Old Drugs, New Function in Cocaine Dependence

BY CARL SHERMAN
Contributing Writer

NEW YORK — Disulfiram, a drug that has long been used for alcohol dependence, appears promising for the treatment of cocaine addiction, Thomas Kosten, M.D., said at the annual conference of the Association for Research in Nervous and Mental Disease.

A variety of medications, most developed for other indications, may ameliorate problems associated with cocaine and other stimulants by addressing diverse points of the complex neurobiological processes involved, said Dr. Kosten, professor of psychiatry at Yale University, New Haven.

Increased release of dopamine, particularly in the nucleus accumbens, is the signature of drug reward; addiction, however, induces a hypodopaminergic state by downregulating dopamine receptors. Treatment that addresses this neural substrate should reverse the stimulant-induced dopamine deficiency.

A variety of medications, most developed for other indications, may ameliorate problems associated with cocaine and other stimulants.

D2 receptor agonists, such as bromocriptine, have proved ineffective in this regard, but indirect dopamine agonists also seem promising. Most prominent is disulfiram, which inhibits the conversion of dopamine to norepinephrine. The compound has been shown to attenuate the craving induced by administration of cocaine and to reduce withdrawal.

Another mechanism by which disulfiram facilitates reduction in cocaine use appears to be tied to the acceleration and accentuation of the nervousness and dysphoria that often follow ingestion of the drug, Dr. Kosten said at the meeting, cosponsored by the New York Academy of Medicine.

A metaanalysis of a series of studies involving 337 individuals given disulfiram or one of several control medications (naltrexone, buprenorphine, or methadone, for example) found that drug-free urines were significantly more frequent in those on disulfiram than controls (55% vs. 40%).

Another study suggested a genetic explanation for the superior efficacy of disulfiram in some patients but not others. In half of the subjects, the drug did not increase nervousness and paranoia after cocaine ingestion, which could be attributed to differences in levels of dopamine β–hydroxylase (DβH), the target of disulfiram: Low endogenous levels of DβH should predict the cocaine-induced dysphoria that is linked to treatment response.

In fact, disulfiram was associated with significantly more cocaine-free urines than placebo among people with at least one copy of the allele linked to low DβH but not among those who lacked that gene, Dr. Kosten said.

Amantadine, an indirect dopamine agonist that facilitates release of the neurotransmitter, has been shown to be more effective than placebo—but only in people who suffer severe withdrawal symptoms.

The same pattern has been seen with adrenergic antagonists: Propanolol was superior to placebo in reducing cocaine use and increasing treatment retention in patients with high but not low withdrawal severity, he said.

The GABA system is also dysregulated in cocaine dependence; a two-thirds reduction in GABA tone compromises the inhibitory function of this neurotransmitter system. The GABA agonist baclofen was significantly superior to placebo in achieving abstinence from cocaine, as indicated by cocaine-free urines, and tiagibine has also looked promising in controlled trials. Although there is less evidence, other drugs with similar mechanisms of activity (gabapentin, vigabatrin, topiramate) may be useful as well.

Modafinil, a glutamate agonist, has been shown superior to placebo in reducing cocaine use, possibly through its enhancement of the ability to stop unwanted behaviors and to learn relapse-prevention skills, Dr. Kosten said.

A vaccine called TA-CD, under development by Xenova Group PLC, generates antibodies that prevent cocaine from crossing the blood-brain barrier. In a study of 11 patients, a five-dose series of vaccinations was associated with reduced cocaine use for 1 year, without major adverse effects, he said. ■