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Modafinil Improves Behavioral Therapy Results In Cocaine Addiction

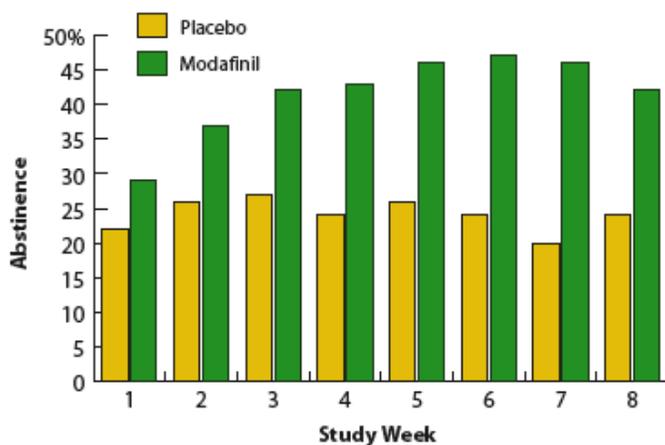
Research Findings
Vol. 20, No. 3 (October 2005)

By Patrick Zickler, *NIDA NOTES* Staff Writer

NIDA-supported researchers evaluating modafinil's potential to enhance behavioral treatment for cocaine addiction have reported a second successful clinical efficacy trial. The new results affirm and extend the promising findings of the earlier, smaller, and less stringent "open label" trial, and they set the stage for large-scale multisite trials that could definitively establish the medication's usefulness.

Dr. Charles Dackis and colleagues at the University of Pennsylvania Treatment Research Center recruited 62 individuals (44 male, 18 female; mean age, 44.5 years) for their double-blind study. All had come to the Center seeking treatment for cocaine addiction, had ingested at least \$200 worth of cocaine in the 30 days prior to presenting for treatment, and met the cocaine-dependence criteria of the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV). The patients agreed to visit the clinic twice a week for individual sessions of cognitive-behavioral therapy (CBT) and provide urine samples 3 times a week for the 8-week course of the study. Once each week, the clinic staff dispensed a week's supply of pills, either modafinil in daily doses of four 100 mg pills (30 patients) or an equal number of identical-looking placebo pills (32 patients).

Combining Modafinil With Behavioral Therapy in Cocaine Addiction Treatment Increases Likelihood of Abstinence



Abstinence rates among patients who received modafinil plus behavioral therapy during 8-week cocaine addiction treatment were consistently higher than rates among patients who received placebo.

Throughout the study, modafinil-treated patients gave fewer cocaine-positive urine samples than the placebo group. "More impressive, though, is the fact that more than twice as many modafinil patients as placebo patients (33 percent compared with 13

percent) were able to attain abstinence for 3 weeks or more," Dr. Dackis says. "Maintaining abstinence for a prolonged period during treatment is an important clinical threshold. Cocaine is a binge drug, and it is common in outpatient treatment for a patient to go 4 or 5 days without using, relapse, then have another clean week. The long continuous abstinence we saw with modafinil is a strong and encouraging signal that this medication can help patients avoid relapse during the critical first weeks of treatment." Both groups of patients attended the same average number of CBT sessions, he adds, further supporting the likelihood that modafinil was the factor accounting for reduced cocaine abuse in those who received it.

Modafinil, a medication currently used to treat narcolepsy, enhances levels of glutamate, a chemical that influences the activity of cells throughout the brain. Animal research has shown that repeated exposure to cocaine depletes glutamate levels in brain regions associated with development of dependence and addiction, and that increasing glutamate concentrations will block reinstatement of cocaine self-administration in rats—a model of relapse to drug abuse in humans (see "[Brain Glutamate Concentrations Affect Cocaine Seeking](#)," *NIDA NOTES*, Vol. 19, No. 3).

Modafinil's modulation of glutamate transmission may account for a striking effect reported by patients: "The mechanism for this isn't clear, but some patients receiving modafinil told us that if they did use cocaine it did not produce the irresistible urge to use more, which they had always felt before," Dr. Dackis says. "Some of the patients told me they had flushed cocaine away. In 25 years of treating addiction, no one ever told me they threw away cocaine."

"The body of research suggesting that modafinil is effective in treating cocaine addiction is growing," says Dr. Ivan Montoya of NIDA's Division of Pharmacotherapies and Medical Consequences of Drug Abuse. "Animal research supports the assumption that modafinil reverses the cocaine-induced neurochemical disruptions of glutamate and of dopamine-containing neurons in the brain's reward centers. Clinically, modafinil has effects that are opposite to the symptoms of cocaine withdrawal, which usually include oversleeping, depression, poor concentration, and craving."

Dr. Dackis and his colleagues are now planning the next test for modafinil: a multisite clinical trial that will include more than 650 participants. The study will evaluate modafinil's efficacy in doses of 200 mg and 400 mg per day in combination with CBT, and results may be available by mid-2006, Dr. Montoya says.

Source

- Dackis, C.A., et al. A double-blind, placebo-controlled trial of modafinil for cocaine dependence. *Neuropsychopharmacology* 30(1):205-211, 2005. [[Abstract](#)]

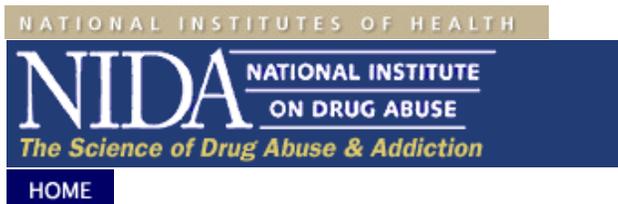
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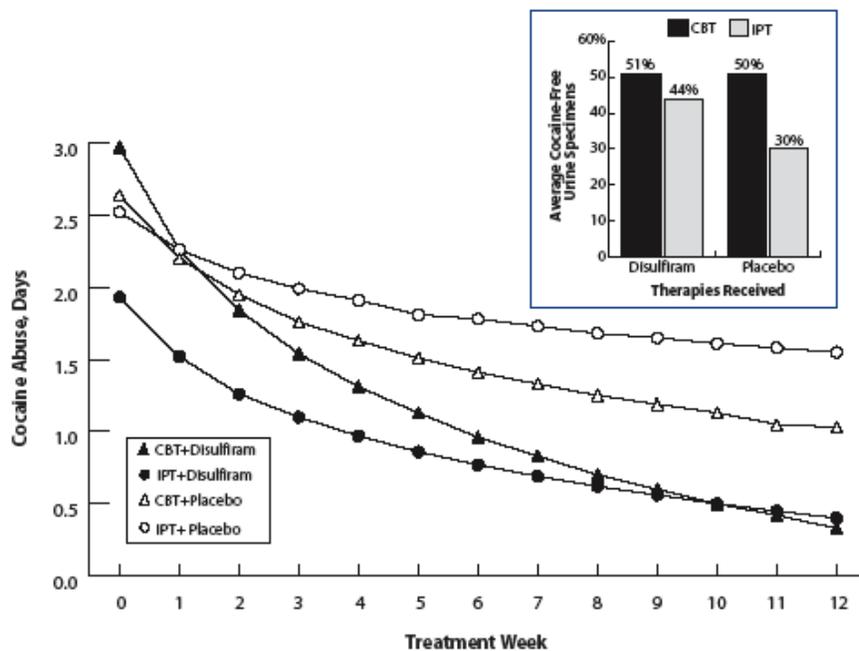
Disulfiram Reduces Cocaine Abuse

By Lori Whitten, *NIDA NOTES* Staff Writer

Disulfiram, a well-established medication for the treatment of alcoholism, has helped people addicted to cocaine reduce abuse of the drug from 2.5 days a week to 0.5 days a week on average. The finding builds on previous studies in which NIDA-funded researchers demonstrated the medication's promise in two subgroups of cocaine abusers—alcoholics and those with co-occurring opioid addiction. Their current results suggest that disulfiram is effective in treating the general population of cocaine-addicted patients, including those who are nonalcoholic. The medication's effectiveness in nonalcoholic patients adds to evidence that disulfiram works directly to reduce cocaine abuse rather than indirectly by reducing concurrent alcohol abuse. The investigators also found that, like disulfiram, cognitive-behavioral therapy (CBT) reduced cocaine abuse by 2 days.

Dr. Kathleen Carroll and her colleagues at Yale University School of Medicine in New Haven, Connecticut, treated 121 outpatients for 12 weeks. The 32 women and 89 men met the criteria for cocaine dependence specified in the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV) and reported abusing cocaine 13 days on average during the month and 2.5 days during the week before treatment. During the study, each patient received either 250 mg/day of disulfiram or placebo and participated in weekly individual sessions of behavioral therapy, either CBT or IPT (interpersonal psychotherapy). CBT coaches patients to recognize and cope with situations that tend to induce drug craving and abuse. In IPT, patients clarify and address key personal problems related to the substance abuse. On average, patients attended eight behavioral therapy sessions. The type of therapy did not affect rates of treatment completion.

Both Disulfiram and CBT Help Patients Reduce Cocaine Abuse



Over the 12-week study, patients taking disulfiram or participating in cognitive-behavioral therapy (CBT) demonstrated greater reductions in cocaine abuse than those taking placebo or receiving interpersonal psychotherapy (IPT).

All patients abused cocaine on fewer days during treatment than they had in the weeks before. The extent of recovery depended on the therapy. By the end of treatment, patients taking disulfiram reduced weekly cocaine abuse by 2 days on average, compared with 1 day for those taking the placebo, no matter which psychotherapy group they participated in. Similarly, patients who participated in CBT reduced weekly cocaine abuse by 2 days on average, compared with 1 day for IPT participants regardless of which medication they received. The data were based on self-reported cocaine abuse, but weekly urine tests generally corroborated (84 percent) patient information. More urine samples from participants receiving disulfiram and CBT (51 percent), placebo and CBT (50 percent), and disulfiram and IPT (44 percent) were cocaine negative during the study than those from participants taking the placebo and IPT combination (30 percent); the latter demonstrated the least favorable treatment outcomes.

Dr. Carroll and her colleagues verified compliance with the daily medication regimen by testing urine samples for tracers that were added to the medication and the placebo. Taking the capsules every day was associated with better outcomes among patients who received either disulfiram or placebo, although disulfiram's effectiveness remained superior to placebo's when the researchers took medication compliance into account. Dr. Carroll emphasizes that "not taking medication can undercut the benefits of all pharmacotherapies, and an important goal of behavioral therapy is improvement of medication compliance." Dr. Dorynne Czechowicz of NIDA's Division of Clinical Neuroscience, Development and Behavioral Treatment says the findings highlight the importance of integrating addiction medication and behavioral treatment. "All patients in the study participated in some form of behavioral therapy, which facilitated recovery from substance abuse and helped patients stick to the medication regimen," she says.

Disulfiram had a more pronounced benefit for patients who were not alcohol-dependent at the outset of the study and for those who abstained from alcohol during the study. Patients who drank while taking disulfiram tended to take less of the medication than those who did not drink. Instead of deterring drinking and thereby reducing cocaine abuse, the unpleasant physical consequences of mixing alcohol with the medication led patients to stop taking disulfiram when they wanted to drink or abuse cocaine. "These findings seem to validate the clinical observation that patients

have to stop drinking before they can kick cocaine abuse," says Dr. Carroll. Patients participating in CBT showed better outcomes than those in IPT, regardless of concurrent drinking. CBT, a well-established behavioral treatment, might be the best option for some patients, including those facing co-occurring alcohol and cocaine addiction, she says. Patients without concurrent alcoholism may be candidates for disulfiram, CBT, or a combination.

Disulfiram interacts with cocaine to produce an unpleasant sense of hyperstimulation. In laboratory studies, people experiencing a disulfiram-cocaine interaction demonstrated increased heart rate and blood pressure and reported anxiety, paranoia, and restlessness. Animal studies suggest that disulfiram, like cocaine, enhances the activity of the neurotransmitter dopamine. Possibly, when someone has taken disulfiram, subsequent administration of cocaine elevates dopamine to excessive levels that produce discomfort and aversion. Animal research suggests that disulfiram increases levels of dopamine by blocking an enzyme that breaks dopamine down. People with low levels of the enzyme, dopamine- β -hydroxylase (DBH), have increased dopamine activity. Hormones, as well as genes, may influence DBH levels. Researchers suspect that estrogen hormones increase DBH, attenuating the effect of disulfiram, which could explain why women seem to benefit less than men.

Source

- Carroll, K.M., et al. Efficacy of disulfiram and cognitive behavior therapy in cocaine-dependent outpatients: A randomized placebocontrolled trial. *Archives of General Psychiatry* 61(3):264-272, 2004. [[Abstract](#)]

Disulfiram May Work for Men, but Not Women

Researchers studying disulfiram, an "old" medication for alcoholism that has emerged as a potential "new" treatment for cocaine abuse, have found a possible sex difference in treatment response: Cocaine-addicted men who were treated with the medication had better outcomes than those who were not, whereas women showed no significant difference in outcome.

Dr. Kathleen Carroll of Yale University School of Medicine and her colleagues have conducted several studies on the medication's effects on cocaine abuse and have moved on to the next step—determining which types of patients benefit from the treatment. There were not enough women in their recent study (see "[Disulfiram Reduces Cocaine Abuse](#)") to analyze sex differences, so the investigators combined data from two of their other treatment studies to compare men's and women's responses to disulfiram. "We know that men and women react to cocaine differently. For example, women progress more quickly to cocaine addiction than men. Sex differences in treatment response seemed likely," says Ms. Charla Nich, lead investigator of the study.

In one study, the investigators treated alcohol- and cocaine-addicted patients with disulfiram and various behavioral therapies; in the second, they tested disulfiram in opioid- and cocaine-addicted patients under treatment with methadone. Altogether, 191 patients participated in the studies, which, when combined, had enough women (36 percent) to permit a valid comparison.

Both studies found that patient groups taking disulfiram reduced cocaine abuse compared with groups receiving placebo. But when the investigators combined and reanalyzed the data, they found that only the men in the groups responded to the medication. The reanalysis indicated that men treated with disulfiram produced a higher percentage of drug-free urine specimens than men in the placebo groups (49 versus 30 percent). Among women, however, the percentage of drug-free specimens was not significantly different with disulfiram or placebo (38 versus 39 percent).

"Our data don't conclusively prove a sex difference in the response to disulfiram," says Ms. Nich. "For that, we need studies that directly compare men and women taking the medication." NIDA's Dr. Dorynne

Czechowicz agrees that researchers should follow up on these intriguing preliminary findings, which "highlight the importance of paying attention to sex differences in medication development and other drug abuse research."

Source: Nich, C., et al. Sex differences in cocaine-dependent individuals' response to disulfiram treatment. *Addictive Behaviors* 29(6):1123-1128, 2004.

[\[Abstract\]](#)

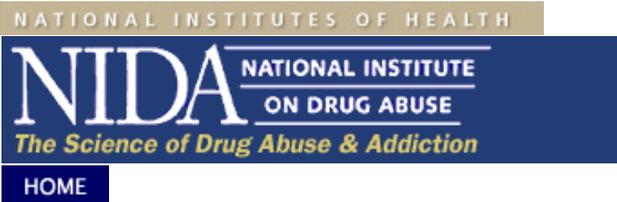
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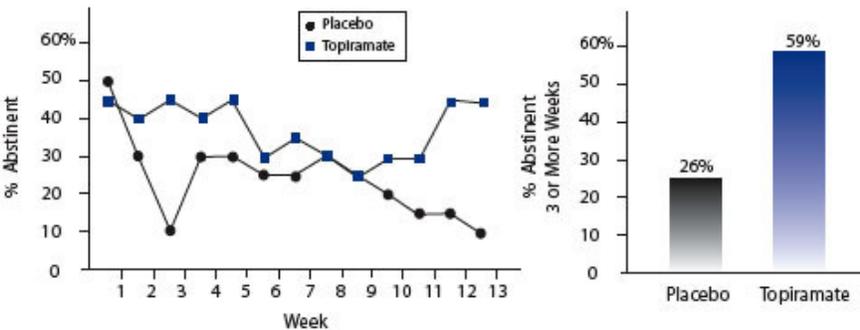
Research Findings
Vol. 19, No. 6 (May 2005)

Topiramate Shows Promise in Cocaine Addiction

By Lori Whitten, *NIDA NOTES* Staff Writer

In a small pilot study, topiramate—a medication currently used to treat seizure disorders—has helped cocaine-addicted outpatients stay off the drug continuously for 3 weeks or more. That may not seem like a long time, but previous research has shown that outpatients who avoid relapse for 3 to 4 weeks during treatment with behavioral therapy and medication have a good chance of achieving long-term cessation. In other clinical trials topiramate has helped prevent relapse to alcohol and opiate addiction; these new results with cocaine add to hopes that it may prove a versatile treatment medication for several drugs of abuse.

Topiramate Helps Outpatients Abstain From Cocaine



In almost every week of the study, more patients were abstinent in the topiramate group than in the placebo group. Of the 40 participants in the study, more patients taking topiramate achieved 3 or more continuous weeks of abstinence from cocaine.

Dr. Kyle M. Kampman and colleagues at the University of Pennsylvania School of Medicine and the Veteran Affairs Medical Center in Philadelphia treated 40 crack-cocaine-smoking outpatients, mostly African American males, for 13 weeks at the University of Pennsylvania Treatment Research Center (TRC). All participants met the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV) criteria for cocaine dependence. They were typical of the chronic, relapsing abusers who seek treatment at the TRC: They abused cocaine an average of 10 years, preferring crack to the powder form, and demonstrated the average level of drug-related problems. However, participants' abuse was atypical in one way; they were on the "milder end of the addiction severity spectrum measured by cocaine withdrawal symptom severity and days of abuse and money spent on cocaine," says Dr. Kampman. On average, participants abused cocaine 6 to 8 days and spent \$300 to \$500 on the drug in the month before treatment compared with the 10 to 13 days and \$400 to \$600 reported by most patients at the facility. Because topiramate exacerbates cocaine withdrawal symptoms, the investigators selected patients who were able to attain at least 3 days of self-reported abstinence immediately before starting the trial and who, based on their level of addiction, were not likely to enter severe withdrawal. Dr. Kampman says that about 40 percent of patients treated at the TRC experience relatively mild

withdrawal symptom severity.

After a 1-week baseline period, Dr. Kampman's team gave topiramate to 20 study participants, and placebo to the other 20. To avoid potential topiramate side effects, including sedation and slurred speech, they initiated treatment with 25 mg/d and increased it by 25 mg/d every week to 200 mg/d. They maintained this maximum dose during weeks 8 through 12, then tapered to zero during week 13. The patients also received cognitive behavioral coping skills therapy twice weekly throughout the study. The researchers verified cocaine abstinence two times a week with urine tests.

By the end of the 13th week, almost 60 percent of patients taking topiramate attained 3 or more weeks of continuous abstinence from cocaine compared with 26 percent of those taking placebo. All 40 patients showed improvement from week 1 to week 13, as reflected by lower

"Patients saw the improvement in their condition, which is an important part of recovery."

Addiction Severity Index (ASI) scores.

Patients taking the medication improved more, with average scores in the topiramate group falling by 69 percent, from 0.210 to 0.066, compared with 50 percent, from 0.162 to 0.081, in the placebo group. Dr. Kampman says the improvement in ASI scores reflects fewer days of cocaine abuse and patients' perceptions of reduced cocaine-related problems. "Patients saw the improvement in their condition, which is an important part of recovery," he says.

"Based on our findings and other work showing this medication's effectiveness as a treatment for alcohol and opiate addiction, topiramate appears to have great potential as a relapse prevention medication for people who have achieved initial abstinence from cocaine," says Dr. Kampman.

Possible Mechanisms

All addictive drugs deliver pleasurable effects by enhancing the neurotransmitter dopamine in the mesocorticolimbic pathway—areas of the brain involved in reward and motivation. Topiramate seems to change the brain's response to cocaine by indirectly influencing dopamine through two other neurotransmitter systems—gamma aminobutyric acid (GABA) and glutamate. Animal studies have suggested to scientists that either activating GABA-producing neurons or blocking glutamate receptors would lessen craving in cocaine-addicted human subjects. "Topiramate does both simultaneously, a unique dual action that appears to underlie its promise as a relapse prevention medication," says Dr. Kampman.

"These are preliminary results, but researchers are very excited about the potential topiramate has shown as a treatment for a range of problems, including addiction to several drugs and some impulse control disorders," says Dr. Frank Vocci, director of NIDA's Division of Pharmacotherapies and Medical Consequences of Drug Abuse. In addition

"Topiramate may prove an effective treatment for patients who are addicted to multiple drugs."

to its initial successes in preventing relapse in patients with alcohol, opiate, and now cocaine addiction, animal studies have suggested it may attenuate nicotine addiction. "Topiramate may prove an effective treatment for patients who are addicted to multiple drugs," Dr. Vocci adds.

Dr. Kampman plans additional studies to further evaluate topiramate as a treatment for cocaine addiction. In addition to confirming the present results, obtained with African American male crack smokers, the medication must be tried in other racial groups, women, and powder-cocaine abusers. Dr. Kampman and his colleagues also plan to study topiramate therapy for patients with coexisting cocaine and alcohol addiction—a group that comprises half of people treated for cocaine abuse.

Source:

- Kampman, K.M., et al. A pilot trial of topiramate for the treatment of cocaine dependence. *Drug and Alcohol Dependence* 75(3):233-240, 2004. [\[Full Text\]](#)

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