Alcoholics Anonymous: Opportunities and Alternatives. New Brunswick, NJ, Rutgers Center of Alcohol Studies, 1993

McCrady BS, Stout N, Noel N, et al: Effectiveness of three types of spouse-involved behavioral alcoholism treatments. Br J Addiction 86:1415–1424, 1991

McKay JR, Alterman AI, McLellan AT, et al: Treatment goals, continuity of care, and outcome in a day hospital substance abuse rehabilitation program. Am J Psychiatry 151:254–259, 1994

McLellan AT, Arndt IO, Metzger DS, et al: The effects of psychosocial services in substance abuse treatment. JAMA 269:1953–1959, 1993

Meyers RJ, Smith JE: Clinical Guide to Alcohol Treatment: The Community Reinforcement Approach. New York, Guilford, 1995

Miller WR, Rollnick S: Motivational Interviewing: Preparing People to Change Addictive Behavior. New York, Guilford, 1991

Miller WR, Brown JM, Simpson TL, et al: What works? a methodological analysis of the alcohol treatment outcome literature, in Handbook of Alcoholism Treatment Approaches: Effective Alternatives, 2nd Edition. Edited by Herster RK, Miller WR. Boston, MA, Allyn & Bacon, 1995a, pp 12–44

Miller WR, Zweben A, DiClemente CC, et al: Motivational Enhancement Therapy Manual: A Clinical Research Guide for Therapists Treating Individuals With Alcohol Abuse and Dependence. Project MATCH Monograph Series, Vol 2 (NIH Publ No 94–3723). Rockville, MD, National Institute on Alcohol Abuse and Alcoholism, 1995b

Naranjo CA, Bremner KE, Lanctot KL: Effects of citalopram and a brief psychosocial intervention on alcohol intake, dependence and problems. Addiction 90:87–99, 1995

Nowinski J, Baker S, Carroll K: Twelve-Step Facilitation Therapy Manual: A Clinical Research Guide for Therapists Treating Individuals With Alcohol Abuse and Dependence. Project MATCH Monograph Series, Vol 1 (DHHS Publ No ADM-92-1893). Rockville, MD, National Institute on Alcohol Abuse and Alcoholism, 1992

Ockene JK, Adams A, Hurley TG, et al: Brief physician- and nurse practitioner-delivered counseling for high-risk drinkers: does it work? Arch Intern Med 11:2198–2205, 1999

O'Connor PG, Farren CK, Rounsaville BJ, et al: A preliminary investigation of the management of alcohol dependence with naltrexone by primary care providers. Am J Med 103:477–482, 1997

O'Farrell TJ, Cutter HSG, Choquette KA, et al: Behavioral marital therapy for male alcoholics: marital and drinking adjustment during the two years after treatment. Behav Ther 23:529–549, 1992

O'Farrell TJ, Choquette KA, Cutter HS, et al: Cost-benefit and cost-effectiveness analyses of behavioral marital therapy as an addition to outpatient alcoholism treatment. J Subst Abuse 8:145–166, 1996

O'Malley SS, Jaffe AJ, Chang G, et al: Naltrexone and coping skills therapy for alcohol dependence: a controlled study. Arch Gen Psychiatry 49:881–887, 1992

O'Malley SS, Jaffe AJ, Chang G, et al: Six-month follow-up of naltrexone and psychotherapy for alcohol dependence. Arch Gen Psychiatry 53:217–224, 1996

O'Malley SS, O'Connor PG, Farren C, et al: Comparison of naltrexone in combination with either CB therapy or medical model counseling (abstract). J Addict Dis 17: 160, 1998

O'Malley SS, O'Connor PG, Farren C, et al: Naltrexone in the treatment of alcoholism: new research (abstract). Biol Psychiatry 49 (8, suppl):14S, 2001

O'Neill K, Baker A, Cooke M, et al: Evaluation of a cognitive-behavioural intervention for pregnant injecting drug users at risk for HIV infection. Addiction 91:1115–1125, 1996

Paokolainen K: Effectiveness of brief interventions to reduce alcohol intake in primary health care populations: a meta-analysis. Prevent Med 28:503–509, 1999

Petry NM: A comprehensive guide to the application of contingency management procedures in clinical settings. Drug Alcohol Depend 58:9–25, 2000

Petry NM, Martin B. Low-cost contingency management for treating cocaine- and opioid-abusing methadone patients. J Consult Clin Psychol 70:398–405, 2002

Petry NM, Martin B, Cooney JL, et al: Give them prizes, and they will come: contingency management for treatment of alcohol dependence. J Consult Clin Psychol 68:250–257, 2000

Pettinati HM: The use of selective serotonin reuptake inhibitors in treating alcoholic subtypes. J Clin Psychiatry 62:26–31, 2001

Pettinati HM, Volpicelli JR, Luck G, et al: Double-blind clinical trial of sertraline treatment for alcohol dependence. J Clin Pharmacol 21:143–153, 2001

Preston KL, Silverman K, Umbricht A, et al: Improvement in naltrexone treatment compliance with contingency management. Drug Alcohol Depend 54:127–135, 1999

Preston KL, Umbricht A, Epstein DH: Methadone dose increase and abstinence reinforcement for treatment of continued heroin use during methadone maintenance. Arch Gen Psychiatry 57:395–404, 2000

Prochaska JO, DiClemente CC: Toward a comprehensive model of change, in Treating Addictive Behaviors: Processes of Change. Edited by Miller WR, Heather N. New York, Plenum, 1986, pp 3–27

Project MATCH Research Group: Matching alcoholism treatments to client heterogeneity: Project MATCH posttreatment drinking outcomes. J Stud Alcohol 58:7–29, 1997

Rawson RA, Huber A, McCann M, et al: A comparison of contingency management and cognitive-behavioral approaches during methadone maintenance treatment for cocaine dependence. Arch Gen Psychiatry 59:817–824, 2002

Rohsenow DJ, Monti PM, Martin RA, et al: Motivational enhancement and coping skills training for cocaine abusers: effect on substance use outcomes. Addiction 99:862–874, 2004

Rosenblum A, Magura S, Palij M, et al: Enhanced treatment outcomes for cocaine-using methadone patients. Drug Alcohol Depend 54:207–218, 1999

Rychtarik RG, Connors GJ, Dermen KH, et al: Alcoholics Anonymous and the use of medications to prevent relapse: an anonymous survey of member attitudes. J Stud Alcohol 61:134–138, 2000

Schottenfeld RS, Chawarski MC, Pakes JR, et al: Methadone versus buprenorphine with contingency management or performance feedback for cocaine and opioid dependence. Am J Psychiatry 162:340–349, 2005

Smith JE, Meyers RJ, Delaney HD: Community reinforcement approach with homeless alcohol-dependent individuals. J Consult Clin Psychol 66:541–548, 1998

Stotts AL, Schmitz JM, Rhoades HM, et al: Motivational interviewing with cocaine-dependent patients: a pilot study. J Consult Clin Psychol 69:858–862, 2001

Volpicelli J, Rhines KC, Rhines JS, et al: Naltrexone and alcohol dependence: role of subject compliance. Arch Gen Psychiatry 54:737–742, 1997

Wilk AI, Jensen NM, Havighurst TC: Meta-analysis of randomized control trials addressing brief interventions in heavy alcohol drinkers. J Gen Intern Med 12:274–283, 1997

Yahne CE, Miller WR, Irvin-Vitela L, et al: Magdalena pilot project: motivational outreach to substance abusing women street sex workers. J Subst Abuse Treat 23: 49–53, 2002

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