

Cocaine and Psychiatric Symptoms

W. Alexander Morton, Pharm.D., B.C.P.P.

Background: Cocaine is an addictive drug that produces numerous psychiatric symptoms, syndromes, and disorders. The symptoms include agitation, paranoia, hallucinations, delusions, violence, as well as suicidal and homicidal thinking. They can be primary to the drug's effect or secondary to exacerbation of comorbid psychiatric disorders.

Data Sources: A computerized literature search was conducted using MEDLINE to identify reports of psychiatric symptoms secondary to cocaine use. Additional reports were found via bibliographies of various published reports.

Data Synthesis: The use of cocaine in the "crack" form is often associated with more frequent and intense symptoms. Paranoia occurs in 68% to 84% of patients using cocaine. Cocaine-related violent behaviors occur in as many as 55% of patients with cocaine-induced psychiatric symptoms. Homicide has also been associated with cocaine use in as many as 31% of homicide victims. In suicide, cocaine has been found to be present in as high as 18% to 22% of cases. Many patients with cocaine dependence have also been found to have a comorbid psychiatric disorder.

Conclusion: Cocaine can produce a spectrum of psychiatric symptoms with which primary care practitioners need to be familiar. Comorbid psychiatric disorders are frequent in patients with cocaine use disorders and can worsen with cocaine use. Nonaddictive medication may be necessary to treat comorbid conditions such as anxiety and depressive disorders. Primary care practitioners need to be familiar with the treatment programs for patients with cocaine use disorders so appropriate referral can easily take place and follow-up care can be understood and maintained.

(Primary Care Companion J Clin Psychiatry 1999;1:109-113)

Received June 21, 1999; accepted July 8, 1999. From the College of Pharmacy and the Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston.

Reprint requests to: W. Alexander Morton, Pharm.D., B.C.P.P., MUSC Institute of Psychiatry, 67 President St., P.O. Box 250861, Charleston, SC 29425 (e-mail: mortona@musc.edu).

The likelihood is high that primary care practitioners will encounter patients with substance use problems, as these disorders are not rare. In the United States, there is currently an 11.3% incidence of substance use disorders and a 26.6% chance that an individual will develop one during his or her lifetime.¹ Cocaine is a frequently used substance that currently causes numerous

problems in our health care programs and society. Chemical dependence to cocaine is a psychiatric, psychological, and biological disorder that affects almost all areas of a person's life. Cocaine has the potential to produce a spectrum of psychiatric symptoms and exacerbate many mental disorders.

OVERVIEW

A computerized literature search was conducted using MEDLINE to identify reports of psychiatric symptoms secondary to cocaine use. Additional reports were located by reviewing the bibliographies of the reports found in the initial search. This article reviews some of the more frequent symptoms, offers an explanation for their presence, and discusses possible treatments of the symptoms as well as the addiction.

"Crack" and Cocaine

Cocaine is one of the most addictive substances used in today's society. Most medical practitioners know "crack" is connected to cocaine, but few clinicians know exactly what crack is. Crack is cocaine (cocaine base), but not in the powder form. The powder form (cocaine hydrochloride) is usually "snorted" intranasally, producing a "high" of less intensity. A high temperature (195°C) is required to vaporize cocaine hydrochloride powder for smoking. The powder has a slower onset of action to produce the euphoric effects compared with crack, which is a solid formed by mixing cocaine powder with water and baking soda. This transformation makes crack a drug that is easier and more economical to market and, consequently, much less expensive.

Crack is in a form that allows it to be vaporized at a much lower temperature (98°C), without burning and destroying excess cocaine. Getting cocaine into a vapor form or smoke is important to cocaine users for 2 reasons. The first is that, when smoked, the drug is delivered through the lungs to the brain almost immediately. It then causes release of brain chemicals in the pleasure centers of the brain, resulting in the desired stimulating, euphoric effects. The second reason is that the crack form does not waste cocaine by burning it up.

Neurochemistry

Cocaine has numerous effects on many important neurotransmitters in the brain; however, the most dramatic effect is on the increase as well as the release of dopamine.

Dopamine is thought to be the primary neurotransmitter involved in the pleasure centers of the brain. Its release is associated with pleasure and a sense of well-being and is often a “reward” for certain behaviors. Excessive dopamine levels have also been hypothesized to be associated with anger, aggressiveness, hallucinations, delusions, and other psychotic symptoms.

Cocaine also initially increases levels of norepinephrine and serotonin, 2 other essential neurotransmitters. Norepinephrine is responsible for alertness, activation, increase in heart rate and blood pressure, and preparing the body for emergencies, such as “fight-or-flight” situations. Serotonin is partially responsible for regulating mood, appetite, and sleep, as well as other essential behaviors. After repeated use of cocaine causing “instant” release of these brain chemicals, an overall depletion of dopamine, norepinephrine, and serotonin gradually occurs. A person’s compulsive use may be an attempt to maintain the neurotransmitters at homeostatic levels.

EFFECTS OF COCAINE USE

Initial Effects

Crack produces effects almost instantaneously, within seconds, whereas intranasal powder cocaine may require 5 to 10 minutes to produce effects. These effects consist of intense euphoria, pleasure, and ecstasy, states in which everything pleasurable is intensified. The following quotes from patient interviews have provided useful descriptions,^{2(pp317–318)} including: “It’s like a hurricane blast of pure white pleasure.” These effects are followed by several minutes of arousal and restlessness. “It’s like you’re speeding. Moving around a lot. Talking a lot. But the rush is gone.” After approximately 5 to 20 minutes of this arousal, the person will start to feel irritable and uncomfortable. “I get restless and agitated and keep doing it. I dunno . . . it’s crazy.” “It’s the most horrible depression I ever got. The only thing to do is do more coke, but it doesn’t help . . .” In an attempt to avoid this discomfort and “recapture” the initial high, people frequently compulsively smoke again.

Cocaine Dependence

When a patient is using cocaine excessively, there is little difficulty in arriving at the diagnosis of cocaine dependence. To satisfy the criteria for the diagnosis of cocaine dependence, only 3 of the following conditions must be present according to the American Psychiatric Association’s *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*³:

- Developing tolerance to the euphoric effects of cocaine and requiring more drug to produce the desired effects.
- Stopping cocaine usually results in withdrawal symptoms (such as fatigue, sleep disturbances,

agitation, or depression), and these symptoms can be relieved by using cocaine again.

- Using cocaine in large amounts whenever it is available. (Seldom do people save some for later.)
- Inability to successfully reduce the amount of cocaine one is using.
- Spending a great deal of time and energy obtaining and using cocaine, which isolates one from friends and family, and/or engaging in unlawful activities such as shoplifting, theft, burglary, or homicide to obtain money to buy cocaine.
- Inability to successfully maintain employment while using cocaine because of ineffectiveness at work, increased absenteeism, inability to hold a job, or inability to find work.
- Continually using cocaine despite knowing one will develop mental symptoms, such as paranoia, hallucinations, and delusions, and/or continually using cocaine despite medical consequences, such as weight loss, anemia, or seizures.

Additional psychiatric disorders can accompany the diagnosis of cocaine dependence and can include cocaine intoxication, cocaine withdrawal, cocaine intoxication delirium, cocaine-induced psychotic disorders with hallucination and/or delusions, cocaine-induced mood disorder, cocaine-induced anxiety disorder, cocaine-induced sexual dysfunction, and cocaine-induced sleep disorder.³

Practitioners may consider the voluntary use of cocaine to be an issue. While voluntary use almost always occurs the first time cocaine is tried, cocaine dependence involving compulsive use frequently follows. This compulsive use is often biologically based, yet many clinicians mistakenly believe the cocaine user can stop using the drug whenever he or she wants.

In helping to understand the compulsive use found in patients with cocaine dependence, the following description and commentary by Dr. Sidney Cohen is quite helpful:

Animals will work more avidly (by pressing a bar repetitively to obtain an intravenous “fix”) for cocaine than any other drug. In an unlimited access situation, monkeys will self-administer cocaine by bar pressing for it until they die in status epilepticus. In one study primates bar pressed 12,800 times in order to get a single dose of cocaine. They will work for cocaine in preference to food even though they are starving. They will continue to bar press even though a receptive female is in their cage. They will prefer an electric shock in order to obtain a large dose of cocaine despite the fact that they could have received a lesser dose without a shock.

Such animal cravings take place in the absence of personality disorders, situation stresses, or some characterological inadequacy. All monkeys respond in this compulsive manner. If humans had unlimited access to cocaine, they probably would behave in a similar way. The highly rewarding proper-

ties of cocaine can make obsessive users of the most mature and well integrated among us.^{4(pp3-4)}

Cocaine is not selective in its effects on neurochemistry. Besides stimulating the pleasure centers in the brain, it at the same time activates other systems that control arousal, survival, appetite, mood, and sleep. Although intense pleasure is experienced, a person can also experience nervousness, restlessness, agitation, suspiciousness, paranoia, confused thinking, delirium, hallucinations, delusions, violence, suicide, and homicide.

Paranoia and Psychosis

Paranoia and suspiciousness are often initial symptoms of psychosis. Paranoia occurs in 68% to 84% of patients using cocaine.^{5,6} Cocaine-induced paranoia can be transient, lasting a few hours⁵ or as long as days or weeks.⁷ Prior exposure to cocaine has been clinically correlated with suspiciousness, a precursor to paranoia.⁸ Patients with ongoing, chronic psychiatric disorders and who use cocaine will have more frequent hospitalizations, often related to cocaine-induced paranoia and depression.^{9,10} Intensity and rapidity of onset of paranoia have been related to a state of "sensitization," in which symptoms increase over time with continued use.¹¹

Psychosis, including hallucinations and delusions, has frequently been reported in cocaine users (from 29%⁶ to 53%¹² of users). These psychotic symptoms may be related to an imbalance of dopamine. Psychosis appears to be more common with the use of crack compared with other routes, such as intravenous and intranasal use.¹³

Violence

Violence has been associated with cocaine use. Cocaine-induced psychiatric symptoms undoubtedly contribute to the emergence of violence. In a study of 31 patients with cocaine-induced psychiatric symptoms, 55% had cocaine-related violent behaviors.⁷ In a telephone survey of 452 cocaine users, the following symptoms were reported: anger (42%), violence (32%), and suspiciousness or paranoia (84%).⁶ Violent crimes were committed by 46% of users, usually to get crack.⁶ In this same report, the authors discuss an additional study, which found that 26% of 200 crack users admitted to committing a crime while on crack; 95% of these crimes were violent.⁶ The authors of this report hypothesized that violent behavior associated with cocaine use is predictable based on the effects cocaine has on neurotransmitter dysfunction. Besides an increase in levels of neurotransmitters in the brain's pleasure centers, dramatic change in levels of norepinephrine and serotonin in other parts of the brain might provoke aggression, hyperactivity, impaired judgment, and paranoia.

Inhalation of crack cocaine has been found to produce a greater amount of anger and violence than intranasal use

of cocaine.¹⁴ Similarly, daily use of crack cocaine has been associated with a greater number of illicit activities.¹⁵

Homicide. Homicide also has been associated with cocaine use. In New York City, 31% of 2824 homicide deaths were found to test positive for cocaine or its metabolite, benzoylecgonine.¹⁶ A marked number of residents of New York City (27%) who had fatal injuries also tested positive for cocaine use. Fatal injuries secondary to homicide accounted for 29% of these victims.¹⁷ Concurrent drug use, including alcohol and marijuana, was cited as an additional factor in this report. Other cities have reported similar disturbing findings. One study found that 18% of homicide victims in New Orleans tested positive for cocaine.¹⁸ In Los Angeles, violent death occurred in 61% of individuals who died and tested positive for cocaine at autopsy.¹⁹

Suicide. Suicide can be viewed as a form of self-destructive, violent behavior. In one study of 749 cases of suicide in New York City, cocaine was present in 18% to 22% of cases.²⁰ Suicide may be caused by depression, which occurs frequently in people using cocaine.

Connection between violence and psychiatric symptoms. One investigator has postulated that cocaine may produce impatience, irritability, paranoia, and edginess leading to violent behavior.²¹ In general, all substance use has been associated with the inability to inhibit hostile and aggressive impulses.²² The neurotransmitter norepinephrine, released by cocaine, is also involved in "fight-or-flight" behavior. Individuals who use cocaine are often hyperalert and "armed to the outside world."^{23(p565)} Any rapid or unexpected movement by those around them "may be interpreted as hostile."^{23(p565)} All of these factors may contribute to a cocaine-violence connection.

Cocaine abusers may have problems with thinking logically. The most frequently reported cognitive difficulties involve impaired executive functioning (decision making, judgment, attention/planning/mental flexibility), and research has shown that this cognitive domain relates primarily to the functional integrity of the prefrontal lobe.²⁴ This area of the brain also regulates impulse control. The resultant effects would be poor judgment in an individual experiencing impulsivity in the face of severe cocaine craving.

Delirium

Delirium, a potentially fatal syndrome marked by severe, fluctuating confusion and autonomic nervous system instability (such as severe blood pressure changes, pulse changes, and sweating), can occur with cocaine use. Changes in dopamine, norepinephrine, and serotonin levels have been associated with these effects. Delirium can be accompanied by psychotic symptoms (such as paranoia, hallucinations, delusions, and agitated behavior). One report noted that 7 individuals with fatal cocaine intoxication developed an excited delirium with intense paranoia and bizarre and violent behavior, requiring forcible restraint.²⁵

Cocaine Withdrawal

Dr. Frank Gawin has stated that "the fundamental effect of cocaine is the magnification of the intensity of almost all normal pleasures."^{26(p1581)} This is an obvious reason why a person repeatedly uses cocaine. However, he has also described the patterns that evolve when cocaine is stopped: the cocaine abstinence syndrome. This syndrome often involves a "crash" and a withdrawal phase. During the withdrawal phase, anxiety, hostility, paranoia, and depression have been observed.²⁷ At this time, levels of the neurotransmitters norepinephrine and serotonin are thought to be significantly lowered due to the chronic depletion caused by cocaine use. The rapid reduction in the intensity of these withdrawal symptoms can constitute a major reason a crack addict continues use.

Cocaine also has potent reinforcing effects, defined as "any effect, positive, negative, or both that maintains the behavior that leads to continued administration of the drug."^{28(p966)} Thus, the use of cocaine "rewards" certain parts of the brain with a release of the neurotransmitter dopamine. In this situation, the reward is a reduction or elimination of the withdrawal symptoms.

CONSIDERATIONS IN TREATING COCAINE DEPENDENCE

Successful treatment often occurs in an outpatient setting. Initially, hospitalization may be necessary to treat withdrawal symptoms and prevent continued, compulsive use of cocaine. Outpatient treatment can be very successful; however, there are many important issues that need to be addressed and many interventions that can be helpful in treating drug-dependent patients.²⁹

Pharmacotherapy utilizing antidepressants and anticonvulsants, as well as dopaminergic and opioid antagonists/mixed agonists, has been used with varying results. These agents continue to play an uncertain role in the primary treatment of cocaine dependence.²⁸ Pharmacologic treatments may be necessary to target secondary (cocaine-induced) or coexistent psychiatric disorders, both of which can complicate treatment if not addressed.^{30,31}

"Sensitization" to cocaine may add to the occurrence of psychiatric symptoms, as a person will have greater hyperactivity when rechallenged with cocaine. "Kindling," a phenomenon in which lower doses over time produce the same or larger undesired effect (such as seizures or hallucinations), is also associated with cocaine usage.³² Kindling might also be responsible for worsening of psychiatric symptoms, especially psychosis¹² and suspiciousness.³³

The incidence of hallucinations appears to be increasing secondary to an increase in cocaine dependence, mainly crack, as evidenced by a reported incidence of hallucinations associated with cocaine dependence of 18% in 1978³⁴ compared with 96% in 1991.¹² This increase would also be consistent with a kindling model. Pharmacologic

agents that decrease kindling, such as valproic acid and carbamazepine, may potentially be useful in treatment.³⁵ All psychiatric symptoms need to be treated aggressively to prevent them from getting worse as well as more frequent. If suspiciousness, paranoia, and hallucinations continue after the person stops using cocaine, a dopamine blocker, such as haloperidol, should be considered.

The reinforcing properties of cocaine leave a positive memory of the cocaine experience, which usually overrides any negative memory produced by the drug. Extinguishing these positive memories of pleasure and ecstasy occurs over years through continued abstinence and intensive treatment. Behavioral "cues" that stimulate intense craving for cocaine must be learned and avoided.

Successful treatment usually involves 12-step programs, behavioral and supportive psychotherapy, as well as family therapy, as this illness affects everyone in a family. Neurotransmitter levels must be allowed to normalize. Recovering addicts may require initial and/or long-term treatment with nonaddictive medications to help normalize brain chemistry. All substances with potential for abuse need to be stopped. Learning and practicing alternative, safe activities that produce pleasure and "reinforcement" are essential in treatment and recovery.³⁶

Comorbidity of substance use disorders and psychiatric disorders is highly likely. In the National Institute of Mental Health Epidemiologic Catchment Area (ECA) study, 53% of patients with a nonalcohol drug disorder were also found to have a comorbid psychiatric disorder.³⁷ Pharmacologic treatments are often useful to deal with secondary (cocaine-induced) or coexistent psychiatric disorders, both of which can complicate treatment and recovery if not addressed.^{30,31}

Treatment for a person with cocaine abuse or dependence requires considerable preplanning before initiation. Practitioners need to be prepared to discuss the psychological and physical consequences of continued use. Having a referral network of practitioners or programs that specialize in the treatment of cocaine use disorders is important. Equally important is understanding the components of the treatment program so one can adequately explain the program and prepare the patient. Practitioners and patients should expect the use of nonaddictive, psychopharmacologic treatments for comorbid and secondary psychiatric disorders. Practitioners' familiarity with current behavioral interventions and support groups can be beneficial in patients' long-term treatment programs.

CONCLUSION

Cocaine dependence is a medical disorder of the brain secondary to numerous changes in the brain's complex neurochemistry. However, chemical dependency needs to be treated at all levels of dysfunction, including psychological, occupational, and family. Cocaine dependence is

not a fun, voluntary activity. A person who becomes dependent does not consciously set out to ruin his or her life with this drug. It would be hard to expect a person to stop using cocaine when it produces instantaneous joy, energy, pleasure, and deliverance from pain, depression, and boredom at the same time. Given unlimited availability and use, cocaine addicts literally self-destruct, carrying many people with them.

Cocaine dependence can occur in any individual regardless of education level, occupation, or social class. The instant pleasure that is experienced in most people can lead anyone to a life of obsessive thoughts of this drug and its compulsive use. Mental health, physical health, family life, social activities, and occupation are usually adversely affected.

Advances in health care are progressing rapidly and are lending support for the biological basis of cocaine dependence. The development of a vaccine to block the pleasurable effects of cocaine is being rapidly pursued.³⁸ Through radiographic scans of the brain, dysfunctional areas can be identified and novel treatments that target those specific areas and symptoms may be employed in the future.³⁹ Identification of the gene responsible for the predisposition to addiction will ultimately happen.

Cocaine is a powerfully addictive drug that produces numerous psychiatric symptoms. These can include agitation, paranoia, hallucinations, and violence, as well as suicidal and homicidal thinking, which left untreated will most likely progressively worsen. Comorbid psychiatric disorders are common and need to be identified and treated appropriately. When practitioners are evaluating patients presenting with unusual psychiatric symptoms or seeing patients with psychiatric disorders that are non-responsive to traditional treatment, cocaine use should be considered as a potential cause.

Drug names: carbamazepine (Tegretol and others), haloperidol (Haldol and others), valproic acid (Depakene).

REFERENCES

- Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. *Arch Gen Psychiatry* 1994;51:8–19
- Siegel RK. Cocaine smoking. *J Psychoactive Drugs* 1982;14:271–343
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American Psychiatric Association; 1994:221–229
- Cohen S. *The Substance Abuse Problems, vol 2: New Issues for the 1980s*. New York, NY: Haworth Press; 1985:3–4
- Satel SL, Southwick SM, Gawin FH. Clinical features of cocaine-induced paranoia. *Am J Psychiatry* 1991;148:495–498
- Miller NS, Gold MS, Mahler JC. Violent behaviors associated with cocaine use: possible pharmacological mechanisms. *Int J Addictions* 1991;26:1077–1088
- Manschreck TC, Laughery JA, Weisstein CC, et al. Characteristics of freebase cocaine psychosis. *Yale J Biol Med* 1988;61:115–122
- Sherer MA. Intravenous cocaine: psychiatric effects, behavioral mechanisms. *Biol Psychiatry* 1988;24:865–885
- Brady K, Anton R, Ballenger JC, et al. Cocaine abuse among schizophrenic patients. *Am J Psychiatry* 1990;147:1164–1167
- Sonne SC, Brady KT, Morton WA. Substance abuse and bipolar affective disorder. *J Nerv Ment Dis* 1994;182:349–352
- Satel SL, Edell WS. Cocaine induced paranoia and psychosis proneness. *Am J Psychiatry* 1991;148:1708–1711
- Brady KT, Lydiard RB, Malcolm R, et al. Cocaine-induced psychosis. *J Clin Psychiatry* 1991;52:509–512
- Honer WG, Gerwitz G, Turey M. Psychosis and violence in cocaine smokers [letter]. *Lancet* 1987;2:451
- Giannini AJ, Miller NS, Loisel RH, et al. Cocaine-associated violence and relationship to route of administration. *J Sub Abuse Treatment* 1993;10:67–69
- Miller NS, Gold MS. Criminal activity and crack addiction. *Int J Addictions* 1994;29:1069–1078
- Tardiff K, Marzuk PM, Leon AC, et al. Cocaine, opiates, and ethanol in homicides in New York City. *J Forensic Sci* 1995;40:387–390
- Marzuk PM, Tardiff K, Leon AC, et al. Fatal injuries after cocaine use as a leading cause of death among young adults in New York City. *N Engl J Med* 1995;332:1753–1757
- Lowry PW, Hassig SE, Gunn RA, et al. Homicide victims in New Orleans: recent trends. *Am J Epidemiol* 1988;128:1130–1136
- Budd RD. Cocaine abuse and violent death. *Am J Drug Alcohol Abuse* 1989;15:375–382
- Marzuk PM, Tardiff K, Leon AC, et al. Prevalence of cocaine use among residents of New York City who committed suicide during a one-year period. *Am J Psychiatry* 1992;149:371–375
- Inciardi JA. The crack-violence connection within a population of hard-core adolescent offenders. *NIDA Res Monogr* 1990;103:92–111
- McCormick RA, Smith M. Aggression and hostility in substance abusers. *Addictive Behav* 1995;20:555–562
- Gay GR. Clinical manifestations of acute and chronic cocaine poisoning. *Ann Emerg Med* 1982;11:562–572
- Bolla KI, Cadet J, London ED. Neuropsychiatry of chronic cocaine abuse. *J Neuropsychiatry Clin Neurosci* 1998;10:280–289
- Wetli CV, Fishbain DA. Cocaine-induced psychosis and sudden death in recreational cocaine users. *J Forensic Sci* 1985;30:873–880
- Gawin FH. Cocaine addiction: psychology and neurophysiology. *Science* 1991;251:1580–1586
- Weddington WW, Brown BS, Haertzen CA. Changes in mood, craving, and sleep during short term abstinence reported by male cocaine addicts. *Arch Gen Psychiatry* 1990;47:861–868
- Mendelson JH, Mello NK. Management of cocaine abuse and dependence. *N Engl J Med* 1996;334:965–972
- Morton WA. Chemical dependency: a look at what does and doesn't work. *J Pharm Practice* 1996;9:1–9
- Cornelius JR, Salloum IM, Thase ME, et al. Fluoxetine versus placebo in depressed alcoholic cocaine abusers. *Psychopharmacol Bull* 1998;34:117–121
- Carroll KM, Nich C, Rounsaville BJ. Differential symptom reduction in the depressed cocaine abusers treated with psychotherapy and pharmacotherapy. *J Nerv Ment Dis* 1995;183:251–259
- Post RM, Weiss SRB, Pert A, et al. Chronic cocaine administration: sensitization and kindling effects. In: Fisher S, Raskin A, Ehlenhuth EH, eds. *Cocaine: Clinical and Biobehavioral Aspects*. New York, NY: Oxford University Press; 1987:109–173
- Sherer MA, Kumor KM, Cone EJ, et al. Suspiciousness induced by four-hour intravenous infusions of cocaine. *Arch Gen Psychiatry* 1988;45:673–677
- Siegel RK. Cocaine hallucinations. *Am J Psychiatry* 1978;135:309–314
- Brady KT, Sonne SC, Anton R, et al. Valproate in the treatment of acute bipolar affective episodes complicated by substance abuse: a pilot study. *J Clin Psychiatry* 1995;56:118–121
- Higgins ST, Budney AJ, Bickel WK. Applying behavioral concepts and principles to the treatment of cocaine dependence. *Drug Alcohol Depend* 1994;34:87–97
- Regier DA, Farmer ME, Rae DS, et al. Comorbidity of mental disorders with alcohol and other drugs of abuse: results from the Epidemiologic Catchment Area (ECA) study. *JAMA* 1990;264:2511–2518
- Fox BS. Development of a therapeutic vaccine for the treatment of cocaine addiction. *Drug Alcohol Depend* 1997;48:153–158
- Gatley SJ, Volkow ND. Addiction and imaging of the living human brain. *Drug Alcohol Depend* 1998;51:97–108