

REVIEW ARTICLE

DRUG THERAPY

ALASTAIR J.J. WOOD, M.D., *Editor*MANAGEMENT OF COCAINE ABUSE AND
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DURING the 20th century, there have been recurrent episodes of cocaine abuse in the United States that have achieved epidemic proportions.¹ Although the total number of people using the drug has decreased in the past decade, cocaine-related biomedical and psychosocial problems remain a major public health problem in the United States and many other countries. The expanding list of cocaine-related toxic effects, acute and chronic, includes reproductive dysfunction, hepatic necrosis, and pulmonary disease.² Abuse of and dependence on cocaine may also be associated with disorders of sexual function, sleep, anxiety, and mood, as well as with delirium and psychotic disorders. Many of these problems begin during intoxication with cocaine, but some are most prominent during withdrawal.

Polydrug abuse, which involves abuse of and dependence on cocaine as well as dependence on alcohol, opiates, and nicotine, appears to be increasing in several subgroups of the population, including minority women of childbearing age.³ One prevalent pattern of such abuse is the concurrent use of cocaine and heroin. The combination of cocaine and heroin, administered intravenously, is called a "speedball," and deaths associated with the use of this combination are increasing.⁴ During 1993–1994, abusers of intravenous cocaine and heroin accounted for a major new group of persons with human immunodeficiency virus (HIV) infection in several large metropolitan areas in the United States and elsewhere.² Those who abuse both cocaine and heroin intravenously are at very high risk for HIV infection as a consequence of needle sharing and the combined immunosuppressive effects of the two drugs.^{5–8}

The 1993 National Household Survey on Drug Abuse estimated that 4.5 million Americans used cocaine in 1992.⁹ Approximately 1.3 million persons reported frequent cocaine use, defined as use at least monthly. The

Drug Abuse Warning Network reported 30,900 cocaine-related visits to the emergency room during the third quarter of 1992,¹⁰ most of which were for cardiovascular, cerebrovascular, and gastrointestinal problems induced by the drug.^{11–13} Concurrent cigarette smoking and cocaine use may also have serious adverse effects on cardiac function.¹⁴ Recent data indicate that cocaine-related injuries are a major cause of death among young adults in New York City.¹⁵

DIAGNOSTIC CRITERIA

Cocaine use and abuse are part of a spectrum of substance-abuse disorders that have been classified according to severity by the American Psychiatric Association, which has enumerated the distinguishing clinical features and medical consequences of cocaine-related problems that practicing physicians may encounter. The diagnostic criteria for cocaine intoxication specified in the fourth edition of the association's *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*¹⁶ are shown in Table 1. Severe cocaine intoxication is associated with potentially life-threatening consequences that require judicious medical management. There are no specific pharmacologic treatments for cocaine intoxication, because the behavioral symptoms and signs (such as psychomotor agitation or retardation) may be diametrically opposite from the physiologic ones (such as elevated or lowered blood pressure). Since cocaine-related deaths¹⁵ and cocaine-induced cardiovascular, cerebrovascular, and gastrointestinal disorders^{11–13} usually occur within 60 to 120 minutes after cocaine use, it is important to retain and monitor all patients who are treated in emergency departments. Fortunately, the drug has a relatively short half-life, and the most severe symptoms and signs of cocaine intoxication decrease within one to two hours after it is used.

The diagnostic criteria for cocaine abuse and dependence are specified in the sections of the DSM-IV¹⁶ listing the criteria for substance abuse (Table 2) and substance dependence (Table 3). In patients with cocaine abuse, drug use is less frequent and less intense than in patients with cocaine dependence. The latter condition is diagnosed partly on the basis of evidence of tolerance for cocaine, compulsive drug acquisition and use, and withdrawal symptoms. The diagnostic criteria specified in the DSM-IV¹⁶ for cocaine withdrawal are shown in Table 4. The dysphoric mood states included among these criteria have also been described by the term "crash" by a number of clinical investigators.^{17,18} However, no symptoms or signs of cocaine withdrawal were noted in several studies of inpatients who were carefully monitored after the cessation of cocaine use.^{19,20}

The inconsistencies in the magnitude and severity of withdrawal symptoms and signs may be due to differences in the doses of cocaine used and the frequency of

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use. Often cocaine abusers do not know the concentration or purity of the cocaine they have purchased and may not later remember how often they used it. Even though they may report using the same amount of cocaine by the same route of administration at different times, the actual concentration of drug may vary greatly. It has long been known that the onset and severity of symptoms and signs of withdrawal vary widely after a person stops using the psychoactive substance, even when the dose is known, as it is in the case of beverage alcohol.²¹ One major factor that could affect the severity of symptoms of cocaine withdrawal is that cocaine-related stimuli are absent in an inpatient setting, whereas neighborhood drug suppliers and cocaine-using acquaintances may be present in outpatient treatment environments.

PHARMACOLOGIC EFFECTS AND MECHANISMS OF ABUSE AND DEPENDENCE

Cocaine is a stimulant as well as a local anesthetic with potent vasoconstrictor properties. It induces a complex pattern of subjective effects that have been described as intense euphoria and alertness, increased confidence and strength, heightened sexual feelings, and indifference to concerns and cares.²² Yet these sensations rapidly change to their antithesis, so that despondency, dejection, and despair prevail. Euphoria is restored by the next dose of the drug, and it is this rapid alternation between ecstasy and dejection that purportedly leads to the "binge" pattern of cocaine use, in which the drug is used repeatedly at short intervals until either the supply or the user is exhausted. Cocaine, like many drugs, produces both pleasure and dysphoria, so the simplistic notion of "reward" does not accurately describe its effects.²³ Instead, cocaine has reinforcing effects, which may be defined as any effect, positive, negative, or both, that maintains the behavior that leads to the continued administration of the drug. The reinforcing properties of

Table 1. Diagnostic Criteria for Cocaine Intoxication.*

A. Recent use of cocaine
B. Clinically significant maladaptive behavioral or psychological changes (e.g., euphoria or affective blunting; changes in sociability; hypervigilance; interpersonal sensitivity; anxiety, tension, or anger; stereotyped behaviors; impaired judgment; or impaired social or occupational functioning) that developed during, or shortly after, use of cocaine
C. Two (or more) of the following, developing during, or shortly after, cocaine use: <ol style="list-style-type: none"> 1. Tachycardia or bradycardia 2. Pupillary dilation 3. Elevated or lowered blood pressure 4. Perspiration or chills 5. Nausea or vomiting 6. Evidence of weight loss 7. Psychomotor agitation or retardation 8. Muscular weakness, respiratory depression, chest pain, or cardiac arrhythmias 9. Confusion, seizures, dyskinesias, dystonias, or coma
D. Symptoms not due to a general medical condition and not better accounted for by another mental disorder

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Table 2. Diagnostic Criteria for Substance Abuse.*

A. A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within a 12-month period: <ol style="list-style-type: none"> 1. Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household) 2. Recurrent substance use in situations in which the substance use is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use) 3. Recurrent substance-related legal problems (e.g., arrests for substance-related disorderly conduct) 4. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with spouse about consequences of intoxication, physical fights)
B. Symptoms that have never met the criteria for substance dependence for this class of substance

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cocaine appear to be related to the rapid onset and brief duration of its stimulant effects.²⁴⁻²⁶

Cocaine can be used orally, intranasally (by insufflation), by inhalation, by intravenous injection, or by the smoking or inhalation of coca paste, cocaine freebase, or "crack" cocaine (freebase prepared with sodium bicarbonate). The onset of salient subjective effects is determined in part by the route of administration and frequency of use. Mood enhancement occurs very rapidly after smoking crack cocaine and after intravenous use, but less rapidly after intranasal administration. Cocaine rapidly increases the heart rate and blood pressure in a dose-related manner.^{25,27} These subjective and physiologic effects are not sustained, however, and cocaine abusers report using the drug repeatedly and frequently during a binge. Cocaine has a relatively short plasma half-life (approximately 60 minutes) and is metabolized primarily by plasma esterases; its metabolites are excreted in urine. It is often used sequentially or simultaneously with other abused drugs. Combinations of cocaine and alcohol produce a metabolite, cocaethylene, that has cardiovascular effects similar to those of cocaine alone.²⁸ Cocaethylene may also lengthen cocaine-induced euphoria and reduce the unpleasant symptoms of withdrawal.

The accelerating frequency of cocaine abuse has economic and social consequences that are well documented. The seemingly evanescent pleasures of using the drug are accompanied by the risk of death from cardiac arrhythmia, respiratory depression, and convulsions.² Disorders of cerebral blood flow and perfusion defects due to the potent vasoconstrictive effects of the drug on cerebral arteries are also associated with chronic cocaine abuse.²⁹

The neurobiologic mechanisms underlying the effects of cocaine are not well understood. There is considerable evidence, however, that the initiation and continuation of cocaine use are associated with the effects of the drug on the dopaminergic and neuroadrenergic modulation of central nervous system function.^{25,30-36} Studies in animals suggest that the mesocorticolimbic

Table 3. Diagnostic Criteria for Substance Dependence.*

- A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three or more of the following, occurring at any time in the same 12-month period:
1. Tolerance, as defined by either of the following:
 - a. 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 (criteria A and B of the criteria for withdrawal from the specific substance)
 - b. The same (or a closely related) substance taken to relieve or avoid withdrawal symptoms
 3. The substance often taken in larger amounts or over a longer period than was intended
 4. A persistent desire or unsuccessful efforts to cut down or control substance use
 5. A great deal of time spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance (e.g., chain-smoking), or recover from its effects
 6. Important social, occupational, or recreational activities given up or reduced because of substance use
 7. Continued substance use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption)

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dopaminergic pathways are important mediators of cocaine's reinforcing properties.³⁷⁻⁴⁰ Species may differ, however, with respect to the distribution and interaction of neurons with dopamine receptors and subtypes. Dopaminergic systems are probably not homogeneous. Recent studies of drug self-administration in rodents indicate that dopamine D3 receptors contribute to its reinforcing properties.³⁷ To date, five dopamine-receptor subtypes have been identified, and their role in inducing and perpetuating cocaine abuse and dependence in humans remains to be determined.

A "dopamine depletion" hypothesis has been advanced to explain the occurrence of symptoms such as depression and anergia after the cessation of cocaine use.^{24,30} Alterations in dopaminergic function after protracted cocaine use may also result in hyperprolactinemia, an indication of impaired dopaminergic regulation of prolactin secretion.^{17,41} Dysregulation of the dopamine system may contribute to immunologic as well as neuroendocrine disorders in cocaine-dependent men and women. The drug also affects serotonergic functions in the central nervous system, and cocaine-induced changes in serotonergic activity may underlie disorders of sleep and wakefulness that occur during chronic cocaine use and during withdrawal.^{30,42}

Cocaine also affects neuroendocrine systems that modulate responsivity to stress and sexual behavior. The drug induces a rapid increase in corticotropin secretion in humans⁴³ and rhesus monkeys.⁴⁴ Cocaine-induced stimulation of corticotropin secretion in rodents was inhibited by the administration of antiserum to corticotropin-releasing hormone.⁴⁵ This increased secretion of corticotropin may be associated in humans with the reinforcing properties of cocaine and its rapid enhancement of perceived pleasure and diminution of concern about environmental stressors.⁴³ Cocaine also stimulates the secretion of luteinizing hormone in rhesus monkeys^{46,47} and humans.⁴³ This effect may be related to

the perception of enhanced sexual interest and responsivity after the drug is used.⁴³ Altered neuroendocrine function during protracted cocaine abuse may result in serious disorders, including altered stress and immune responses, as well as impairment of reproductive function in both sexes.²

Important advances have been made in understanding the neuropharmacologic concomitants of cocaine use by humans, subhuman primates, and rodents, but the specific neurochemical and neurophysiologic bases of cocaine reinforcement remain to be determined. Although neuroadrenergic, dopaminergic, and serotonergic functions of the central nervous system are directly affected by cocaine,^{2,23,48} it is likely that inter-

actions between these neurochemical systems are of considerable importance in understanding the reinforcing properties of cocaine.

PHARMACOTHERAPY FOR COCAINE ABUSE AND DEPENDENCE

Cocaine abuse and dependence may be initiated and perpetuated by a wide range of physiologic, behavioral, and sociocultural factors. Recent treatment-center evaluations of urban, economically disadvantaged cocaine abusers revealed that 73 percent had one or more personality disorders.⁴⁹ Accordingly, the use of existing medications and the development of new ones should be based on accurate diagnosis and a consideration of the multiple interactive processes that may have contributed to the genesis and continuation of cocaine abuse and dependence.

A number of drugs have been used to treat cocaine-related problems, in part because of the postulated role of antecedent disorders in the genesis of chronic abuse, as well as the neurobiologic consequences of abuse and dependence. For example, clinical observations of dysphoric mood changes during cocaine intoxication and withdrawal (Tables 1 and 4) have led to the use of an-

Table 4. Diagnostic Criteria for Cocaine Withdrawal.*

- A. Cessation of (or reduction in) cocaine use that has been heavy and prolonged
- B. Dysphoric mood and two (or more) of the following physiologic changes, developing within a few hours to several days after criterion A:
 1. Fatigue
 2. Vivid, unpleasant dreams
 3. Insomnia or hypersomnia
 4. Increased appetite
 5. Psychomotor retardation or agitation
- C. Symptoms in criterion B causing clinically significant distress or impairment in social, occupational, or other important areas of functioning
- D. Symptoms not due to a general medical condition and not better accounted for by another mental disorder

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antidepressant drugs to treat cocaine abuse and dependence. However, the diversity of patterns of use and routes of administration, as well as the concurrent abuse of other drugs, complicates judgments about the efficacy of medication. The conclusions of studies of drugs in persons who use cocaine intranasally (by insufflation) may not apply to persons who inhale cocaine (as crack) or use intravenous cocaine, alone or in combination with opiates. Moreover, drugs that appear to be effective in cocaine abusers may not be useful in treating cocaine dependence.

The evaluation of drug efficacy must be based on the severity of illness. The Addiction Severity Index is one test that facilitates the grading of substance-abuse disorders⁵⁰ and is important for research on the treatment of cocaine abuse and dependence. Judgments about drug efficacy can only be made in relation to ratings of the biobehavioral severity of cocaine abuse or dependence. This position was clearly articulated in a recent review of research and clinical perspectives on the treatment of cocaine abuse and dependence that was prepared for the National Institute on Drug Abuse.⁵¹ This report emphasized the need to pay more attention to research design, the analysis of treatment methods, research on treatment, and the specification of important diagnostic and demographic characteristics of patients participating in studies of pharmacologic or behavioral treatment.

Many approaches to the treatment of cocaine abuse and dependence have also been used in treating patients with alcoholism and other substance-abuse disorders.^{32,52,53} There has been interest in comparing the effectiveness of drug therapy with that of psychotherapy, as well as with behavioral treatments of cocaine abuse and dependence.⁵⁴⁻⁵⁷ In this review we primarily discuss pharmacotherapeutic approaches to the management of cocaine abuse and dependence, but some recent advances in behavioral treatment are also described. The rationale for the use of various classes of medications is presented in the following sections, with data on treatment outcome. Any assessment of the efficacy of therapy for cocaine abuse and dependence is complicated by the high frequency of abuse of other substances.

Antidepressant Drugs

Dysphoric moods (Table 4) are frequently reported after the cessation of cocaine use. Clinical observations of depression have provided a rationale for exploring the effectiveness of antidepressant drugs in treating cocaine abuse. Although depression may precede or follow cocaine use, it was hypothesized that ameliorating symptoms of depression might decrease such use. Desipramine, an antidepressant, has been used for both cocaine detoxification and the maintenance of abstinence. A 1984 report that this drug was safe and effective in treating cocaine abuse⁵⁸ led to a placebo-controlled, double-blind assessment of the relative efficacy of desipramine in 72 cocaine-dependent persons treated at an outpatient clinical facility.⁵⁹ The results indicated that desipramine was beneficial, but in subsequent trials it

was found not to be effective in treating patients with cocaine dependence.^{60,61} The assessment of this treatment is complicated by the fact that many cocaine abusers often abuse other substances, such as opiates, and there is considerable disagreement about the effectiveness of desipramine for patients who abuse or are dependent on opiates.^{62,63} At present, desipramine appears to be most effective for persons with diagnosed cocaine abuse (Table 2) who have antecedent or consequent symptoms of severe depression. Desipramine is often ineffective in treating cocaine dependence (Table 3). The results of two recent clinical trials indicated that fluoxetine is ineffective in treating cocaine dependence with or without concurrent dependence on opiates.⁶⁴ Other antidepressant drugs, including imipramine and trazodone, have also been used, but they have more adverse effects than desipramine.^{31,65-67}

Drugs Affecting Dopaminergic Function

The rationale for the use of dopaminergic drugs to treat cocaine abuse and dependence is based in part on the effects of cocaine on dopamine-transporter systems; cocaine blocks the reuptake of dopamine and acts as an indirect dopamine agonist.^{33,68} Moreover, chronic exposure to cocaine is postulated to affect dopaminergic function in the brain adversely (dopamine depletion).³⁰ A less toxic drug similar to cocaine could be substituted for cocaine in a manner analogous to the use of methadone in opiate-abuse treatment. Unfortunately, the relative effectiveness of dopaminergic drugs in treating cocaine abuse and dependence is often severely compromised by adverse effects, including gastrointestinal disorders such as nausea and abdominal pain, headaches, cardiovascular instability, hypertension, and psychosis-like illness.^{31,69,70} A number of agonists and antagonists for highly selective dopamine D1, D2, and D3 receptors have also been developed, and although preclinical studies show many to be effective in reducing cocaine use, none are approved for clinical use.⁷¹

Bromocriptine, a dopaminergic drug used to treat hyperprolactinemia, has been evaluated in both open and placebo-controlled trials.^{69,72-75} Bromocriptine was reported to decrease the craving for cocaine during detoxification and to reduce dysphoria during both detoxification and abstinence. The dopamine agonist methylphenidate was found to increase rather than decrease the craving for cocaine.⁷⁶ Amantadine has also been used in the detoxification of cocaine-dependent patients. An encouraging report of the effectiveness of amantadine in reducing cocaine craving⁷⁷ was not confirmed by a double-blind, placebo-controlled study.⁷⁸ Both open⁷⁹ and placebo-controlled, double-blind⁶³ studies designed to compare amantadine with desipramine as a treatment for patients in methadone-maintenance programs who also had cocaine abuse or dependence indicated that both drugs increased the time during which patients remained in the programs.^{63,79}

Mazindol inhibits the binding of cocaine to dopamine transporters in the brain. In controlled studies,

mazindol neither attenuated the subjective effects associated with intravenous cocaine use in abusers of the drug nor reduced cocaine-induced craving.⁸⁰ Bupropion, an antidepressant, was no more effective than placebo in treating cocaine dependence in patients in methadone-maintenance programs.⁸¹ Flupentixol, a dopamine-receptor antagonist, has antidepressant effects at low doses and neuroleptic effects at high doses. Initial open-label studies suggest that flupentixol may be useful in treating cocaine abuse and dependence.⁸²

Tryptophan and tyrosine, dietary amino acid precursors of dopamine, have been administered in open-label studies for both cocaine detoxification and the maintenance of abstinence.⁸³ However, there is no evidence that either is effective for the treatment of cocaine abuse and dependence.^{65,84-86} In a placebo-controlled, double-blind study, levodopa and carbidopa together did not attenuate symptoms of abstinence after the cessation of cocaine use.⁸⁷

Opioid Antagonists and Mixed Agonist–Antagonists

One rationale for the use of opioid antagonists (such as naltrexone) or opioid mixed agonist–antagonists (such as buprenorphine) to treat cocaine abuse and dependence is that these conditions may be preceded or accompanied by abuse of or dependence on opiates.^{88,89} Endogenous opioid systems in the brain may also be involved in the reinforcing effects of other abused substances, including cocaine^{90,91} and alcohol.⁹²⁻⁹⁴ Compliance with naltrexone therapy for opiate abuse and dependence has been poor, however, even when there is no cocaine abuse or dependence.^{95,96} No clinical trials of the effectiveness of naltrexone in treating cocaine abuse and dependence have been conducted as yet, but naltrexone appeared more effective than methadone in reducing the abuse of cocaine by opiate-dependent patients.⁹⁷ Naltrexone has usually been ineffective in reducing cocaine self-administration in preclinical studies.⁷¹

In contrast, the opioid-agonist properties of buprenorphine appear to make it more acceptable to patients than naltrexone, even though the two drugs antagonize opioid effects equally well.^{91,98} Buprenorphine is currently under review by the Food and Drug Administration (FDA) for the treatment of opioid dependence, and initial clinical trials were encouraging.^{99,100} In preclinical studies, buprenorphine reduced cocaine use significantly.^{71,90} Clinical studies of inpatients have demonstrated that buprenorphine is safe in combination with cocaine.^{101,102} Ongoing clinical trials suggest that buprenorphine reduces cocaine abuse as well as opiate abuse in patients who are dependent on both drugs according to the criteria in the third edition of the *Diagnostic and Statistical Manual of Mental Disorders*, revised.^{91,97,103-105}

Carbamazepine

Carbamazepine is an anticonvulsant drug used to treat seizure disorders. In an open trial, 200 to 800 mg of carbamazepine two to four times daily suppressed

the craving for cocaine and decreased cocaine use,¹⁰⁶ but carbamazepine was no more effective than placebo in several subsequent clinical trials.¹⁰⁷⁻¹¹⁰

PSYCHOTHERAPY AND BEHAVIORAL THERAPY

A number of cognitive and behavioral therapies have been recommended to prevent relapse in patients with cocaine abuse or dependence. These include aversion therapy, network therapy, behavioral treatment, exposure to cocaine-related cues, contingency-based contracting, and cognitive therapy.^{53,111-113} Although no specific cognitive or behavioral treatment is uniquely effective in patients with cocaine abuse or dependence,^{57,114} the systematic application of behavioral concepts to drug-abuse treatment is relatively new.⁵⁶ One 24-week behavioral study indicated that giving patients incentives (in the form of vouchers exchangeable for retail items) to provide cocaine-free urine specimens significantly improved compliance and outcomes.¹¹⁵ The effectiveness of behavior-related contingency management appears to be enhanced by having patients' significant others participate in the treatment program.¹¹⁶ Therapeutic endeavors are likely to benefit when there is psychosocial support. In psychotherapy, mutual trust and confidence in the therapist are important ingredients of success.⁵⁷ Having the patient take part in selecting the therapeutic regimen may also facilitate treatment.

NEW MEDICATIONS — PROMISES AND PROBLEMS

The prospects for developing more specific drugs to treat cocaine-related disorders should be greatly improved by advances in research on the neurobiology of cocaine and by the availability of preclinical models of drug abuse that are useful in evaluating medications.^{33,38,40,71,117} For example, clarifying the relative contributions of the various subtypes of dopamine receptors to the reinforcing effects of cocaine should lead to more specific pharmacologic interventions.^{33-35,37} Identifying the molecular structures of glycoprotein dopamine transporters⁶⁸ and discovering unique ligands, such as the polyamine spermine, that bind to these transporters¹¹⁸ provide a promising approach to the development of medications. In addition, the development of specific antibodies for the catalyzed degradation¹¹⁹ and immune binding¹²⁰ of cocaine may also contribute to more effective medications for the treatment of cocaine abuse. On the basis of these discoveries, it is reasonable to anticipate that molecular pharmacology will contribute to the successful development of specific cocaine antagonists. However, the effectiveness of such antagonists as compared with that of less toxic cocaine-like agonists remains to be determined.⁷¹

Theoretically, a safe and effective antagonist would block the reinforcing properties of cocaine and decrease cocaine use. However, it is also possible that patients will use higher doses of cocaine in an effort to surmount the pharmacologic blockade.⁷¹ Empirically, the treatment of opiate abuse and dependence with antagonists has been disappointing. With few exceptions, the

FDA-approved selective opioid antagonist naltrexone has not proved effective in treating opioid abuse, because of poor compliance.^{95,96} Patients usually discontinue antagonist therapy in the anticipation of resuming illicit-drug use. In the treatment of opiate abuse, an opiate agonist, methadone, and a partial agonist, buprenorphine, have been most effective.^{99,100}

Whatever drug is used to treat cocaine abuse and dependence, adequate evaluation will require using appropriate and realistic criteria for efficacy. However, defining efficacy has been an ongoing source of divisive polemics, and the prospects of a general consensus are remote. Traditionally, total abstinence has been the accepted standard for success, and any result less than abstinence has been regarded as a failure of treatment. Yet, in other areas of medicine it is recognized that most treatments have relative rather than complete efficacy. For example, a partial reduction of angina pectoris is very important to the patient, even though there may not be a total remission of symptoms. Similarly, in treating substance-abuse disorders, any reduction in drug use may create an opportunity for the patient to be more receptive to counseling and job-skills training and to learn constructive alternatives to drug acquisition and use. Moreover, any reduction in intravenous drug use, needle use, and needle sharing should lower the risk of HIV infection.^{91,121} The clinical reality is that most abusers of cocaine and other substances continue to use some drugs during maintenance treatment,^{2,62,63,89,103} and a 30 to 60 percent reduction in drug use should benefit society as well as the patient. Future evaluations of new medications for the treatment of cocaine abuse and dependence should include the use of quantitative urine screening¹²² to ascertain the degree of relative abstinence from cocaine.

As we have noted, the evaluation of any treatment to reduce cocaine abuse and dependence is complicated by the pervasiveness of polydrug abuse.^{88,89} Developing effective medications to treat polydrug abuse is increasingly important, because many persons do not abuse a single substance in order to achieve a salient effect. Paradoxically, drugs with differing or even opposite effects on mood and behavior may be used, for reasons that are poorly understood.²³

CONCLUSIONS

At present, no drug therapy is uniquely effective in treating cocaine abuse and dependence. A number of medications that were initially developed to treat other disorders have been used to treat the biobehavioral disorders often associated with cocaine abuse and dependence. Unfortunately, none are considered to be highly effective for either cocaine detoxification or the maintenance of abstinence.^{83,114} However, the limitations of the medications currently available should not lead investigators to give up their search, because medication is only one element of humane and comprehensive therapy for persons with drug dependence. There is compelling evidence that many cocaine abusers have had major psychological and psychosocial impairments that

contributed to and may have been compounded by subsequent problems of drug dependence.¹¹⁴ These impairments include cognitive and learning disorders, interpersonal and social problems, and legal and financial difficulties. The recent report of the first randomized clinical trial in which the efficacy of the interaction between pharmacotherapy and psychotherapy was evaluated in the treatment of cocaine abuse stressed the "heterogeneity among cocaine abusers and the need to develop specialized treatment for clinically distinct subgroups."⁵⁴ It is axiomatic that treatment for persons with cocaine abuse or dependence should be selected on the basis of all biomedical and psychosocial factors associated with the patients' illness.

Persons who abuse cocaine and also have antecedent or concurrent depressive disorders may benefit from treatment with an antidepressant drug, such as desipramine. It is unlikely, however, that patients dependent on cocaine will remain abstinent as a function of treatment with either antidepressant or anxiolytic agents. Cocaine-dependent persons who take that drug by inhalation (as crack cocaine) often have major psychosocial, cognitive, and legal problems and may require referral to an intensive program of psychosocial treatment. In contrast, persons who abuse or depend on cocaine and administer the drug intranasally (by insufflation) may enter remission after being referred to specialists in psychiatry or addiction medicine. The most seriously ill patients with cocaine abuse or dependence are those who use the drug intravenously, either by itself or with heroin or morphine, and are at high risk for myocardial infarction, stroke, and the acquired immunodeficiency syndrome. These patients need the most intensive medical and psychiatric observation and should be referred to programs that provide multimodal treatment for polydrug abuse and dependence. Developing safe and effective medications to treat cocaine abuse and dependence is an ongoing challenge. However, as is true of good medical practice generally, the treatment of drug abuse or dependence relies on a triad of compassion, psychosocial enrichment, and safe and effective pharmacotherapy.

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