Chapter **48**

Illicit Opiate Abuse

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Illicit drugs are those banned by international drug control treaties. They include cannabis products (for example, marijuana, hashish, and bhang); stimulant drugs (such as cocaine and methamphetamine); so-called dance-party drugs (such as 3, 4-methylenedioxymethamphetamine, also known as *ecstasy* or *MDMA*); and illicit opioids (for instance, heroin and opium) and diverted pharmaceutical opioids (such as buprenorphine, methadone, and morphine) (see annex 48.A).

Worldwide, 185 million people were estimated to have used illicit drugs during 1998–2002 (UNODC 2004; UNODCCP 2002). Cannabis was the most widely used illicit drug, with 146.2 million users in 2002, or 3.7 percent of the global population over age 15. The stimulant drugs were the next most widely used illicit drugs: 29.6 million people worldwide used amphetamines; 13.3 million used cocaine; and 8.3 million used ecstasy. An estimated 15.3 million, or 0.4 percent of the world population age 15 to 64, used illicit opioids; more than half used heroin and the remainder used opium or diverted pharmaceutical opioids. Illicit opioids continue to be the major illicit drug problem in most regions of the world in terms of impact on public health and public order (UNODC 2004).

Even though cannabis use accounts for about 80 percent of illicit drug use worldwide, the mortality and morbidity attributable to its use are not well understood, even in developed countries (W. Hall and Pacula 2003; Macleod and others 2004; WHO Programme on Substance Abuse 1997). The same is true of the morbidity and mortality attributable to cocaine and amphetamine-type stimulants (Macleod and others 2004). Dance-party drugs have been used for too short a time in most developed societies to enable a good assessment of their potential for harm (Boot, McGregor, and Hall 2000; Macleod and others 2004). The remainder of this chapter is concerned with disease control priorities for illicit opioid dependence, because dependent users account for most of the illicit opioids consumed and experience most of the harm such dependence causes (W. Hall, Degenhardt, and Lynskey 1999).

NATURE, CAUSES, AND HEALTH CONSEQUENCES OF ILLICIT OPIOID USE

Before considering interventions, we briefly summarize what is known about the antecedents, causes, and health consequences of illicit opioid use.

Antecedents of Heroin Use

Law enforcement efforts to reduce the availability of heroin aim to increase its price, deter illicit drug use, and promote social values that discourage heroin use (Fergusson, Horwood, and Lynskey 1998; Hawkins, Catalano, and Miller 1992; Newcomb and Bentler 1988). These gains may be at the cost of increasing harm among the minority who use opioids despite the prohibition—for example, by encouraging injecting use as the most efficient way to use an expensive drug and increasing needle sharing because clean injecting equipment is not freely available (Rhodes and others 2003; Strathdee and others 2003).

Two aspects of the family environment are associated with increased rates of both licit and illicit drug use in young people in developed countries. The first is exposure to a disadvantaged home environment, with parental conflict and poor discipline and supervision; the second is exposure to parents' and siblings' use of alcohol and other drugs (Hawkins, Catalano, and Miller 1992). In developed countries, children who perform

poorly in school because of impulsive or problem behavior and those who are early users of alcohol and other drugs are most likely to use illicit opioids (Fergusson, Horwood, and Swain-Campbell 2002). Affiliation with drug-using peers is a risk factor for drug use that operates independently of individual and family risk factors (Fergusson, Horwood, and Lynskey 1998; Hawkins, Catalano, and Miller 1992).

Health Consequences of Heroin Use

The following sections describe the major health consequences of heroin use. They include dependence, increased mortality and morbidity attributable to drug overdoses, and bloodborne viruses.

Heroin Dependence. In household surveys, 1 to 2 percent of adults in Australia, the United States, and Europe report using heroin at some time in their lives (Australian Institute of Health and Welfare 1999; EMCDDA 2002; SAMHSA 2002). The highest rates are typically among adults age 20 to 29. Self-reported heroin use in population surveys probably underestimates rates of use because heroin users are undersampled and those who are sampled underreport their use (W. Hall, Lynskey, and Degenhardt 1999).

In developed countries, one in four of those who report heroin use become dependent on it (Anthony, Warner, and Kessler 1994). People who are heroin dependent continue to use heroin in the face of problems that they know (or believe) to be caused by its use. These problems include being arrested or imprisoned, having interpersonal and family problems, catching infectious diseases, and suffering from drug overdoses. Many heroin users who seek treatment have typically been daily heroin injectors, although in Europe (EMCDDA 2002), North America (Office of National Drug Control Policy 2001), and parts of Asia, illicit opioid users also smoke or "chase" the drug (inhale the fumes released when heroin is heated) (UNODC 2004).

The American Psychiatric Association defines *drug dependence* as "a cluster of cognitive, behavioral, and physiologic symptoms indicating that the individual continues use of the substance despite significant substance-related problems" (American Psychiatric Association 1994, 176). In the fourth edition of the association's *Diagnostic and Statistical Manual of Mental Disorders* (1994,), a diagnosis of substance dependence requires that three or more of the following occur together:

At any time in the same 12-month period:

1. tolerance, as defined by either of the following:
   a. need for markedly increased amounts of the substance to achieve intoxication or desired effect
   b. markedly diminished effect with continued use of the same amount of the substance;
2. withdrawal, as manifested by either of the following:
   a. the characteristic withdrawal syndrome for the substance
   b. the same (or closely related) substance is taken to relieve or avoid withdrawal symptoms;
3. the substance is often taken in larger amounts or over a longer period than was intended;
4. there is a persistent desire or unsuccessful efforts to cut down or control substance use;
5. a great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors, driving long distances), use the substance (e.g., chain smoking), or recover from its effects;
6. important social, occupational, or recreational activities are given up or reduced because of substance use;
7. the substance 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 the substance.

Indirect estimation methods suggest that in Australia, the United Kingdom, and the European Union fewer than 1 percent of adults age 15 to 54 are heroin dependent (EMCDDA 2002; W. Hall and others 2000). Research in the United States indicates that dependent heroin users who seek treatment or who come to the attention of the legal system may use heroin for decades (Goldstein and Herrera 1995; Hser, Anglin, and Powers 1993), with periods of use punctuated by abstinence (Bruneau and others 2004; Galai and others 2003), drug treatment, and imprisonment (Gerstein and Harwood 1990). When periods of abstinence are included, dependent heroin users use heroin daily for 40 to 60 percent of the 20 years that they typically are addicts (Ball, Shaffer, and Nurco 1983; Maddux and Desmond 1992).

Illicit opioid use increased in Asia, Europe, and Oceania and, to a lesser extent, in Africa and South America in the 1990s, but it has stabilized or declined since 2000 (UNODC 2004). Most illicit opioid users (7.8 million) live in Asian countries that surround the major opium-producing countries, Afghanistan and Myanmar. Europe accounts for about 25 percent of illicit opioid use (4 million users or 0.8 percent of the adult population age 15 to 64). Two-thirds of users are in Eastern Europe, which reported large increases in illicit opioid use during the second half of the 1990s (Atlani and others 2000; Hamers and Downs 2003; Kelly and Amirkhanian 2003; Rhodes and others 1999; Uuskula and others 2002).

Illicit opioid use stabilized in much of Asia between 2000 and 2002 (UNODC 2004) as a result of decreased opium production after the rapid expansion during the 1990s (Dorabjee and Samson 2000; Reid and Crofts 2000). After 2000, India and Pakistan reported stabilizing rates of illicit opioid use but increased injection of pharmaceutical opiates (Ahmed and others 2003; Dorabjee and Samson 2000; Strathdee and others

2003). China has reported a steady rate of growth in illicit opiate use in its southern and northern provinces (Beyrer 2003; Beyrer and others 2000; Yu and others 1998) and a 15-fold increase in the number of registered opioid addicts between 1990 and 2002, bringing the total to about 1 million (UNODC 2004).

Oceania experienced a marked rise in heroin use in the late 1990s, largely driven by a dramatic increase in the availability of heroin in Australia (Darke, Topp, and others 2002; W. Hall, Degenhardt, and Lynskey 1999). In late 2000, an abrupt heroin shortage resulted in a large reduction in fatal and nonfatal overdoses (Day and others 2004; Degenhardt, Day, and Hall 2004).

Mortality, Morbidity, and Heroin Dependence. In developed countries, dependent heroin users have an increased risk of premature death from drug overdoses, violence, suicide, and alcohol-related causes (Darke and Ross 2002; Goldstein and Herrera 1995; Vlahov and others 2004). Heroin users treated before the HIV epidemic were 13 times more likely to die prematurely than their peers (Hulse and others 1999), with opioid overdose the most frequent cause of death (W. Hall, Degenhardt, and Lynskey 1999). In countries with a high prevalence of HIV infection, AIDS is a major cause of premature death among drug users (EMCDDA 2002; UNAIDS and WHO 2002). Fatal opioid overdose deaths increased in many developed countries during the 1990s before declining after 2000 (UNODC 2004).

In parts of Asia, Eastern Europe, and the United States, the sharing of contaminated injecting equipment accounts for a substantial proportion of new HIV infections (EMCDDA 2002; UNAIDS and WHO 2002; UNODC 2004). Injecting opioid use has been a major driver of HIV epidemics in China (Yu and others 1998), Myanmar (Beyrer and others 2000), the Russian Federation and former Soviet republics (Hamers and Downs 2003), and Vietnam (Beyrer and others 2000; Hien and others 2001).

The prevalence of infection with hepatitis B and C viruses among injecting drug users is greater than 60 percent in Australia (National Centre in HIV Epidemiology and Clinical Research 1998), Canada (Fischer and others 2004), China (Ruan and others 2004), the United States (Fuller and others 2004), and the European Union (EMCDDA 2002). Chronic infection occurs in 75 percent of infections, and 3 to 11 percent of chronic hepatitis C virus carriers develop liver cirrhosis within 20 years (Hepatitis C Virus Projections Working Group 1998).

Heroin-related deaths primarily occur among young adults and account for a large number of life years lost in developed societies. In Australia in 1996, for example, such deaths accounted for 2.2 percent of life years lost, with each death accounting for 22 years of life lost (Mathers, Vos, and Stephenson 1999). In Scotland and Spain, opiate-related deaths account for 25 to 33 percent of deaths of young adult males (EMCDDA 2002).

Economic Costs of Illicit Opioid Use. In Canada, Xie and others (1996) calculate the costs of illicit drugs as 0.2 percent of gross domestic product (GDP). In Australia, Collins and Lapsley (1996) estimate the economic costs of illicit drug abuse at 2 percent of GDP.

CONTRIBUTION OF OPIOID DEPENDENCE TO THE GLOBAL BURDEN OF DISEASE

Degenhardt, Hall, and others (2004) estimate the contribution of illicit opioid dependence to the global burden of disease using data on deaths caused by opioid and other drug overdoses, suicides and accidents, and HIV/AIDS. When estimates of morbidity attributable to illicit drug use were added in, illicit opioid use accounted for 0.7 percent of global disability-adjusted life years (DALYs) in 2000 (WHO 2003).

These estimates suggest that illicit opioid use is a significant global cause of premature mortality and disability among young adults. Even so, they probably underestimate the disease burden attributable to illicit opioids, because they omit differences across subregions in the quality of data on causes of mortality and estimates of mortality and morbidity attributable to hepatitis and violence (Degenhardt, Hall, and others 2004).

INTERVENTIONS FOR ILLICIT OPIOID DEPENDENCE

Methods adopted to control the problems arising from illicit opioid dependence include source-country control; interdiction of supply into end-use countries; enforcement by the police force and the criminal justice system of legal prohibitions on the supply, possession, and use of opioids; treatment of those who are opioid dependent, both voluntarily and under legal coercion from the criminal justice system; school-based and mass media preventive educational programs; and regulatory policies restricting the prescription of opioids (Manski, Pepper, and Petrie 2001).

Prevention of Heroin Use

Countries use a variety of interventions in attempts to prevent the initiation of use of illicit drugs such as cannabis (Manski, Pepper, and Petrie 2001; Spooner and Hall 2002), in the belief that early initiation of cannabis use leads to an increased risk of using illicit opioids (Fergusson, Horwood, and Swain-Campbell 2002). These interventions include legal prohibitions on the manufacture, sale, and use of opioid drugs

for nonmedical purposes; enforcement of these sanctions by law enforcement officials by means of fines and imprisonment; and enforcement of restrictions on medically prescribed opioids to prevent their diversion (Manski, Pepper, and Petrie 2001). Preventive measures also include mass media and school-based educational campaigns about the health risks of opioid and other illicit drug use (Spooner and Hall 2002). It is unclear how effective these interventions are in preventing cannabis use and even less clear whether they reduce the initiation of opioids (Caulkins and others 1999; Manski, Pepper, and Petrie 2001).

The most popular interventions against illicit opioid use in many developed societies have been the interdiction of drug supply and the enforcement of legal sanctions against the possession, use, and sale of opioid drugs (Manski, Pepper, and Petrie 2001). As a consequence, imprisonment is the most common intervention to which many illicit opioid users have been exposed (Gerstein and Harwood 1990). In Asia and Eastern Europe, high rates of imprisonment of drug users have been a factor in HIV transmission, because drug users engage in high-risk injecting while imprisoned (Beyrer and others 2000).

Interventions to Reduce Heroin-Related Harm

The most effective intervention to reduce bloodborne virus infection arising from illicit injecting of opioids and other drugs is the provision of clean injecting equipment to reduce users' risks of contracting or transmitting bloodborne viruses. This intervention has been widely supported in most developed countries, but it has been incompletely adopted in developing countries that have problems with the concept of facilitating the injection of illicit drugs (UNAIDS and WHO 2002). Vaccinations are available against hepatitis B but not hepatitis C. These important interventions are covered in chapter 18.

A number of strategies can potentially reduce deaths from opioid overdoses (Darke and Hall 2003; Sporer 2003). First, injecting drug users can be educated about the dangers of combining the use of opioids with alcohol and benzodiazepines (McGregor and others 2001), both of which heighten the risk of a fatal opioid overdose (Darke and Zador 1996; Warner-Smith and others 2001). Heroin users also need to be discouraged from injecting in the streets or alone, thereby denying themselves assistance in the event of an overdose. These interventions have yet to be evaluated.

A second strategy is to encourage drug users who witness overdoses to seek medical assistance and to use simple resuscitation techniques until help arrives. A more controversial option is to distribute the opioid antagonist naloxone to high-risk heroin users (Darke and Hall 1997; Strang and others 1996). Neither of these interventions has been evaluated.

A third strategy is to provide supervised injecting facilities in areas with high rates of injecting opioid use (Dolan and others 2000; Kimber and others 2003). Supervised injecting facilities have been introduced in Germany, the Netherlands, and Switzerland (Dolan and others 2000; Kimber and others 2003), but their effect on overdose deaths has not been rigorously evaluated to date. A supervised injecting facility was evaluated in Australia, but the evaluation was limited by the concurrent onset of a heroin shortage that resulted in a 40 percent decline in overdose deaths (Kaldor and others 2003).

A fourth strategy is to increase methadone maintenance among older, high-risk opioid-dependent people, because individuals enrolled in methadone maintenance treatment (MMT) are substantially less likely to suffer from a fatal overdose (Caplehorn and others 1994; Gearing and Schweitzer 1974; Langendam and others 2001).

Treatment Interventions for Dependent Opioid Users

The range of treatment interventions includes voluntary programs such as detoxification, abstinence-oriented treatments, and oral Methadone maintenance treatment, as well as involuntary options imposed by criminal justice systems.

Detoxification. Detoxification is supervised withdrawal from a drug of dependence that attempts to minimize withdrawal symptoms. It is not a treatment for heroin dependence; it provides a respite from opioid use and may be a prelude to abstinence-based treatment (Mattick and Hall 1996).

Naltrexone is a longer-acting opiate antagonist than naloxone; it can be used to accelerate the opioid withdrawal process. Ultra-rapid opioid detoxification accelerates withdrawal by giving the patient naltrexone under general anesthetic. There is no evidence that accelerated withdrawal in itself reduces the high rate of relapse to heroin use in the absence of further treatment (W. Hall and Mattick 2000).

Abstinence-Oriented Treatments. Abstinence-oriented treatments aim to achieve enduring abstinence from all opioid drugs by providing some type of intervention after withdrawal to reduce the high rate of relapse to opioids (Mattick and Hall 1996). The interventions may include social and psychological support only or such support supplemented by pharmacological methods.

Residential treatment in therapeutic communities and outpatient drug counseling may entail encouraging patients to become involved in self-help groups such as Narcotics Anonymous. These approaches share a commitment to achieving abstinence from all opioids, using group and psychological interventions to help dependent heroin users remain abstinent. Therapeutic communities and drug counseling are usually provided through specialist addiction or mental health services. The former are residential, and the latter are provided on an outpatient basis.

No randomized controlled trials of therapeutic communities or outpatient drug counseling have been carried out. Observational studies in the United Kingdom (Gossop, Marsden, and Stewart 1998; Gossop and others 1997) and the United States (Hubbard and others 1989; Simpson and Sells 1982) have found that therapeutic communities and drug counseling were less successful than MMT in attracting and retaining dependent heroin users, but they substantially reduced heroin use and crime among those who remained in treatment for at least three months (Gerstein and Harwood 1990; Gossop, Marsden, and Stewart 1998; Gossop and others 1997). Some evidence indicated that therapeutic communities may be more effective if they are used in combination with legal coercion to ensure that heroin users are retained in treatment long enough to benefit from it (Gerstein and Harwood 1990).

Recovering drug users run Narcotics Anonymous groups using an adaptation of the 12-step philosophy of Alcoholics Anonymous. Some individuals use these groups as their sole form of support for abstinence, whereas for others these groups complement therapeutic communities that are based on the same principles. Such groups are usually not open to people who are in opioid substitution treatment programs.

The most extensive research on self-help has been in the treatment of alcohol dependence. Treated alcoholics who participate in Alcoholics Anonymous groups have higher rates of abstinence than those who do not (see, for example, Tonigan, Connors, and Miller 2003; Tonigan, Toscova, and Miller 1996). The good outcome in those who attend Alcoholics Anonymous meetings may reflect the self-selection of motivated participants into self-help groups. Recent studies that have attempted to control for this possibility using sophisticated statistical methods have produced mixed results, with some showing the persistence of an effect of self-help after correction (Tonigan, Connors, and Miller 2003) while others do not (Fortney and others 1998).

Shepard and others (forthcoming) evaluate the effect of self-help participation on substance abuse 24 months after treatment for members of a mixed population of substance abusers treated at two treatment facilities in the United States, some of whom had problems with heroin. They find that participation in self-help groups was associated with longer abstinence from all drugs. Correction for self-selection did not eliminate the association in one treatment setting, but it made the results much more equivocal in the other.

Oral Methadone Maintenance Treatment. This treatment substitutes a long-acting, orally administered opioid for the shorter-acting heroin, with the aim of stabilizing dependent heroin users so that they are amenable to rehabilitation (Marsh and others 1990; Ward, Hall, and Mattick 1998). When given in high or blockade doses, methadone blocks the euphoric effects of injected heroin, allowing the individual to take advantage of psychotherapeutic and rehabilitative services.

Every one of the small number of randomized controlled trials of MMT compared with placebo or no treatment has produced positive results (W. Hall, Ward, and Mattick 1998; Mattick and others 2003). Large observational studies show that MMT decreases heroin use and criminal activity and reduces HIV transmission while patients remain in treatment (Gerstein and Harwood 1990; Simpson and Sells 1990; Ward, Hall, and Mattick 1998). MMT is the best-supported form of opioid maintenance treatment (Farre and others 2002; Marsch 1998; Mattick and others 2003).

Buprenorphine is a mixed agonist-antagonist that also blocks the effects of heroin. When given in high doses, its effects can last for up to three days, while its antagonist effects substantially reduce overdose and abuse (Oliveto and Kosten 1997; Ward, Hall, and Mattick 1998). Meta-analyses have found that buprenorphine is effective in the treatment of heroin dependence (Mattick and others 2003) and is of equivalent efficacy to MMT when delivered in primary health care and specialist treatment settings in Australia (Gibson and others 2003).

Bammer and others (2003) have proposed injectable heroin maintenance as a way of attracting into treatment those heroin users who are not interested in or have failed to respond to MMT. This method has recently been evaluated in the Netherlands (Central Committee on the Treatment of Heroin Addicts 2002) and Switzerland (Perneger and others 1998; Uchtenhagen, Gutzwiller, and Dobler-Mikola 1998). Perneger and others (1998) report a randomized controlled trial of injectable heroin maintenance in people who had failed at MMT. Stabilizing and safely maintaining heroin addicts on injectable heroin (self-administered on-site in a comprehensive health and social service) proved feasible for six months and substantially improved their health and social well-being. The Swiss trials showed that it was possible to maintain opioid addicts on injectable heroin for up to two years (Rehm and others 2001; Uchtenhagen, Gutzwiller, and Dobler-Mikola 1998). A recent randomized controlled trial in the Netherlands (Central Committee on the Treatment of Heroin Addicts 2002) confirms the findings of Perneger and others (1998).

Criminal Justice Interventions for Dependent Illicit Opioid Users. The most common intervention for illicit opioid dependence in most developed societies is imprisonment (EMCDDA 2003; Gerstein and Harwood 1990). Imprisonment is not intended to be a health intervention. Nonetheless, it is an ineffective way of reducing opioid dependence, when judged by the high recidivism in longitudinal studies of dependent heroin users (see, for example, Hser, Anglin, and Powers 1993; Manski, Pepper, and Petrie 2001).

Legally coerced treatment is treatment that is legally forced on those who have been charged with or convicted of an

offense to which their drug dependence has contributed (W. Hall 1997). It is most often provided as an alternative to imprisonment, under the threat of imprisonment if the person fails to comply with the treatment (W. Hall 1997; Manski, Pepper, and Petrie 2001; Spooner, Hall, and Mattick 2001). Its major justification is that it is an effective way of treating offenders' drug dependence that reduces the likelihood of their offending again (Gerstein and Harwood 1990). A consensus view prepared for the World Health Organization (WHO) (Porter, Arif, and Curran 1986) was that compulsory treatment was legally and ethically justified only if the rights of the individuals were protected by due process and if the treatment provided was effective and humane.

Research into the effectiveness of legally coerced treatment for opioid dependence has been limited to observational studies (W. Hall 1997; Manski, Pepper, and Petrie 2001; Wild, Roberts, and Cooper 2002). Anglin's (1988) quasi-experimental studies of the California Civil Addict Program provide the strongest evidence of efficacy. These studies compared heroin-dependent offenders who entered the program between 1962 and 1964 with a group of similar offenders who went through the criminal justice system during the same period. They found that compulsory hospital treatment followed by close supervision in the community substantially reduced heroin use and crime.

The effectiveness of less coercive forms of treatment has been supported by analyses of the effectiveness of community-based treatment provided while on probation or parole (Hubbard and others 1989; Simpson and others 1986). These studies showed that individuals who entered community-based therapeutic communities and drug-free outpatient counseling under legal pressure did as well as those who did so voluntarily (Hubbard and others 1988; Simpson and Friend 1988). The recent creation of specialized drug courts in the United States to process those arrested for drug-related offenses awaits rigorous evaluation (Belenko 2002; Manski, Pepper, and Petrie 2001).

Legally coerced MMT is also effective. The strongest evidence comes from a study in which drug offenders were randomly assigned to parole with and without community-based MMT (Dole and others 1969). This study showed a greater reduction in heroin use and lower rates of incarceration among those enrolled in MMT in the year following their release from prison. These findings are supported by observational studies that found no major differences in response to MMT between those who enrolled under legal coercion and those who did not (Anglin, Brecht, and Maddahain 1989; Brecht, Anglin, and Wang 1993; Hubbard and others 1988).

Economic Evaluations of Interventions for Illicit Opioid Dependence

The few published economic evaluations of treatment interventions for illicit opioid dependence indicate varying levels of cost-effectiveness.

Detoxification. The National Evaluation of Pharmacotherapies for Opioid Dependence Project in Australia conducted a cost-effectiveness analysis of five interventions:

- naltrexone-induced rapid opioid detoxification under anesthesia
- naltrexone-induced rapid opioid detoxification under sedation
- conventional inpatient detoxification
- conventional outpatient detoxification
- buprenorphine outpatient detoxification.

A successful outcome was defined as achieving abstinence from heroin for one week (Mattick and others 2001).

Rapid detoxification under sedation was the most cost-effective method of detoxification (US$2,355 for one week of abstinence) and conventional outpatient detoxification the least cost-effective (US$12,031). Rapid detoxification under anesthesia achieved high rates of abstinence in the first week, but its expense reduced its cost-effectiveness (Mattick and others 2001).

Doran and others (2003) compared the cost-effectiveness of detoxification from heroin using buprenorphine in a specialist Australian clinic and in a shared care setting. They conducted a randomized controlled trial with 115 heroin-dependent patients receiving a five-day treatment regime of buprenorphine. The specialist clinic was a community-based treatment agency in Sydney. Shared care involved treatment by a general practitioner, supplemented by weekend dispensing and some counseling at the specialist clinic. They estimate that buprenorphine detoxification in the shared care setting was US$17 more expensive per patient than the costs of treatment at the clinic (US$236 per patient).

Drug-Free Treatment. The limited economic evaluations of drug-free treatment have used data from observational studies of treatment outcomes in samples of patients who have mixed substance abuse problems that include opioids. For example, Shepard, Larson, and Hoffmann (1999) calculate a range of estimated costs for achieving an abstinent year in 408 patients at two different treatment facilities in the United States. The cost-effectiveness depended on the severity of the problem and the intensiveness and cost of the intervention. For outpatients with the least severe drug problems, the cost of an abstinent year was US$7,000, whereas the same outcome in patients with more severe problems who received long-term residential treatment cost US$20,000.

Shepard and others (forthcoming) use these data to estimate the cost-effectiveness of involvement in mutual self-help groups, such as Alcoholics Anonymous and Narcotics Anonymous, in sustaining abstinence for up to 24 months after treatment. They find a positive association between self-help

involvement and abstinence 12 and 24 months after treatment. Applying statistical methods to correct for the effects of self-selection into self-help, they find that in a Veterans Administration hospital, the effects of self-help on abstinence persisted after the statistical correction, but at the other site, the results depended on the method of analysis that was used. They estimate the cost of achieving an abstinent year by means of self-help in the year following treatment at US$13,000, all of that due to the costs that participants incurred in attending a group.

Oral Opioid Maintenance Treatment. Goldschmidt's (1976) economic evaluation of MMT found that it was as effective as a therapeutic community intervention and twice as cost-effective. Cartwright's (2000) review of the literature since 1976 identified a number of studies, all of which reported positive benefit-cost ratios for MMT.

Gerstein, Harwood, and Suter's (1994) California Drug and Alcohol Treatment Assessment study is the most comprehensive cost-benefit analysis carried out to date. The authors examine the effects of treatment—residential programs, outpatient programs, and methadone programs—on alcohol and drug use, criminal activity, health and health care utilization, and source of income. For each treatment modality, they found that the benefits during the first year of treatment significantly exceeded the cost of delivering the care. The benefit-cost ratio was 4.8 for residential treatment and 11.0 and 12.6 for outpatients and discharged methadone participants, respectively.

Doran and others (2003) compared the cost-effectiveness of buprenorphine and methadone treatment for opioid dependence. In a randomized controlled trial, 405 subjects were randomly assigned to each treatment at one of three specialist outpatient drug treatment centers. The study found that treatment with methadone was less expensive and more effective than treatment with buprenorphine, but the difference in cost (US$143 per additional heroin-free day gained) had a wide range of uncertainty around it (−US$1,469 to US$1,284).

The National Evaluation of Pharmacotherapies for Opioid Dependence Project also provided a cost-effectiveness analysis of methadone, buprenorphine, LAAM (levo-alpha-acetylmethadol), and naltrexone maintenance treatments (Mattick and others 2001). The daily costs of these maintenance treatments were similar for methadone and LAAM, but naltrexone was slightly more expensive. Buprenorphine maintenance treatment (BMT) was more expensive, but its cost-efficiency could have been improved to make its cost similar to that for the other treatments. MMT was the most cost-effective treatment for opioid dependence because it achieved one of the highest rates of retention in treatment among the four pharmacotherapies examined. Naltrexone treatment was the least cost-effective.

The costs of injectable heroin maintenance in the Dutch study was between US$18,015 and US$23,243 per patient per year (Bammer and others 2003). Most of the costs arose from the supervision of heroin use and the security required to prevent the diversion of heroin to the black market. Injectable heroin maintenance needs to produce substantially greater benefits for each participant than MMT to make it as cost-effective as MMT.

Economic Modeling of the Cost-Effectiveness of Opioid Maintenance Treatment. Barnett (1999), using data on the efficacy of MMT in reducing mortality derived from Gronbladh, Ohlund, and Gunne's (1990) Swedish study and U.S. cost data, estimated that MMT saved an additional year of life at a cost of US$5,900. Barnett, Zaric, and Brandeau (2001), using a similar approach, estimated that the use of buprenorphine by patients who would not use methadone would cost less than US$45,000 per quality-adjusted life year. Overall, however, they found that BMT was much less effective and more costly than MMT. Zaric, Barnett, and Brandeau (2000) assessed the economic benefits of using MMT to reduce HIV transmission in heroin users. They found that for heroin users living in a community with a high prevalence of HIV infection, expanding MMT use produced an additional year of quality-adjusted life at a cost of US$8,200.

Comparing the Cost-Effectiveness of Different Interventions

Comparative cost-effectiveness analyses of these interventions face major obstacles because the small number of published studies used different methods to cost interventions and different endpoints to assess the outcome of treatment. The following list, therefore, only ranks treatment interventions in the approximate order of their cost-effectiveness. We believe that estimates of their likely contribution to DALYs worldwide would be too speculative.

- *Detoxification.* Buprenorphine and supervised naltrexone-accelerated withdrawal delivered on an outpatient basis are the most efficient and effective ways to achieve withdrawal from opioids.
- *Self-help groups.* These groups provide the simplest form of postwithdrawal support for enduring abstinence and are also a low-cost intervention, because patients bear most of the costs; however, they have a low rate of uptake, and their effectiveness is only modest.
- *Oral opioid agonist maintenance treatment.* This form of treatment is the most widely used intervention for illicit opioid dependence in developed societies. It has a better uptake than other interventions, and it is moderately effective under the usual delivery conditions.
- *Drug-free residential treatment.* This form of treatment has a relatively low rate of treatment uptake and is costly because

of its residential character and the need for intensive staff-patient interaction. It is effective for the minority of people who are retained in treatment long enough to benefit from it (usually three months). Retention in treatment may be improved if patients enter treatment under some form of legal coercion.

- *Naltrexone maintenance treatment.* This form of treatment has not been rigorously evaluated.
- *Injectable opioid maintenance.* This intervention is a more expensive variant of agonist maintenance treatment that has been used for patients with more severe cases of dependency but for whom retention and treatment outcomes have been good.

Calculation of the Averted, Avertable, and Unavertable Burden

Assuming that the disease burden from opioid dependence is potentially avertable, we used the following approach to estimate the avoidable burden of opioid dependence. We initially modeled the avertable burden using MMT and used this model for BMT. The first step was to establish the base case for opioid dependence using 2002 as the baseline year. We established the model of the base case for opioid dependence for regions and subregions according to WHO country classifications. We used population estimates for each region for those age 15 to 59, the age range in which heroin dependence is most prevalent. We incorporated Degenhardt, Hall, and others' (2004, table 13.1) figures for the prevalence of opioid use by region, assuming that the prevalence was 30 percent higher among male users than female users.

We obtained population-attributable fractions related to opioid dependence from the editors of this volume. We used nine relevant WHO categories to estimate the burden of disease attributable to opioid dependence—namely HIV/AIDS, drug-use disorders, road traffic accidents, poisonings, falls, fires, drownings, other unintentional injuries, and self-inflicted injuries.

We calculated the mortality rate for opioid deaths by dividing the number of deaths by the estimated number of users. We took estimates of years of life lost (YLLs) and years lived with disability (YLDs), by gender, for each region from data obtained from the editors of this volume. We then used those estimates to calculate the DALYs for male users, female users, and all users (YLL + YLD = DALY). We discounted the YLLs, YLDs, and DALYs using a 3 percent discount rate.

The second step was to estimate the avertable burden by treatment with methadone or buprenorphine. Using the population and prevalence data, we assumed, in the first instance, that 50 percent of those dependent on opioids entered treatment. In the sensitivity analysis, we varied this proportion from 25 to 75 percent coverage. On the basis of Caplehorn and others' (1994) meta-analysis, we assumed that MMT reduced mortality by 25 percent. In the sensitivity analysis, we varied the reduction from 15 to 35 percent (using the confidence intervals around the estimated reduction). We assumed that the reduction in mortality associated with BMT was 20 percent, which we varied in the sensitivity analysis from 10 to 30 percent. Finally, we assumed that those who were alive and in treatment experienced a 25 percent reduction in disability, consistent with the Dutch disability weights.

The third step was to estimate the burden for those not treated. For those users not in treatment, we calculated DALYs using the original mortality rates.

The fourth step was to estimate the total avertable burden from treatment with methadone or buprenorphine by (a) adding the results of the second and third steps, the revised DALYs for those in treatment, and the residual for those not in treatment and (b) subtracting those figures from the base case estimates.

The fifth step was to cost the interventions using data on MMT and BMT from Doran and others (2003). They estimated the cost of MMT at $A 1,415 and of BMT at $A 1,729 for six months of treatment. We converted these estimates into U.S. dollars and multiplied them by two to provide yearly estimates of treatment costs of US$1,732 for MMT and US$2,117 for BMT.

We applied relative price weights for each region using the Western Pacific as the reference case (1.00). We calculated the relative price weights for each cost type using data provided by the World Bank. The prices are a reflection of the public health systems in each region, and as far as possible they reflect the opportunity cost of health care resources in these regions.

Results. Our results are presented in table 48.1. We explored various combinations of coverage and reductions in mortality for MMT and BMT. For each intervention, as coverage and reductions in mortality increased, the number of DALYs averted increased. The wide discrepancies in DALYs averted within regions primarily reflect differences in population-attributable fractions for HIV/AIDS. Costs increased as a consequence of increased coverage for both interventions, whereas results for cost-effectiveness differ by both intervention and mortality.

The cost-effectiveness analysis suggests that for MMT (with a coverage of 25, 50, or 75 percent and reductions in mortality of 35 percent) the cost in international dollars per DALY averted ranges from a low of $128 in Africa, with high child and adult mortality where the prevalence of illicit opioid dependence is low (0.01 percent), to a high of $3,726 in Eastern Europe, with low child and adult mortality where the prevalence of illicit opioid dependence is high (0.55 percent). Across all the regions, the average cost-effectiveness ratio for MMT (with 25, 50, and 75 percent coverage and 35 percent reduction in mortality) is estimated at $2,236 per DALY averted.

Assessment. The results shown in table 48.1 provide a first approximation of the potential avertable burden in DALYs if

Table 48.1 Cost-Effectiveness Results

			Total effect (DALYs averted per 1 million population)													
			Africa		The Americas			Eastern Mediterranean		Europe			Southeast Asia		Western Pacific	
Treatment	Coverage (%)	Mortality (%)	AFR-D	AFR-E	AMR-A	AMR-B	AMR-D	EMR-A	EMR-D	EUR-A	EUR-B	EUR-C	SEAR-B	SEAR-D	WPR-A	WPR-B
MMT	25	15	125	79	153	107	158	179	105	117	48	198	63	48	39	26
MMT	50	15	251	158	306	214	316	358	210	234	96	397	126	97	77	53
MMT	75	15	376	237	459	321	474	538	315	352	144	595	190	145	116	79
MMT	25	25	150	81	184	121	173	217	151	141	59	264	93	70	51	35
MMT	50	25	300	163	369	243	347	435	303	283	117	527	185	140	102	70
MMT	75	25	450	244	553	364	520	652	454	424	176	791	278	211	152	105
MMT	25	35	174	84	216	136	189	256	198	165	69	329	122	92	63	43
MMT	50	35	349	167	432	272	378	511	396	331	139	657	244	184	126	87
MMT	75	35	523	251	648	408	566	767	594	496	208	986	367	276	189	130
BMT	25	10	113	78	137	100	150	160	82	105	43	166	48	38	32	22
BMT	50	10	226	156	274	199	301	320	163	210	85	331	97	75	65	44
BMT	75	10	339	234	412	299	451	480	245	315	128	497	145	113	97	67
BMT	25	20	138	80	169	114	166	198	128	129	53	231	78	59	45	31
BMT	50	20	275	160	337	228	332	397	256	258	107	462	156	119	89	61
BMT	75	20	413	240	506	342	497	595	384	388	160	693	234	178	134	92
BMT	25	30	162	82	200	129	181	237	175	153	64	296	107	81	57	39
BMT	50	30	324	165	400	258	362	473	350	307	128	592	215	162	114	78
BMT	75	30	487	247	601	386	543	710	524	460	192	888	322	243	171	117
Total costs (US$ per 1 million population)																
MMT	25	15, 25, 35	0.10	0.01	0.25	0.06	0.12	0.95	0.65	0.20	0.16	0.35	0.06	0.19	0.07	0.03
MMT	50	15, 25, 35	0.19	0.02	0.50	0.11	0.24	1.90	1.30	0.40	0.32	0.71	0.11	0.39	0.13	0.07
MMT	75	15, 25, 35	0.29	0.03	0.74	0.17	0.36	2.86	1.95	0.60	0.49	1.06	0.17	0.58	0.20	0.10
BMT	25	10, 20, 30	0.12	0.01	0.30	0.07	0.15	1.16	0.80	0.24	0.20	0.43	0.07	0.24	0.08	0.04
BMT	50	10, 20, 30	0.24	0.03	0.60	0.14	0.29	2.33	1.59	0.49	0.40	0.86	0.14	0.47	0.16	0.08
BMT	75	10, 20, 30	0.35	0.04	0.91	0.20	0.44	3.49	2.39	0.73	0.59	1.29	0.20	0.71	0.24	0.12
Cost-effectiveness (US$ per DALY averted)																
MMT	25, 50, 75	15	768	136	1,618	520	755	5,315	6,213	1,711	3,379	1,782	875	3,984	1,716	1,284
MMT	25, 50, 75	25	643	132	1,342	458	688	4,381	4,300	1,419	2,764	1,341	597	2,749	1,301	974
MMT	25, 50, 75	35	552	128	1,146	408	632	3,726	3,288	1,212	2,339	1,074	453	2,099	1,048	784
BMT	25, 50, 75	10	1,041	168	2,204	682	969	7,269	9,764	2,329	4,646	2,606	1,396	6,277	2,493	1,867
BMT	25, 50, 75	20	855	164	1,793	595	880	5,869	6,210	1,895	3,716	1,869	867	3,975	1,809	1,354
BMT	25, 50, 75	30	726	159	1,510	527	805	4,921	4,553	1,598	3,096	1,458	629	2,909	1,419	1,062
DALYs averted per US$1 million spent																
MMT	25, 50, 75	15	1,302	7,363	618	1,922	1,325	188	161	585	296	561	1,142	251	583	779
MMT	25, 50, 75	25	1,556	7,575	745	2,185	1,453	228	233	705	362	746	1,676	364	768	1,027
MMT	25, 50, 75	35	1,811	7,787	873	2,448	1,582	268	304	825	428	931	2,210	476	954	1,275
BMT	25, 50, 75	10	961	5,939	454	1,465	1,032	138	102	429	215	384	717	159	401	536
BMT	25, 50, 75	15	1,170	6,112	558	1,681	1,137	170	161	528	269	535	1,153	252	553	739
BMT	25, 50, 75	20	1,378	6,286	662	1,896	1,242	203	220	626	323	686	1,590	344	705	942

MMT and BMT were applied to 50 percent of the opioid-dependent population in each region. Because the methods and data used to estimate avertable DALYs are subject to certain limitations, those results should be considered preliminary.

RELEVANCE TO DEVELOPING COUNTRIES

Much of the epidemiological research on illicit opioid dependence, its disease burden, and its societal harm comes from Australasia, Europe, and the United States. The major exception is research on the role of injecting drug use in HIV transmission in developing countries (see, for example, Beyrer and others 2000; Yu and others 1998). In addition, research on the effectiveness and cost-effectiveness of interventions for illicit opioid dependence has been conducted primarily in developed countries (Ward, Hall, and Mattick 1998), with the exception of studies of the effectiveness of methadone treatment in Hong Kong, China (see, for instance, Newman and Whitehill 1979), and in Thailand (Vanichseni and others 1991), both of which showed comparable effectiveness to that found in developed countries (W. Hall, Ward, and Mattick 1998).

Translating findings on interventions for opioid dependence in developed countries into disease control priorities for opioid dependence in developing countries presents three major challenges. First, countries differ in the scale of illicit opioid use and in the resulting disease burden. This variation reflects the effects of differences in the prevalence of injecting and noninjecting opioid users; the dependent opioid users' access to treatment and health services for overdoses, bloodborne viruses, and other complications of drug use; the access to needle and syringe programs; the extent to which illicit opioid use is concentrated in socially disadvantaged minority groups; and the capacity of public health services to monitor and respond to emerging infectious disease and drug-use epidemics. The burden is likely to be greatest in settings where the primary route of administration is injecting and where public and personal health services are poorly developed, as appears to be the case in Asia and in Eastern Europe.

Second, societal wealth and health care infrastructure affect the capacity of developing societies to treat illicit opioid dependence. A country's capacity to provide opioid substitution treatment will be affected by the cost of oral opioid drugs, such as methadone, LAAM, and buprenorphine, and the existence of specialist drug treatment centers; trained medical, nursing, and pharmacy staff; and a drug regulatory system, which are required so as to deliver opioid substitution treatment safely and effectively. Few developing countries possess this infrastructure. However, examples exist of apparently successful drug substitution programs, using such tools as sublingual buprenorphine, that have been conducted with minimal resources in extremely poor settings (Crofts and others 1998).

Third, in societies with a sizable illicit opioid dependence problem, cultural attitudes and beliefs will affect societal responses, especially attitudes toward illicit opioid use and dependence (Gerstein and Harwood 1990). A critical determinant of the social response will be the relative dominance of moral and medical understandings of drug dependence in general and opioid dependence in particular. A moral model of addiction sees addiction as largely a voluntary behavior, in which case it is seen as an excuse for bad behavior that allows drug users to continue to take drugs without assuming responsibility for their conduct (Szasz 1985). In this view, drug users who offend against the criminal code should be imprisoned (Szasz 1985). This model is the dominant one in many developed societies, which imprison drug users at high rates without any effect on the prevalence of drug abuse. Countries that adopt punitive policies toward drug users are reluctant to embrace harm reduction measures, such as needle and syringe programs and opioid maintenance treatment (Ainsworth, Beyrer, and Soucat 2003). A medical model of addiction, by contrast, recognizes that dependent opioid users require specific treatment if the sufferer is to become and remain abstinent (see, for example, Leshner 1997).

These competing views will affect the societal acceptability of opioid maintenance and abstinence-oriented approaches to the treatment of opioid dependence (Cohen 2003). Those who have a moral view of addiction will tend to prefer drug-free and self-help approaches toward treatment. Supporters of medical models of addiction will favor some form of opioid substitution treatment and the provision of clean needles and syringes to reduce the transmission of bloodborne viruses by injecting opioid and other drug users. Stronger advocacy by international organizations and agencies is needed for the adoption of such harm reduction measures as needle and syringe programs and agonist substitution programs.

RESEARCH AND DEVELOPMENT

Two main areas are important for research and development. First, better estimates are needed of the prevalence of illicit opioid dependence and prospective studies of the morbidity and mortality that it causes in both developed and developing countries. These estimates are especially needed in countries where illicit opioid use is high because of their proximity to source countries. Second, we need evaluations of the effectiveness and cost-effectiveness of self-help, drug-free, and oral opioid substitution treatment in developing countries. A priority should be the identification of safe, innovative, and less expensive ways of effectively delivering culturally acceptable forms of opioid maintenance treatments in developing countries. This effort may require experimentation with a range of substitute opioids, such as buprenorphine, and cheaper options, such as codeine and opium tincture.

CONCLUSIONS: PROMISES AND PITFALLS

Illicit opioid use, especially injecting use, contributes to premature mortality and morbidity in many developed and developing societies. Fatal overdoses and HIV/AIDS resulting from the sharing of dirty injecting equipment are major contributors to mortality and morbidity, and the economic costs of illicit opioid dependence are substantial. Illicit opioid dependence generates substantial externalities that are not included in burden-of-disease estimates, principally law enforcement costs incurred in handling drug dealing and property crime.

The most popular interventions for illicit opioid dependence in many developed societies have been law enforcement efforts to interdict the drug supply and enforce legal sanctions against the use of opioid drugs. One consequence of this strategy has been that most illicit opioid users have been exposed to the least effective intervention: imprisonment for drug or property offenses. Prisons rarely take the opportunity to treat dependence using opioid maintenance or to reduce the harm caused by illicit opioid use by providing access to clean injecting equipment.

In treatment settings, the most popular interventions have been detoxification (which is not a treatment but a prelude to treatment) and drug-free treatment (which is the least attractive and the least effective in retaining opioid-dependent people in treatment). Opioid agonist maintenance treatment has been ambivalently supported in many developed societies despite its being the treatment for which there is the best evidence of effectiveness, safety, and cost-effectiveness. The range of opioid agonists available for maintenance treatment is increasing. A number of developed countries have approved the use of BMT, which the limited data suggest may be approximately equivalent to MMT in efficacy and cost-effectiveness. Opioid antagonists have a niche role in the treatment of opioid dependence because of poor compliance and an increased risk of overdose on return to heroin use. Their efficacy may improve with the development of long-acting injectable forms of the drug.

ANNEX 48.A: PREVALENCE OF USE, ADVERSE HEALTH EFFECTS OF AND INTERVENTIONS FOR CANNABIS, COCAINE, AMPHETAMINES, AND MDMA USE AND DEPENDENCE

Cannabis

Cannabis is the most widely used illicit drug globally, with about 150 million users, or 3.7 percent of the world's population age 15 and older (UNODCCP 2003). Patterns of cannabis use have been most extensively studied in Australia, Canada, the United States, and Europe (W. Hall and Pacula 2003). Europe generally has lower rates of use than Australia, Canada, and the United States, with the highest rates in Denmark, France and the United Kingdom (EMCDDA 2002; W. Hall and Pacula 2003). The limited data from developing countries suggest that, with some exceptions (for example, Jamaica and South Africa), rates of cannabis use are lower in Africa, Asia, the Caribbean, and South America than they are in Europe and in English-speaking countries (W. Hall, Johnston, and Donnelly 1999).

Surveys in the United States have found long waves of cannabis use among young people since 1975. Cannabis use increased during the 1970s to peak in 1979, before declining steadily between 1980 and 1991. Use rose sharply in 1992 and increased throughout the 1990s, before leveling off in the late 1990s (Johnston, O'Malley, and Bachman 1994a, 1994b). There was also a rise in cannabis use during the early 1990s in Australia, Canada, and some European countries (W. Hall and Pacula 2003).

The natural history of cannabis use in the United States typically begins in the mid to late teens and reaches its maximum in the early 20s before declining in the mid to late 20s. Only a minority of young adults continue to use cannabis into their 30s (Bachman and others 1997; Chen and Kandel 1995). Getting married and having children substantially reduces rates of cannabis use (Bachman and others 1997).

Cannibis use can have several adverse health effects, as discussed below.

Acute Effects of Cannabis Use. The most frequent unpleasant effects of cannabis use are anxiety and panic reactions, which most often occur in users who are unfamiliar with the drug's effects. Psychotic symptoms such as delusions and hallucinations may be experienced following very high doses. There are no cases of fatal cannabis poisoning in the medical literature, and the fatal dose in humans is likely to exceed what recreational users are able to ingest (W. Hall and Pacula 2003).

Cannabis intoxication impairs a wide range of cognitive and behavioral functions that are involved in driving an automobile or operating machinery (Beardsley and Kelly 1999; Jaffe 1985). It has been difficult to determine whether these impairments increase the risk of being involved in motor vehicle accidents (Smiley 1999). Studies of the effect of cannabis on driving performance on the road have found only modest impairments, because cannabis-intoxicated drivers drive more slowly and take fewer risks than drivers intoxicated by alcohol (Smiley 1999).

Cannabinoids are found in the blood of substantial proportions of persons killed in motor vehicle accidents (Bates and Blakely 1999; Chesher 1995; Walsh and Mann 1999), but these findings have been difficult to evaluate because they have not distinguished between past and recent cannabis use (Ramaekers and others 2004). More recent research using better indicators of recent cannabis use has found a dose-response

relationship between cannabis and risk of motor vehicle crashes (Ramaekers and others 2004). Cannabis used in combination with alcohol substantially increases risk of accidents (Bates and Blakely 1999; Ramaekers and others 2004).

Health Effects of Chronic Cannabis Use. Cannabis smoke is a potential cause of cancer because it contains many of the same carcinogenic substances as cigarette smoke (Marselos and Karamanakos 1999). Cancers have been reported in the aerodigestive tracts of young adults who were daily cannabis smokers (W. Hall and MacPhee 2002), and a case-control study has found an association between cannabis smoking and head and neck cancer (Zhang and others 1999). A prospective cohort study of 64,000 adults did not find any increase in rates of head and neck or respiratory cancers (Sidney and others 1997). Further studies are needed to clarify the issue.

Three studies of different types of cancer have reported an association with maternal cannabis use during pregnancy (W. Hall and MacPhee 2002). There have not been any increases in the rates of these cancers that parallel increases in rates of cannabis use (W. Hall and MacPhee 2002).

High doses of cannabinoids impair cell-mediated and humoral immunity and reduce resistance to infection by bacteria and viruses in rodents (Klein 1999). Cannabis smoke impairs the functioning of alveolar macrophages, the first line of the body's immune defense system in the lungs. The doses that produce these effects have been very high, and extrapolation to the doses used by humans is complicated by the fact that tolerance to these effects develops (Hollister 1992). There is as yet no epidemiological evidence that rates of infectious disease are higher among chronic heavy cannabis users. Several large prospective studies of HIV-positive homosexual men have not found that cannabis use makes it more likely that HIV-positive men develop AIDS (W. Hall and Pacula 2003).

Chronic administration of tetrahydrocannabinol (THC) disrupts male and female reproductive systems in animals, reducing testosterone secretion and sperm production, motility, and viability in males and disrupting ovulation in females (Brown and Dobs 2002). It is uncertain whether cannabis use has these effects in humans because of the limited research on human males and females (Murphy 1999).

The use of cannabis during pregnancy is associated with smaller birthweight (English and others 1997; Fergusson, Horwood, and Northstone 2002), but it does not appear to increase the risk of birth defects (W. Hall and Pacula 2003). In some studies, infants exposed to cannabis during pregnancy show behavioral and developmental effects during the first few months after birth; these effects are smaller than those seen after tobacco use during pregnancy (Fried and Smith 2001).

The changes that cannabis smoking causes in heart rate and blood pressure are unlikely to harm healthy young adults, but they may harm patients with hypertension, cerebrovascular disease, and coronary atherosclerosis (Chesher and Hall 1999; Sidney 2002). One controlled study suggests that cannabis use can precipitate heart attacks in middle-aged cannabis users who have atherosclerosis in the heart, brain, and peripheral blood vessels (Mittleman and others 2001).

Regular cannabis smoking impairs the functioning of the large airways and causes chronic bronchitis (Tashkin 1999; Taylor and others 2002). Given that tobacco and cannabis smoke contain similar carcinogenic substances, it is likely that chronic cannabis smoking increases the risks of respiratory cancer (Tashkin 1999).

Psychological Effects of Chronic Cannabis Use. Psychological effects of chronic cannabis use can include a dependence syndrome, cognitive effects, and psychotic disorders.

Dependence Syndrome A cannabis dependence syndrome occurs in heavy chronic users of cannabis (American Psychiatric Association 1994). Regular cannabis users develop tolerance to THC. Some experience withdrawal symptoms on cessation of use (Kouri and Pope 2000), and some report problems controlling their cannabis use (W. Hall and Pacula 2003). The risk of dependence is about 1 in 10 among those who ever use the drug, between 1 in 5 and 1 in 3 among those who use cannabis more than a few times, and about 1 in 2 among daily users (W. Hall and Pacula 2003).

Cognitive Effects Long-term daily cannabis use does not severely impair cognitive function, but it may more subtly impair memory, attention, and the ability to integrate complex information (Solowij 1998; Solowij and others 2002). It remains uncertain whether these effects are due to the cumulative effect of regular cannabis use on cannabinoid receptors in the brain or whether they are residual effects of THC that will disappear after an extended period of abstinence (W. Hall and Pacula 2003).

Psychotic Disorders There is now good evidence that chronic cannabis use may precipitate psychosis in vulnerable individuals (see, for example, Arseneault and others 2002; van Os and others 2002; Zammit and others 2002). It is less likely that cannabis use can cause psychosis de novo, because the incidence of schizophrenia has either remained stable or declined while cannabis use has increased among young adults (Degenhardt, Hall, and Lynskey 2003).

Effects of Cannabis Use on Adolescents. Cannabis use has a number of effects on adolescents.

Gateway Hypothesis Adolescents in developed societies typically use alcohol and tobacco before using cannabis, which in turn, they use before using hallucinogens, amphetamines, heroin, and cocaine (Kandel 2002). Generally, the earlier the age of first use and the greater the involvement with any drug

in the sequence, the more likely a young person is to use the next drug in the sequence (Kandel 2002). The role played by cannabis in this sequence remains controversial (W. Hall and Lynskey forthcoming; W. Hall and Pacula 2003).

The simplest hypothesis is that cannabis use has a pharmacological effect that increases the risk of using drugs later in the sequence. Equally plausible hypotheses are that it is due to a combination of (a) early recruitment into cannabis use of nonconforming and deviant adolescents who are likely to use alcohol, tobacco, and illicit drugs; (b) a shared genetic vulnerability to dependence on alcohol, tobacco, and cannabis; and (c) socialization of cannabis users within an illicit drug–using subculture, which increases the opportunity, and encouragement to use other illicit drugs (W. Hall and Pacula 2003).

Adolescent Psychosocial Outcomes Cannabis use is associated with early withdrawal from high school, early family formation, poor mental health, and involvement in drug-related crime. In the case of each of these outcomes, the strong associations in cross-sectional data are more modest when account is taken of the fact that cannabis users show characteristics before they use cannabis that predict these outcomes. For example, they have lower academic aspirations and poorer school performance than peers who do not use cannabis (Lynskey and Hall 2000; Macleod and others 2004). Nonetheless, the evidence increasingly suggests that regular cannabis use adds to the risk of these outcomes in adolescents already at risk (W. Hall and Pacula 2003).

Interventions for Cannabis Dependence. Although many dependent cannabis users may succeed in quitting without professional help, some are unable to stop on their own and will need assistance to do so. There has not been a great deal of research on pharmacological treatments for cannabis dependence, although a recent study trialed divalproex sodium with promising results (Levin and others 2004). Limited research exists on the effectiveness of different types of psychosocial treatments for dependent cannabis use (Budney and others 2000; Copeland and others 2001; Stephens, Roffman, and Simpson 1994). These approaches have involved short-term cognitive behavioral treatments modeled on similar treatments for alcohol dependence, usually given in three to six sessions on an outpatient basis.

In all of these studies, rates of abstinence at the end of treatment have been modest (20 to 40 percent), and subsequent high rates of relapse mean that rates of abstinence after 12 months have been very modest (Budney and Moore 2002). Nonetheless, treatment does substantially reduce cannabis use and problems. These outcomes are not very different from those observed in the treatment for alcohol and other forms of drug dependence (Budney and Moore 2002). Much more research is needed before sensible advice can be given about the best ways to achieve abstinence from cannabis.

Cocaine

After cannabis, cocaine is one of the most widely used illicit drugs in developed and developing societies. Some 14 million people were estimated to have used cocaine globally in 2003, with demand for treatment second only to heroin (UNODCCP 2003). The highest rates of reported cocaine use—and the best data on trends in cocaine use—come from the United States, the world's largest cocaine market. Rates of cocaine use in the United States increased from the mid 1970s until 1985, when 5.7 million Americans age 12 and older reported using cocaine in the preceding month. Rates of cocaine use in the preceding month have declined steadily since 1985. In 2000, 11.2 percent of Americans over age 12 reported that they had used cocaine at some time in their lives, and 0.4 percent (800,000 people) reported weekly cocaine use (SAMHSA 2001). Among young U.S. adults age 18 to 25, lifetime prevalence was 14.9 percent in 2001, rising slightly to 15.4 percent in 2002 (SAMHSA 2003). In 2002, annual prevalence figures from student surveys were 15 percent lower than 1998 figures and 60 percent lower than 1985 figures (UNODCCP 2003). A more recent study of U.S. adults age 35 years found that 6 percent of men and 3 percent of women had used cocaine within the preceding 12 months (Merline and others 2004).

The reported prevalence of cocaine use in other developed societies is much lower than that in the United States. In Europe, for example, rates of lifetime cocaine use range from 0.5 percent to 5 percent (EMCDDA 2003), compared with 12.3 percent among American adults in 2001 (SAMHSA 2001). Rates of cocaine use in Australia resemble those in Europe, with 4.3 percent of adults reporting lifetime use (Darke and others 2000).

The prevalence of cocaine use is likely to be lower in developing societies, but the poor quality of the available data makes it difficult to be sure (UNDCP 1997). There probably has been an increase in cocaine use in some developing countries in recent years, but it is difficult to estimate the size of the increase (United Nations Commission on Narcotic Drugs 2000). The region with the highest rates of cocaine use among developing societies is likely to be Central and South America. The botanical source is indigenous to the region and has traditionally been used by local populations. Moreover, several nations in Central and South America have a history of production and export to global markets. Recent reports indicate that cocaine abuse is increasing in South America (UNODCCP 2003), and a recent household survey on drug abuse in São Paulo, Brazil, estimated cocaine prevalence at 2.1 percent (Galduroz and others 2003).

Adverse Health Effects of Cocaine. Most cocaine use is infrequent; regular cocaine use (monthly or more frequently) can be a major public health problem. Regular cocaine users who

inject cocaine or smoke crack cocaine are especially likely to develop dependence and to experience problems related to their cocaine use (Platt 1997). In the United States, it has been estimated that one in six of those who ever use cocaine become dependent on the drug (Anthony, Warner, and Kessler 1994). High rates of cocaine dependence are found among people treated for alcohol and drug problems and among arrestees in the United States (Anglin and Perrochet 1998).

In large doses, cocaine may be harmful in both cocaine-naive and cocaine-tolerant individuals (Platt 1997; Vasica and Tennant 2002). The vasoconstrictor effects of cocaine in large doses place great strains on a number of the body's physiological systems (McCann and Ricaurte 2000). Effects on the cardiovascular system can result in a range of difficulties, from chest pain to fatal cardiac arrests (Lange and Hillis 2001). Neurological problems include cerebral vascular accidents such as strokes or seizures. Other effects of cocaine can include gastrointestinal problems such as vomiting, colitis, and bowel infarction and respiratory problems such as asthma, respiratory collapse, pulmonary edema, and bronchitis. Hyperthermia may occur because of the increased metabolism, peripheral vasoconstriction, and inability of the thalamus to control body temperature (Crandall, Vongpatanasin, and Victor 2002). Obstetric complications can include irregularities in placental blood flow, premature labor, and low neonate birthweight (Majewska 1996; Platt 1997; Vasica and Tennant 2002).

Adverse health effects from cocaine are potentially fatal and can occur among healthy users irrespective of cocaine dose and frequency of use (Lange and Hillis 2001; Vasica and Tennant 2002). Although the likelihood of health problems may increase with dosage and frequency of use, there is wide individual variation in reactions to cocaine and, therefore, no specific combination of conditions under which adverse health effects can be predicted. There is no antidote to cocaine overdose as there is for an overdose of heroin (Platt 1997).

The impact of cocaine on mental health is also complex. Although cocaine can produce feelings of pleasure, it may also result in negative psychological symptoms such as anxiety, depression, paranoia, hallucinations, and agitation (American Psychiatric Association 1994). Regular cocaine users experience high rates of psychiatric disorders. In the United States, regular cocaine users report high rates of anxiety and affective disorders (Gawin and Ellinwood 1988; Platt 1997). The repeated use of large doses of cocaine can also produce a paranoid psychosis (Majewska 1996; Manschreck and others 1988; Platt 1997; Satel and Edell 1991). People who are acutely intoxicated by cocaine can become violent, especially those who develop a paranoid psychosis (Platt 1997).

Animal studies suggest that cocaine use may be neurotoxic in large doses—that is, it can produce permanent changes in the brain and neurotransmitter systems (Majewska 1996; Platt 1997). It is unclear whether use is also neurotoxic in humans. Previous studies have documented a variety of neuropsychological effects of cocaine use, including deficits in memory and problem solving (Beatty and others 1995; Hoff and others 1996; O'Malley and others 1992). More recently, a twin study indicated that cocaine may lead to impaired attention and motor skills up to one year after the conclusion of heavy use (Toomey and others 2003).

The method by which cocaine is administered can result in adverse health effects (Platt 1997). Snorting cocaine through the nose can lead to rhinitis, damage to the nasal septum, and loss of the sense of smell. Smoking cocaine can lead to respiratory problems, and injecting cocaine leads to the risks of infections and bloodborne viruses associated with all injecting drug use.

Users who inject cocaine, either on its own or in combination with heroin ("speedballs"), inject much more frequently than other injecting drug users and, as a consequence, engage in more needle sharing, take more sexual risks, and have higher rates of HIV infection (Chaisson and others 1989; Schoenbaum and others 1989; van Beek, Dwyer, and Malcolm 2001). Associations between cocaine use and HIV risk-taking have been reported in Europe (Torrens and others 1991), Australia (Darke and others 1992), and the United States (Chaisson and others 1989). Recent Australian research has indicated that injecting cocaine users report more problems related to injecting drug use—such as vascular problems, abscesses, and infections—than other injecting drug users (Darke, Kaye, and Topp 2002).

The link between cocaine use and HIV risk is not restricted to those who inject cocaine. Crack smoking has been linked to higher levels of needle risk, sexual risk taking, and HIV infection (Chaisson and others 1989; Chirgwin and others 1991; Desjalais and others 1992; Grella, Anglin, and Wugalter 1995). Two mechanisms probably underlie the relationship between cocaine use and HIV infection. First, the short half-life of cocaine promotes a much higher frequency of injecting by users than that seen in heroin injectors. Second, cocaine itself disinhibits and stimulates users, encouraging them to take greater risks with sexual activity and needle use (Darke and others 2000).

Cocaine is associated with a risk of intentional injuries and injuries in general. A recent review reported that 28.7 percent of people with intentional injuries and 4.5 percent of injured drivers tested positive for cocaine (Macdonald and others 2003). Users are also at risk of death from an accidental overdose of cocaine. A recent study of accidental deaths from drug overdose in New York between 1990 and 1998 found that 70 percent of deaths were caused by cocaine, often in combination with opiates (Coffin and others 2003). The causes of cocaine-related deaths are usually related to cardiovascular complications (Vasica and Tennant 2002), but death may also be due to brain hemorrhage, stroke, and kidney failure (Brands, Sproule, and

Marshman 1998). Injection of cocaine is most likely to cause an overdose, followed by smoking it, with intranasal use involving the least risk (Pottieger and others 1992).

Much less is known about nonfatal cocaine overdose. A study in Miami, Florida, found that 40 percent of users had overdosed on cocaine at least once (Pottieger and others 1992). More recently, a study in Brazil found that 20 percent of users had experienced an overdose, with 50 percent knowing someone who had died from an overdose (Mesquita and others 2001). A study in Sydney, Australia, found that 17 percent of injecting cocaine users and 6 percent of noninjecting cocaine users had ever overdosed, with 9 percent and 3 percent, respectively, overdosing in the preceding 12 months (Kaye and Darke 2003). Frequency of cocaine use, severity of dependence, and route of administration did not predict an overdose, supporting the view that cocaine overdose is an unpredictable event.

Interventions for Cocaine Dependence. Efforts at intervention have included pharmacological treatments as well as psychotherapy and cognitive behavioral therapy.

Pharmacological Interventions Despite much research effort there are no effective pharmacological treatments for cocaine dependence (Kreek 1997; McCance 1997; Mendelson and Mellon 1996; Nunes 1997; Silva de Lima and others 2002; van den Brink and van Ree 2003). Attempts have been made to develop longer-acting agonist drugs that act on the same molecular targets as cocaine without producing its euphoric effects (for example, methylphenidate) (Kreek 1997) or that block its rewarding and euphoric effects (McCance 1997). There has also been a search for drugs that indirectly change the effects that cocaine has on the brain by acting on other neurotransmitter systems, such as the serotonergic system (for example, fluoxetine) (McCance 1997). None of these approaches has produced an effective pharmacotherapy for cocaine dependence (Lima and others 2003; Platt 1997; Soares and others 2003).

Development of pharmacological therapies for cocaine dependence and their evaluation is complicated by the multiple interactive processes that may have contributed—for example, coexisting substance abuse or mental health issues (Mendelson and Mellon 1996). Many of the approaches to the treatment of cocaine dependence have also been used in treating patients with alcoholism and other substance abuse disorders.

A number of drugs have been used to treat cocaine based on their relevance to the symptoms of cocaine dependence (Silva de Lima and others 2002; van den Brink and van Ree 2003). The frequency of depressive symptoms has led to the exploration of the effectiveness of antidepressant drugs. Desipramine has been used with mixed effectiveness for cocaine detoxification and the maintenance of abstinence (Covi and others 1994; Gawin, Kleber, and Byck 1989), but it appears to be most effective when there is evidence of previous or consequent symptoms of depression. Other antidepressants have been used with mixed results: imipramine and trazodone have been found to have more adverse effects than desipramine, and fluoxetine has not been found to be effective (Mendelson and Mellon 1996). A recent systematic review found no current evidence to support the use of antidepressants in the treatment of cocaine dependence (Lima and others 2003).

Dopamimetic drugs have also been used to treat cocaine dependence; such treatments are based on the action of cocaine to block reuptake of dopamine. Unfortunately, although some of these drugs are relatively effective, they also result in quite severe adverse effects (Mendelson and Mellon 1996). Current evidence does not support the clinical use of dopamine agonists for cocaine dependence (Soares and others 2003). Opioid antagonists (for example, naltrexone) or opioid mixed agonist-antagonists (such as buprenorphine) have been explored, on the basis that cocaine dependence may be accompanied by dependence on opiates. Although there have been problems with compliance with naltrexone therapy (National Research Council Committee on Clinical Evaluation of Narcotic Antagonists 1978), buprenorphine has shown promising preclinical and clinical trial results (Kosten, Kleber, and Morgan 1989). Other promising directions include cannabinoid receptor antagonists and cortisol synthesis inhibitors (van den Brink and van Ree 2003) and vaccination against the effects of cocaine (Kantak 2003), but there is as yet no evidence on the effectiveness of any of these interventions.

Acupuncture has also been used to treat cocaine dependence. Auricular acupuncture is frequently used, but the small number of trials that have been conducted have not provided sufficient evidence of effectiveness (van den Brink and van Ree 2003).

Psychotherapy and Cognitive Behavioral Therapy The lack of evidence for pharmacological therapy means that treatment for cocaine dependence currently relies on cognitive behavior therapies combined with contingency management strategies. Unfortunately, psychosocial treatments for cocaine dependence are also of limited effectiveness. Treatments such as therapeutic communities, cognitive behavioral treatments, contingency management, and 12 step–based self-help approaches benefit cocaine-dependent people by reducing their rates of cocaine use and improving their health and well-being, but rates of relapse to cocaine use after treatment remain high (Platt 1997).

Mendelson and Mellon (1996) conclude that there are no specific cognitive or behavioral interventions that are uniquely effective in treating cocaine dependence. However, some success has been demonstrated with incentive-based programs in which rewards are provided for urine samples that are free of cocaine, although there is doubt about whether results are sustained (Roozen and others 2004). Such programs are generally more

effective when the patient's family and friends are involved (Higgins and others 1994). Petry and others (2004) suggested that contingency management was effective in reducing cocaine use in a community-based treatment setting. They found that the benefits of treatment depended on the magnitude of reward, with those earning up to US$240 obtaining better results than those earning up to US$80. They suggested that this form of intervention may work best for people with more severe dependence on cocaine.

A multicenter investigation examining the efficacy of four psychosocial treatments for cocaine-dependent patients concluded that individual drug counseling in combination with group drug counseling showed the most promise for effective treatment of cocaine dependence over two forms of traditional psychotherapy (Crits-Christoph and others 1999). Community reinforcement involving an intensive, biopsychosocial, multifaceted approach to lifestyle change has shown positive effects over four to six weeks and has the advantage of being tailored to individual goals (Roozen and others 2004).

The few studies of the long-term effects of treatment have not shown particularly encouraging results. A one-year follow-up of the U.S. Drug Abuse Treatment Outcome Studies reported that reductions in the use of cocaine in the year following treatment were associated with longer duration of treatment, particularly six months or more in long-term residential or outpatient treatments (Hubbard, Craddock, and Anderson 2003). A five-year national follow-up study of 45 U.S. treatment programs found that only 33 percent of the sample had highly favorable outcomes (Flynn and others 2003).

Amphetamines

According to WHO, amphetamines and methamphetamines are the most widely abused illicit drugs after cannabis, with an estimated 35 million users worldwide (Rawson, Anglin, and Ling 2002).

In Australia, the lifetime prevalence of amphetamine use is between 6 and 8 percent in the general population, making amphetamines the most commonly used illicit drug after cannabis during that period (Makkai and McAllister 1998). In 1998, the lifetime prevalence of amphetamine use was highest (25 percent) among male users age 20 to 29.

The use of amphetamines is generally less frequent than that of opioids (Darke and Hall 1995; Darke, Kaye, and Ross 1999; W. Hall, Bell, and Carless 1993; Hando, Topp, and Hall 1997; Vincent and others 1998). This pattern is no doubt due to the physical and psychological toll taken by regular amphetamine use. Although such use is less frequent overall, however, there is widespread bingeing on amphetamines, with frequent use over several consecutive days, which may be followed by benzodiazepine use to "come down." Polydrug use is particularly common among amphetamine users, who show a marked preference for stimulant drugs such as hallucinogens and cocaine (Darke and Hall 1995; Hando and Hall 1994; Vincent and others 1998).

Globally, Europe is the main center of amphetamine production, particularly Belgium, the Netherlands, and Poland, with production increasing in Eastern Europe (UNODCCP 2003). Half of all Western European countries reported an increase in amphetamine abuse in 2000, but in 2001 the figure fell to 33 percent (UNODCCP 2003). Lifetime use of amphetamines is reported to be between 0.5 percent and 6 percent among European Union countries, with the exception of the United Kingdom, where the figure is 11 percent. Denmark and Norway also have relatively higher rates of use (EMCDDA 2003).

Adverse Health Effects of Amphetamine Use. Amphetamine users who inject the drug are at high risk of bloodborne infections through needle sharing. Amphetamine users are as likely as opioid users to share injection equipment (Darke, Ross, Cohen, and others 1995; Darke, Ross, and Hall 1995; W. Hall, Bell, and Carless 1993; Hando and Hall 1994; Kaye and Darke 2000; Loxley and Marsh 1991). In addition, the youth of amphetamine users places them at risk of sexual transmission of diseases such as HIV and hepatitis B virus (although not hepatitis C). Primary amphetamine users have been demonstrated to be a sexually active group, and small proportions engage in paid sex to support their drug use (Darke, Ross, Cohen, and others 1995; Hando and Hall 1994). Among gay and bisexual men, amphetamines may be used to enhance sexual encounters, which may lead to unprotected anal intercourse and increased risk of HIV infection (Urbina and Jones 2004).

High-dose amphetamine use, especially by injection, can result in a schizophreniform paranoid psychosis, associated with loosening of associations, delusions, and hallucinations (Gawin and Ellinwood 1988; Jaffe 1985). The psychosis could be reproduced by the injection of large doses in addicts (Bell 1973) and by the repeated administration of large doses to normal volunteers (Angrist and others 1974).

High proportions of regular amphetamine injectors describe symptoms of anxiety, panic attacks, paranoia, and depression. The emergence of such symptoms is associated with injecting the drugs, greater frequency of use, and dependence on amphetamines (W. Hall and others 1996; McKetin and Mattick 1997, 1998). Recent evidence also suggests that women may experience more emotional effects of amphetamine intoxication than men and higher rates of anorexia nervosa than women without amphetamine disorders (Holdcraft and Iacono 2004).

In sufficiently high doses, amphetamines can be lethal (Derlet and others 1989). However, the risk is low compared with the high risks of overdose associated with central nervous system depressants such as heroin. Typically, amphetamine-related deaths are associated with the effects of amphetamines on the cardiovascular system—for example, cardiac failure and cerebral vascular accidents (Mattick and Darke 1995).

There is evidence that amphetamines are neurotoxic (Robinson and Becker 1986). Evidence from animal studies indicates that heavy amphetamine use results in dopaminergic depletion (Ellison 1992; Fields and others 1991). The few studies of the neuropsychological effects of amphetamine abuse report findings similar to those found with cocaine abuse. Deficits in memory and attention have been attributed to amphetamine use (McKetin and Mattick 1997, 1998). More recently, a twin study indicated that amphetamine abuse might lead to impaired attention and motor skills up to one year after the conclusion of heavy use (Toomey and others 2003).

Interventions for Amphetamine Dependence. Treatment for methamphetamine abuse has been a relatively recent development and has generally been based on previous treatments for cocaine abuse (Huber and others 1997). Cretzmeyer and others (2003) reviewed treatments for methamphetamine abuse, noting that there has been little research on the effectiveness of drug treatment, probably because many amphetamine users use multiple drugs. The combination of methamphetamine use with use of marijuana or other sedating drugs indicates that effective treatments need to address the use of multiple drugs. A Cochrane Review concluded that evidence for success in treatment of amphetamine dependence is very limited, with no pharmacological treatment demonstrated to be effective (Srisurapanont, Jarusuraisin, and Kittirattanapaiboon 2003).

An early study explored the use of aversion therapy in a multimodal treatment program using educational groups, individual counseling, occasional family counseling, and aftercare planning. The intervention paired an aversive stimulus (either chemical or electrical) with the act of using methamphetamines. Cocaine use was also treated in this way. After 12 months, 53 percent of patients were abstinent and the researchers noted that their results were promising, despite a number of limitations to the study (Frawley and Smith 1992).

An intervention combining imipramine, a tricyclic antidepressant, with intensive group counseling has been evaluated with cocaine and methamphetamine abusers. Patients received either a low or higher dose (as needed) of imipramine, as well as intensive group counseling and access to medical and psychiatric care. Those who received the higher dose stayed in treatment longer, but the results did not support the use of imipramine for methamphetamine abuse (Galloway and others 1994).

The Matrix Program for methamphetamine and cocaine abusers has also been evaluated. The Matrix Program uses a cognitive behavioral approach with an emphasis on relapse prevention (Huber and others 1997). The study evaluated the effectiveness of three conditions: Matrix treatment alone, Matrix treatment plus desipramine, and Matrix treatment plus placebo (Shoptaw and others 1994). The researchers concluded that those who received more Matrix treatment had better abstinence rates than those who had less treatment but that desipramine had no effect on treatment outcome.

J. Hall and others (1999) conducted an evaluation of the effectiveness of the Iowa Case Management Project. The project was designed to supplement interventions provided by a drug abuse treatment agency and is a comprehensive social work intervention, including outreach activities and provision of limited emergency funds. The results of the evaluation showed that comprehensive case management was effective in improving employment status among amphetamine users subsequent to treatment. There was an almost significant lower incidence of depression among those who received the program compared with controls. Drug use decreased significantly for clients in both control and program conditions.

More recently, an Australian study evaluated the effectiveness of brief cognitive-behavioral interventions among regular users of amphetamines (Baker, Boggs, and Lewin 2001). The researchers found a clinically significant reduction in daily amphetamine use among the intervention groups compared with controls and concluded that further studies of brief cognitive-behavioral interventions are feasible and warranted. Although some promising interventions have been identified to assist methamphetamine abusers, no single treatment option has yet been established as better than any other in a randomized controlled trial (Cretzmeyer and others 2003).

Methylenedioxymethamphetamine

Methylenedioxymethamphetamine is more widely known as *ecstasy* or *MDMA*. In Australia, the lifetime prevalence of MDMA use increased from 1 percent of the population in 1988 to 4.6 percent (about one in 20 persons) in 1998, with 2.3 percent reporting MDMA use in the preceding 12 months (Topp and others 1998). In 2001, 6.1 percent of Australians age 14 years or older reported lifetime use of MDMA, with 2.9 percent reporting use within the preceding year (Degenhardt, Barker, and Topp 2004). Rates of use are generally higher among males than females (3.1 percent versus 1.5 percent). MDMA use in the preceding 12 months is most common among those age 20 to 29 (5 percent of females and 12 percent of males) (Topp and others 1998).

The availability of MDMA has also increased, as indicated by the proportion of the population who have been offered MDMA (from 4 percent in 1988 to 7 percent in 1991) (Makkai and McAllister 1998), with 14 percent of those age 14 to 29 reporting that they had been offered MDMA in the preceding year.

Research suggests that the pattern of MDMA use changed during the 1990s (Topp and others 1998). Users of MDMA are commencing use at a younger age, and they appear to be using larger doses more frequently. The incidence of bingeing on MDMA appears to have increased, as does the prevalence of the parenteral use of this drug. The increase in the use of MDMA

by injection has been noted among surveys of MDMA users and of injecting drug users generally.

An examination of trends in the United States suggested that, although the use of MDMA has increased over time, its prevalence is significantly less than that of other drugs of abuse (Yacoubian 2003b). A study of 14,520 U.S. college students indicated 6 percent lifetime use of MDMA, 3 percent within the preceding 12 months, and 1 percent within the preceding 30 days. Those who had used MDMA in the preceding 12 months were more likely to be white and a member of a fraternity or sorority and to have used a range of other drugs (Yacoubian 2003a). Rates of use are much higher in surveys of club attendees. A recent U.S. survey found 86 percent reporting lifetime use, 51 percent 30-day use, and 30 percent use within the preceding 2 days (Yacoubian and others 2003).

Abuse of MDMA had showed signs of decreasing in Western Europe but has recently shown signs of increase (UNODCCP 2003). Although MDMA use appears to be still diffusing, in 2003 only four countries (Ireland, the Netherlands, Spain, and the United Kingdom) reported a rate of more than 3 percent use among young adults in the preceding 12 months (EMCDDA 2003). In the United States, use declined in 2002 for the first time, but it increased in other regions, particularly the Caribbean, parts of South America, Oceania, Southeast Asia, the Near East, and southern Africa (UNODCCP 2003). Lifetime experience of MDMA is reported to range from 0.5 percent to 5 percent in European Union countries, with use more common in the Netherlands (EMCDDA 2003).

Population survey findings from New Zealand reported an increase in the preceding-year use of MDMA from 1.5 percent in 1998 to 3.4 percent in 2001. The increase was particularly evident among young men age 20 to 24 (from 4.3 percent to 12.5 percent) (Wilkins and others 2003).

Adverse Health Effects of MDMA. Early studies of MDMA use in Australia and the United States documented relatively few problems associated with the drug's use (Beck 1990; Beck and Rosenbaum 1994; Downing 1986; Solowij, Hall, and Lee 1992). A survey of 100 MDMA users (Solowij, Hall, and Lee 1992) found that the most common adverse effects were the side effects of acute use, such as appetite loss, dry mouth, palpitations, and bruxism (teeth grinding). Among the few heavy users in the study, only two reported feeling dependent on the drug.

With a change in the pattern of MDMA use in Australia, there has been an increase in the MDMA-related harms reported (Topp and others 1998). Some of the acute physical and psychological adverse effects that MDMA users have attributed to the use of this drug include energy loss, irritability, muscular aches, insomnia, and depression. More chronic adverse effects were also reported, including weight loss, depression, energy loss, insomnia, anxiety, and teeth problems. A recent U.K. study of 430 regular users of MDMA reported that 83 percent of participants reported low mood and 80 percent experienced impaired concentration. Long-term effects of MDMA included the development of tolerance to MDMA (59 percent), impaired ability to concentrate (38 percent), and depression (37 percent) (Verheyden and others 2003).

Physical symptoms that were perceived as being due to MDMA use alone (Topp and others 1998) included an inability to urinate, blurred vision, vomiting, numbness or tingling, loss of sexual urge, and hot and cold flushes. As with amphetamines, the use of MDMA to facilitate sexual encounters may lead to risky sexual behavior and risk of sexually transmitted infections such as HIV. Studies of gay and bisexual men have found an association between MDMA use and high-risk sexual behavior (Urbina and Jones 2004).

MDMA has been implicated in a growing number of deaths, both in Australia and in other countries (Henry, Jeffreys, and Dawling 1992; Solowij 1993; White, Bochner, and Irvine 1997). Although the reasons for extreme reactions have yet to be clearly determined, deaths have most often been attributed to hyperthermia when MDMA was used at dance venues. A combination of sustained exertion, high ambient temperatures, and inadequate fluid replacement appears to compound the effect of MDMA on thermoregulatory mechanisms, causing a rapid and fatal rise in body temperature (Topp and others 1998). Some deaths have been attributed to excessive water consumption, which causes cerebral edema (Cook 1996; Matthai and others 1996).

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