The Treatment of Cocaine Addicts: Bromocriptine or Desipramine

By IRL L. EXTEIN, MD and MARK S. GOLD, MD

Several factors have contributed to recent interest and research in the pharmacological treatment of cocaine dependence. Many of these factors are reviewed in detail elsewhere in this issue of Psychiatric Annals.

First, the epidemic of cocaine abuse in the 1980s has flooded treatment resources, which have struggled to adapt traditional psychiatric and substance abuse programs to the particular problems of the cocaine addict. Second, increasing clinical experience with patterns of regular cocaine use have established cocaine as a truly addicting drug.1,2 with regular users demonstrating compulsive drug seeking behavior and withdrawal symptomatology. Thus, the concept of cocaine dependence is recognized in the DSM-III-R. The symptoms of low energy, depressed mood, and intensive cocaine craving that comprise the cocaine withdrawal syndrome suggest physiological changes that might be treated pharmacologically, as physiological withdrawal syndromes from other addicting substances (such as alcohol, sedatives, or opioids) are treated.

Third, basic research has enhanced our understanding of the neurochemical substrate of cocaine's effects.3 The cocaine "high" or euphoric effect seems related to neuronal systems in the brain's "pleasure centers" that utilize dopamine as neurotransmitter.4 The mechanism of this stimulation is primarily by blockage of dopamine reuptake.

There is evidence that over the course of cocaine dependence and withdrawal a dopamine deficiency syndrome develops, suggesting possible modification by medications that can facilitate dopaminergic neurotransmission.5,6 Cocaine blocks the reuptake of norepinephrine as well, an effect it shares with many tricyclic antidepressants. This has suggested a role for noradrenergic tricyclics in treating cocaine dependence and depressions associated with cocaine use.2,6,7

Fourth, the association of cocaine dependence with psychiatric disorders—primarily depression—has stimulated interest in the application of psychotropic medication in cocaine users. The high incidence of

Dr. Extein is Medical Director, Fair Oaks Hospital, Delray Beach, Florida.
Dr. Gold is Director of Research, Fair Oaks Hospital, Delray Beach, Florida.
Address reprint requests to Irl L. Extein, MD, Medical Director, Fair Oaks Hospital, Delray Beach, Fl 33484.
major depressive disorder in cocaine addicts and their families suggests that not only can cocaine use predispose to depression (by psychosocial and physiological mechanisms), but also that depressive disorders may predispose to cocaine abuse.

Fifth, the increasing use of crack has raised the stakes for cocaine addicts and those treating them. Crack is relatively cheap and available and allows the user to inhale the potent and fast acting cocaine freebase. Patients abusing crack seem to develop a more intense level of dependence with more severe withdrawal symptoms on cessation of use. Such intense abstinence symptoms (including cocaine craving) are one cause of treatment drop-out and underline the need for effective pharmacological intervention to maintain patients in the treatment and recovery process.

Though effective nonaddictive pharmacotherapy of cocaine abstinence symptomatology would be of obvious theoretical and practical clinical significance, the effects of pharmacological treatments for cocaine withdrawal remain controversial and have been the subject of several reviews. Dackis and Gold first reported the efficacy of the dopaminergic agonist bromocriptine in reducing cocaine withdrawal craving in a single-blind, placebo control study using single doses of 0.625 mg orally. Our group followed upon this initial study and reported that in an open study of hospitalized patients, bromocriptine up to 1.875 mg orally t.i.d. for up to three weeks improved cocaine craving, depressed mood, and low energy without evidence of euphoric effect or abuse potential and without significant side effects. It should be noted that this dosage range is below that used in other clinical indications, such as the use of bromocriptine in Parkinson's disease, prolactin secreting pituitary tumors, or infertility.

Other groups also reported efficacy for bromocriptine in cocaine withdrawal. A randomized, double-blind, placebo control study demonstrated that bromocriptine 1.25 mg significantly reduced the craving associated with exposure to cocaine paraphernalia. Bromocriptine 2.5 mg/day has been shown to reduce cocaine use and craving in methadone patients in a recent report. A double-blind study showed that bromocriptine as well as amantadine (a medication with dopaminergic effects) relieved cocaine withdrawal symptomatology. The dosage of bromocriptine was up to 2.5 mg t.i.d. orally, higher than that used in the previous studies cited, and may account for the high rate of drop-out due to side effects in this study.

Three studies have now reported that desipramine improves outcome in double-blind trials, and one study of desipramine 75 to 100 mg/day for an average of three weeks failed to demonstrate improvement compared to placebo. Most studies have reported a lag time of at least 10 days before tricyclics are efficacious in cocaine abusers. An open pilot trial of lithium carbonate in cocaine abusers showed lithium to be effective only in cyclothymic subjects.

**BROMOCRIPTINE OR DESIPRAMINE**

Bromocriptine and desipramine have thus emerged as the two main pharmacological treatments for cocaine abstinence symptomatology. To compare directly the efficacy of bromocriptine and desipramine in the acute stages of cocaine abstinence, we studied 12 young adults (three women, nine men) with DSM-III-R cocaine dependence (predominantly crack) and clinically significant cocaine withdrawal symptoms within 72 hours of hospital admission. Patients gave written informed consent for oral administration of single doses of bromocriptine 1.25 mg and desipramine 50 mg on consecutive days utilizing a double-blind, random assignment, crossover design. Craving, mood, and energy were self-rated before and 1, 3, 6, 8, and 12 hours after each medication on 100 mm lines.

Though variability was high, baseline symptoms on bromocriptine and desipramine days did not differ. Peak medication effects were noted at three to six hours. At six hours bromocriptine reduced mean craving 48% (P<.05, paired t test), improved depressed mood 38% (P<.10), and increased energy 21% (NS); whereas desipramine reduced craving 41% (P<.10), had no effect on mood, and reduced energy 19% (P<.10). In patients with higher baseline symptomatology, both medications reduced craving (P<.05) but only bromocriptine significantly improved depressed mood and energy (P<.05). There was a trend (P<.10) for bromocriptine to improve depressed mood and energy compared with desipramine. Patients reported minimal side effects. Headaches and dry mouth were the most common side effects mentioned, neither of which was specific to either medication.
CONCLUSION

Further studies should attempt to distinguish among the efficacy of pharmacological agents in: 1) relieving cocaine withdrawal symptoms; 2) relieving the depressive syndrome that sometimes persists following withdrawal from cocaine; and 3) reducing recurrent cocaine craving and associated relapse into patterns of cocaine abuse. These three main foci of medication treatment—detoxification, treatment of depression, and maintenance of abstinence—must be distinguished, and may or may not respond independently and selectively to pharmacotherapy. The majority of cocaine addicted patients go through acute withdrawal distress and a moderately intense low energy depression associated with cocaine craving that are ameliorated by bromocriptine. In many cases this withdrawal syndrome remits spontaneously in several weeks with supportive care in a structured inpatient setting. Vitamin and amino acid supplementation may also be useful adjuncts during this withdrawal phase.

It is conceivable that bromocriptine may emerge as the treatment of choice for acute withdrawal distress and craving during the first one to two weeks of treatment for acute cocaine abstinence, and desipramine as the treatment of choice for depressive syndromes that persist past the first few weeks of cocaine abstinence.

We would like to emphasize that the current pharmacological treatments of cocaine addiction are not cures or panaceas. Rather, they are options and adjuncts to the complete treatment process allowing detoxification, relief of distress, and full participation in a structured program that includes the 12 Steps of recovery.

REFERENCES