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Pharmacologic Approaches to the Treatment of Cocaine Dependence

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When pharmacologic agents are considered in the treatment of cocaine addiction, the objective of such treatment—sustained abstinence—must be considered. Medication and medical approaches have been disappointing in the treatment of cocaine overdose. The central neurobiologic mechanism(s) involved in cocaine toxicity are poorly understood. Without a cocaine antagonist, pharmacologic approaches have been less than promising in preventing relapse. Various psychoactive medications have been tried in early cocaine abstinence, with some success.

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There has been a resurgence in the use of cocaine, and this has caused havoc in our neighborhoods, schools, family, legal system, and on our peace of mind. Reports of the use of this alkaloid go back many centuries.[1] The Incas in South America chewed coca leaves and referred to cocaine as a "gift from the Sun God." With the Spanish Inquisition, the rulers first prohibited the use of this drug but then later promoted it because of difficulties "motivating" Indian mine workers. In fact, these conquerors became the largest cultivators of cocaine in South America.[2]

It was the Austrian scientist Albert Nieman in 1860 who isolated the cocaine alkaloid, and the famous self-experiments of Freud provided much knowledge regarding the physiologic effects of cocaine. Freud, however, also used this amazing drug to "cure" many psychiatric ailments from depression, hysteria, and digestive disorders to ailments such as alcoholism and opiate addiction.[3]

The continued use of cocaine into the early 20th century brought "cure-all" formulas such as Vin Mariani, a wine made by Angelo Mariani that contained cocaine. This wine received endorsements from famous figures such as Pope Leo XVIII and Thomas Edison. The other widely known formula, Coca-Cola, contained cocaine as its active ingredient until the Pure Food and Drug Act of 1906.[4] The horrors of cocaine addiction were all too clear. With the Harrison Narcotic Act of 1914, cocaine was banned, and this drug has been underground since then. Cocaine use lost its popularity until its resurgence in the 1970s.[2,5]

What makes this drug so enticing and has led to a resurgence of use is multifactorial:

- Multiple perceived freedoms—the 1960s were a time of experimentation in instant pleasure-seeking with sex and drugs;
- Increased production in South America;
- Increased dose—presumably a purer cocaine is being seen as a result of this increased production. In the 1970s cocaine was often adulterated in street preparations, with the amount of cocaine ranging from 10% to 50%[6];
- Decreased price—promoting use in a younger-aged and lower socioeconomic population;
- Drug effect—cocaine is a powerful reinforcing agent because of its biochemical and psychological properties; and
- Innovations in drug delivery—freebase, or "crack"—deliver drugs in concentrations and a latency previously reported only for intravenous use.

In this article we will address the medical consequences of freebase cocaine use and the current pharmacologic adjuncts in treatment.

Medical Complications

There are several routes of cocaine self-administration: intranasal, intravenous, oral, pulmonary, and applying to various mucous membranes—oral, genital, or rectal. The intensity, immediacy, and duration depend on the route and quantity used (Table 1).

Regardless of the route used, the initial central nervous system (CNS) effect is one of euphoria: the user is alert and full of self-confidence. This CNS effect is brief, and what remains with increasing intoxication is insomnia, anorexia, feelings of grandeur, malnutrition, aggressiveness, impaired judgment, and hypersexuality. Other symptoms include irritability, depression, fatigue, poor concentration, panic,[7-9] and a paranoid psychosis.

Several of the medical complications are related to the route of use,[10] as, for example, perforation of the nasal septum due to vasoconstriction in the nostrils causing inflammation and ulcerations. In those who smoke cocaine, there is evidence of obstructive airway disease.[11] Nathan and coworkers did spirometric measurements and measured the diffusing capacity of the lungs for carbon monoxide on 22 subjects with a heavy history of "freebasing." A third of these subjects had evidence of obstructive airway disease.[11]

Although cocaine overdose has been thought to be rare, it is becoming far more common. A study by the National Institute on Drug Abuse has shown a significant rise in drug-related emergency department visits through 1988, in which

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TABLE 1.—*Differential Effects Dependent on Routes of Cocaine Administration*

Administration		Initial Onset of Action, s	Duration of "High," min	Average Acute Dose, mg	Peak Plasma Levels, ng/ml	Purity, %	Bioavailability, % absorbed
Route	Mode						
Oral	Coca leaf chewing	300-600	45-90	20-50	150	0.5-1	...
Oral	Cocaine HCl	600-1,800		100-200	150-200	20-80	20-30
Intranasal	"Snorting" cocaine HCl	120-180	30-45	5×30	150	20-80	20-30
Intravenous	Cocaine HCl	30-45	10-20	25-50	300-400	7-100	100
				>200	1,000-1,500	×58	
Smoking, intrapulmonary	Coca paste	8-10	5-10	60-250	300-800	40-85	6-32
	Freebase			250-1,000	800-900	90-100	
	Crack				?	50-95	

HCl=hydrochloride

the number of substance abuser emergency department contacts because of drug overdose was 41.1%. This increase has occurred nationwide from 1987 to 1988, with the number of cocaine-related incidents up by 37.4% and 39.4% in the Northeast and West, respectively, and by 50.7% and 17% in the southern and central regions, respectively ("Drug Study Finds Regional Basis," *USA Today,* November 16, 1989).[12] These data, which were compiled from 26 metropolitan areas, also revealed a 38.5% rise in drug abuse deaths involving cocaine use.

Overdose can occur from any route and at any time and is not related to long-term use. One clue to this phenomenon is the finding of several studies of animals that show hyperthermia to be an important contribution to cocaine death.[13] This hyperthermia may occur through central thermoregulatory mechanisms as well as peripheral mechanisms such as vasoconstriction and increased muscle activity.[13] Life-threatening cardiac arrhythmias and seizure activity can result from hyperpyrexia. Gold and associates suggest vigorously cooling these patients. They found that the administration of bicarbonate may be contraindicated in the treatment of cocaine-related metabolic acidosis; the intravenous administration of sodium bicarbonate lowered the amount of cocaine required to produce a major seizure by 18%.[13]

The morbidity from cocaine overdose can be complicated by the concomitant involvement of other drugs such as amphetamines, barbiturates, opiates, and alcohol.[14,15] Cardiovascular complications include myocardial infarction, arrhythmias, and asystole. Central nervous system complications include stroke, subarachnoid hemorrhage, hyperpyrexia, seizures, and fungal cerebritis.[16,17] Ischemic bowel results from vasoconstriction of the mesenteric vasculature. Deaths have been reported from the accidental rupture of bags filled with cocaine by people who had swallowed them in attempting to smuggle the drug through customs.[15] Pneumopericardium and spontaneous pneumomediastinum have been reported. Administering cocaine through contaminated needles can lead to hepatitis, endocarditis, and the acquired immunodeficiency syndrome.[18,19] Rhabdomyolysis has been reported.[20] Sexual dysfunction may result from cocaine-induced hyperprolactinemia.[21,22]

Women of childbearing age have become an increasing proportion of cocaine abusers.[23] The New York State Division of Substance Abuse Services has revealed that 34% of crack addicts admitted to publicly financed programs are women.[24] In New York City from 1986 through 1988, the number of babies born with drugs in their urine has tripled. Chasnoff and co-workers studied 75 pregnant cocaine users and the perinatal outcome. Those women who used cocaine throughout their pregnancy had higher rates of preterm deliveries and infants with low birth weights.[25] There was also a higher rate of intrauterine growth retardation. These effects may be due to placental vasoconstriction decreasing the flow of blood to the fetus. There are also reports of neonatal seizures, cerebral infarctions, and birth defects.[25,26]

Biochemistry

For cocaine to produce its euphoric and rewarding effects, the integrity of the dopaminergic tracts originating in the midbrain ventral tegmental area projecting to the mesolimbic and mesocortical pathways must be maintained.[27,28] This theory is supported by drug self-administration studies in animals where destruction of the nucleus accumbens blocks intracranial cocaine self-administration. The mesolimbic pathway, which includes the nucleus accumbens, and the mesocortical pathway, which includes the frontal cortex, are integral to the reward-mediating function in the brain. Cocaine activates the dopaminergic circuits in the brain.[29] These circuits can be blocked by agents such as neuroleptic drugs and neurotoxins such as 6-hydroxydopamine, which in turn diminishes or blocks the euphoric effects of cocaine.[28,30]

Dopamine is released by a complex mechanism at the neurons.[29] After its release, it is taken back up into the neuron and stored for further use. Cocaine blocks the reuptake of dopamine into the neuron. In the initial use of cocaine, this reuptake blockade leads to an increased exposure of dopamine on the neuron, with resultant euphoria. With long-term use, however, a different pattern is found. When dopamine is released into the synapse, a portion is recycled, but a certain portion of it is metabolized in the synapse by catechol-*o*-methyltransferase, which cannot be recycled to dopamine.[31] Chronic cocaine exposure depletes the dopamine in the brain by blocking its reuptake and thus increasing synaptic metabolism by catechol-*o*-methyltransferase, leaving less dopamine for recycling.[28,29]

The overall effect of regular use is to decrease the amount of the total available dopamine in the brain. There is evidence of postsynaptic hypersensitivity in response to this chronic depletion.[29] This depletion of dopamine and the hypersensitivity of postsynaptic neurons are felt to relate to the craving that occurs with long-term cocaine use.

Other neurochemical systems involved in the effects of cocaine include norepinephrine. Cocaine inhibits the reuptake of norepinephrine, which is analogous to the effect on the dopamine system. The major mechanism in clearing norepinephrine from the synapse is by reuptake and recycling the neurotransmitter. This norepinephrine reuptake blockade leads to an accumulation of norepinephrine in the synapse

and the resultant stimulatory effects on the norepinephrine system. This stimulatory effect may be responsible for the adrenergic effects seen with cocaine intoxication, such as tachycardia, hypertension, increased sweating, mydriasis, and tremors.

Just as with dopamine, the long-term administration of cocaine leads to norepinephrine depletion. This is felt to explain the occurrence in cocaine users of "crushing" depressive symptoms, suicidal tendencies, poor concentration, sleep and appetite disturbances, decreased sexuality, and anhedonia.[15]

Cocaine's effect on serotonin (5-hydroxytryptamine) is predominantly inhibitory. It blocks reuptake and reduces concentrations of serotonin and its metabolites. There is also a reduction in tryptophan hydroxylase activity and the availability of precursors. The net result is a reduction in the synthesis and turnover of serotonin in the brain.[15]

Although the major known effects of cocaine are on the dopamine, norepinephrine, and serotonin systems, there seems to be other biochemical involvement as well. It appears that the opioid peptides may play a role in the effects of cocaine. Naloxone, an opiate antagonist, can increase the stimulatory and euphoric effects of cocaine.[32] Other neuroactive substances under investigation are vasopressin, γ-aminobutyric acid, acetylcholine, the calcium-calmodulin system, and phenylethylamine, which is an endogenous amine.[33]

Pharmacology

Cocaine use is a major public health problem in the United States. It has had far-reaching effects on our health, legal, family, and financial systems. Treatment has taken a comprehensive approach, taking into account these multifactorial problems to include education, relapse prevention measures, peer support groups, family therapy, 12-step programs, and urine monitoring to assess abstinence. New pharmacologic treatments have been developed as adjuncts to the treatment of cocaine addiction. The objectives of such treatment are to obtain and sustain abstinence. In addressing the biologic aspects of cocaine abuse, one pharmacologic approach has been toward lessening the cocaine withdrawal symptoms, dysphoria, and craving.

TABLE 2.—*Bromocriptine Mesylate Regimen for Cocaine Withdrawal**

Day	Bromocriptine Dose, mg	Frequency, times/d
1.....	0.625	3
2.....	0.625	3
3.....	0.625	4
4.....	1.25	2
5.....	1.25	3
6.....	1.25	3
7.....	1.25	3
8.....	2.5	3
9.....	2.5	3
10.....	2.5	3
11.....	1.25	3
12.....	1.25	2
13.....	0.625	2
14.....	0.625	2
15.....	Discontinue	

*The dose should be titrated, with anticraving and antiwithdrawal effects weighed against possible side effects. Maintenance bromocriptine treatment may be necessary if symptoms recur after discontinuation.

Various psychoactive medications have been tried in the early phase of cocaine abstinence with some success. Several studies have confirmed that dopamine plays a major role in the euphoria and rewards of cocaine use.[27,28,30] Habitual cocaine use leads to dopamine depletion, and this may cause the drug craving and other withdrawal symptoms that lead to repeated drug use.[34]

The dopamine agonist, bromocriptine mesylate, has been administered to cocaine addicts in several studies. There are rapid anticraving effects seen in open trials and double-blind placebo-controlled studies.[35-38] Several other studies have confirmed this finding.[27,31] In one report bromocriptine was found to block the cocaine-induced euphoria.[39] Bromocriptine is administered for 14 days to cocaine abusers. Treatment can continue as necessary if craving reoccurs (Table 2).

Bromocriptine actions appear to reduce the dopamine depletion and receptor density. The administration of a precursor of dopamine, tyrosine, may have limited use, as well as the replacement of vitamins involved as cofactors in catecholamine synthesis.[40,41]

Tennant and Sagherian in a double-blind study compared the use of high-dose bromocriptine and amantadine hydrochloride and found both effective in reducing the symptoms of cocaine withdrawal.[39] In another study comparing the use of bromocriptine with that of amantadine in the outpatient treatment of cocaine abuse, the initial effect of these agents was similar in decreasing cocaine craving.[31] In this preliminary study, however, the investigators found bromocriptine to have longer effects than amantadine in reducing cravings. In fact, there was no significant difference between the use of placebo and that of amantadine by day 25. Amantadine acts by releasing dopamine into the synaptic cleft. Whereas there may be an initial relief, this action may reduce already depleted dopamine stores.[31]

Khantzian has reported that methylphenidate will reduce craving in cocaine abusers who have residual attention deficit disorder.[42] Gawin and Kleber, however, studied patients who did not have attention deficit disorder and reported a transient decrease in craving with the use of methylphenidate hydrochloride, but after two weeks methylphenidate appeared to stimulate cocaine craving.[43] At best it appears methylphenidate may have limited use in the treatment of cocaine abuse, except for those persons with a residual attention deficit disorder, because of the stimulatory effects and its abuse potential.

Another dopamine agent that has been studied is a combination drug containing levodopa and carbidopa.[9] In an open study using these agents, patients reported decreased cocaine cravings.[44] Cocores and associates have reported abstinence for as long as 120 days among crack users using bromocriptine or levodopa in an outpatient setting.[45]

Several investigators have evaluated the use of tricyclic antidepressants in cocaine abuse treatment. The initial rationale was that these agents reverse the anhedonic symptoms in major depression. Antidepressants may also be of use in the withdrawal symptoms of chronic cocaine abuse because one of their actions is to block the reuptake of catecholamines and stabilize the receptor.[46]

In an open study, desipramine hydrochloride in doses of 25 to 100 mg was used, resulting in a reduction in craving.[47] Gawin in an outpatient, open clinical trial evaluated the use

of desipramine in cocaine abusers,[48] excluding patients with a diagnosis of major depression to avoid the possibility that desipramine was treating a major affective illness. Ten patients reported decreased cocaine use and craving. Other antidepressants studied include trazodone hydrochloride and imipramine hydrochloride with similar findings of reduced craving. In a placebo-controlled, double-blind study, desipramine, 75 to 100 mg, was used and no difference was found between the placebo and desipramine groups.[49] Kosten and colleagues found the same positive effects when desipramine was used by patients maintained with methadone hydrochloride who abused cocaine.[50]

A double-blind pilot study comparing desipramine and amantadine use in the treatment of cocaine dependence in methadone-maintained patients showed decreased craving in both study groups. The desipramine group, however, was more likely to remain in treatment at the end of three months. Of interest are their findings of no significant difference among the groups, including the placebo group, in abstaining from cocaine use, the amount of craving, self-reports of cocaine use, and changes in depressive symptoms.[50] The authors suggest that this is probably due to the comprehensive treatment service delivery system of cocaine abusers in a methadone maintenance program. Woody and co-workers have also shown the importance of providing psychosocial services as well as detoxification for these patients.[51] Antidepressants have demonstrated some effectiveness in decreasing cocaine cravings in some populations; this response has a lag time of 10 to 21 days.

Lithium carbonate has been used to treat cocaine abuse by decreasing craving, but this effect seems to apply only in those patients with a bipolar disorder.[52]

Because dopamine plays a prominent role in producing the euphoric effects of cocaine, there have been suggestions to look to agents that block dopamine receptors such as neuroleptic agents. A preliminary report on the use of low-dose flupentixol in crack addicts shows a decrease in cravings.[53] Flupentixol is a xanthene that reportedly has antidepressant activity at low doses and neuroleptic activity at higher doses. Although neuroleptic agents may have a beneficial effect in reducing craving, they may have limited use because of the long-term complications of tardive dyskinesia. Other drugs under investigation include calcium channel blockers.

Treatment Issues

Cocaine addiction is a chronic, progressive, relapsing disease in which medical, psychiatric, and social deterioration occurs. Treatment should take into account the extent of addiction and the degree of deterioration in an addict's life.

Pharmacologic agents are used in both outpatient and inpatient settings. The task is to achieve abstinence, and these agents are used to promote a safe detoxification and to lessen the discomfort of withdrawal. To date there are no agents to assure abstinence. There is no "magic bullet."

When treating the addicted population, the overall medical state of a person needs a thorough evaluation to avoid unwarranted complications. This is especially true if pharmacologic agents are used; for example, the cardiovascular status needs careful evaluation if tricyclic antidepressants are used. A complete medical history, physical examination, and laboratory tests are indicated in this population because of the numerous medical complications from cocaine abuse. Anyone with signs of severe infection or of overdose—for example, severe hyperthermia, cardiac arrest, or seizures—needs aggressive medical treatment.

For many, a structured, comprehensive outpatient program using a peer support group, a 12-step program, educational sessions, family assessment, and urine monitoring to assess the program's goal of abstinence is warranted.

Cocores and Gold, in a preliminary study, compared drop-out rates of intranasal cocaine users versus freebase users in a structured outpatient setting.[54] It was found that the dropout rate in freebasers was double that of intranasal users. It appears that additional therapeutic interventions may be warranted in those using high-delivery systems that are characterized by increased concentration, a quicker onset of activity, higher peak blood levels, and shorter duration.

Indications for hospital treatment include the repeated failure of outpatient programs; concomitant medical complications; the presence of psychiatric illnesses such as psychosis or suicidal or homicidal thoughts; a concomitant dependence on other addicting substances such as sedative-hypnotic agents, where abstinence may lead to substantial morbidity such as withdrawal seizures; continued drug use in spite of concomitant medical complications such as seizures, serious infections, or cardiac disease; and the extent and degree of a patient's engagement in highly addictive methods such as long-term intravenous use or crack use.

The need for treatment in cocaine addiction is emphasized by the many medical complications as well as the family and legal complications. As an example of the legal complications, the Drug Use Forecasting program of the National Institute of Justice has released information regarding drug use among arrestees from 13 cities in a three-month period in 1989.[55] Urine specimens were collected on a voluntary basis with the exclusion of those charged with traffic offenses or vagrancy. Also, the number of participants charged with the sale or possession of drugs was 25% or less of the sample. Urine tests were positive for cocaine in 76% of male arrestees in New York, 74% in Philadelphia, 65% in Washington, DC, 59% in New Orleans, and 56% in Cleveland. The popularity of cocaine among women is evidenced by the number of female arrestees with positive urine tests: 72% in New York, 74% in Philadelphia, 73% in Washington, DC, 61% in Kansas City, and 56% in New Orleans. Multiple-drug use (alcohol was not included in the urine screens) was 30% in male arrestees in New York, Philadelphia, San Diego, and Washington, DC. Cocaine and heroin were the most frequently injected drugs, and of the current intravenous users in ten cities, more than 20% reported sharing needles.

Conclusion

Whenever pharmacologic agents are employed in addicted patients, the primary goal is obtaining and sustaining abstinence. The use of these agents has been moderately successful in the initial phase of abstinence, but they have been more than disappointing in promoting sustained abstinence. In fact, because of the powerful positive reinforcement properties of crack and the negative reinforcement of withdrawal,[56] relapse has been more the rule than the exception. The central neurobiologic mechanisms involved in cocaine toxicity are still poorly understood. There are no cocaine antagonistic agents such as naltrexone is to heroin.

Pharmacologic agents are to be considered at best as adjuncts to a comprehensive treatment approach. Continued investigation of cocaine's psychobiologic effects is warranted.

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