Research Findings
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Combination Treatment Extends Marijuana Abstinence

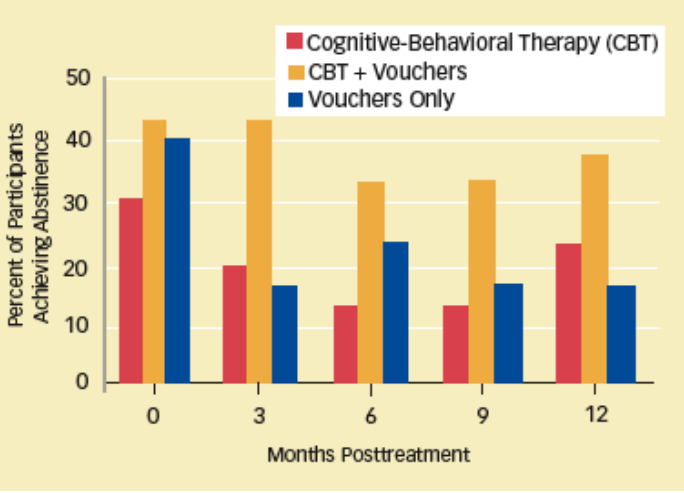
Vouchers provide a strong incentive for abstinence during treatment, and cognitive-behavioral therapy helps patients maintain abstinence after treatment ends.

BY DEBRA P. DAVIS, *NIDA Notes* Senior Editor

Treatment that combines vouchers and cognitive-behavioral therapy (CBT) may be more effective in keeping marijuana abusers abstinent in the longer term than vouchers-only and CBT-only programs. In a study by Dr. Alan Budney and colleagues at the University of Vermont, vouchers alone generated the longest periods of abstinence during 14 weeks of treatment, while vouchers and CBT in combination yielded superior abstinence during a 12-month posttreatment period.

"This is our second study demonstrating that an abstinence-based voucher program can increase positive outcomes for folks seeking treatment for marijuana dependence," says Dr. Budney, who is now at the University of Arkansas for Medical Sciences. "It provides evidence that vouchers used as adjuncts to traditional behavioral therapy can improve outcomes."

COMBINED TREATMENT HELPS MAINTAIN ABSTINENCE Over the 12 months following treatment, abstinence levels for all treatment conditions tended to decline, but levels for the combined treatment remained consistently higher than those for CBT or vouchers only.



The current study extended the earlier one by including post-treatment assessments. Vouchers provided a strong incentive for abstinence during treatment, as they did in the earlier study, but the effect of vouchers alone did not hold up as well as the combined treatment once the program ended. The higher posttreatment abstinence rates for the combined treatment relative to the vouchers-only treatment suggest that the behavioral therapy helped to maintain the effect of the vouchers, Dr. Budney says. He attributes this maintenance effect to the coping skills and motivational training provided by the CBT.

For the study, 90 adults (69 men, 21 women) seeking treatment for marijuana dependence at a university-based outpatient clinic in Burlington, Vermont, were randomly assigned to treatment with vouchers (30), CBT (30), or both (30). Most were smoking marijuana daily and presenting themselves for treatment for the first time; their average length of marijuana abuse was 14 years. Each time a participant in the vouchers-only or combination treatment submitted a marijuana negative urine sample, he or she received a voucher worth $1.50; a second consecutive negative sample earned $3.00, a third $4.50, and so on. In addition, each consecutive pair of negative samples netted a bonus voucher worth $10. A full 14-week run of weekly drug-free samples would net vouchers worth $570, which were redeemable for retail goods or services.

The CBT included 50-minute weekly sessions involving motivational counseling, drug refusal, and coping skills. To encourage cooperation with the urine screens and help equalize retention and treatment contact across the groups, researchers paid the CBT-only participants $5 in vouchers each time they showed up for a screen, regardless of their test results. Complete adherence to the sessions and screens would earn $140 over the 14-week period.

During treatment, vouchers-only patients produced the most marijuana-negative urine specimens (55 percent versus 43 percent for combined treatment and 32 percent for CBT only), weeks of continuous abstinence (mean 6.9 versus 5.3 for combined treatment and 3.5 for CBT only), and continuous abstinences lasting 6 or more weeks (50 percent versus 40 percent for combined treatment and 17 percent for CBT only). In addition to duration of abstinence, researchers measured days of self-reported marijuana abuse, changes in marijuana-related problems, and psychosocial outcomes. Participants in all three groups showed similar improvements in these areas at the end of treatment (see chart).

COMBINED TREATMENT BENEFITS

At the end of treatment and at each of four quarterly followups, patients who received the combined treatment had the highest abstinence prevalence, averaging 38 percent over the 12 months, compared with 23 percent for vouchers only and 20 percent for CBT only. The combined treatment group also had the highest rate of continuous abstinence throughout treatment and followup, 37 percent, compared with 30 percent for CBT and 27 percent for vouchers. On average, patients who received the combination treatment used marijuana 13 days out of 30 during followup, compared with 18 days among patients who received the single treatments.

VOUCHERS BOOST ABSTINENCE RATES DURING TREATMENT Participants in the vouchers-only group had better abstinence outcomes than those in the combination or CBT-only groups during treatment. All three groups reported substantial improvements over the 14-week period, but no significant intergroup differences, on measures such as the number of days participants used marijuana and how often they experienced marijuana-related problems.

	CBT	CBT+V	V
Primary abstinence outcomes			
Mean weeks of continuous abstinence [a]	3.5	5.3	6.9
% of participants who achieved 6 or more weeks of continuous abstinence [a,b]	17.0	40.0	50.0
% marijuana-negative urine specimens	32.0	43.0	55.0
Secondary self-report measures			
Number of days marijuana used during prior month [c]			
Intake	26.1	24.8	25.8
End of Treatment	8.6	9.7	11.3

Number of times marijuana used per day [c]			
Intake	3.7	4.2	3.8
End of Treatment [a]	1.6	2.7	2.6
Marijuana Problem Scale [c]			
Intake	7.9	7.8	7.8
End of Treatment	5.1	3.6	4.1

Data for all analyses were based on all participants (n = 30 per treatment condition).
Mean data reflect means adjusted for abstinence prior to treatment.
[a]CBT vs. V, comparison $p < .05$
[b]CBT+V vs. CBT, comparison $p < .05$
[c]Significant main effect for time, $p < .01$

"The findings of this study show that vouchers are effective in producing initial abstinence during treatment," says Ms. Debra Grossman of NIDA's Division of Clinical Neuroscience and Behavioral Research. "The addition of cognitivebehavioral therapy did not enhance initial abstinence, but helped maintain abstinence and produced better long-term outcomes. These findings are consistent with other studies." In two previous studies with cocaine abusers, vouchers alone performed as well as vouchers plus CBT during treatment. One of the studies indicated that CBT augmented the effects of the vouchers during the posttreatment period.

Dr. Budney says his team set the value of the vouchers arbitrarily, with the aim of keeping costs down; he believes bigger payoffs would produce better outcomes. The escalating values for consecutive negative urine samples progressively strengthened the incentive for participants to avoid lapses; each time a participant submitted a positive sample or missed a screening, the reward for the next negative sample reverted to the original $1.50 voucher. Dr. Budney suggests that future studies might cut costs by incorporating behavioral therapy only at key points in the treatment, rather than weekly throughout. In the researchers' experience, such a point often comes in the fourth to sixth week of abstinence, when patients may start to lose motivation and become vulnerable to relapse.

Fewer than half of the participants in Dr. Budney's study had positive outcomes, indicating that more effective treatments are needed for marijuana dependence. "Despite the promising findings, the majority of patients are not being sufficiently helped, and thus we need continued research focused on maximizing the outcome," Ms. Grossman notes. "Marijuana is the most commonly used illegal drug in the United States, yet among the least studied, and treatment based on abstinence-based vouchers has been found to be effective for other drugs of abuse."

SOURCE

Budney, A.J., et al. Clinical trial of abstinence-based vouchers and cognitive-behavioral therapy for cannabis dependence. *Journal of Consulting and Clinical Psychology* 74(2):307-316, 2006. [Abstract]

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Research Findings
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Sertraline Does Not Help Methamphetamine Abusers Quit

Selective serotonin reuptake inhibitors do not relieve the depressive symptoms of methamphetamine withdrawal and may produce unpleasant side effects.

BY ELIZABETH ASHTON, *NIDA Notes* Staff Writer

In a recent NIDA-funded study, the antidepressant sertraline (Zoloft) made quitting methamphetamine harder. Prescribed to relieve depression during the methamphetamine withdrawal process, sertraline produced a number of unpleasant side effects and may have interfered with behavioral interventions as well.

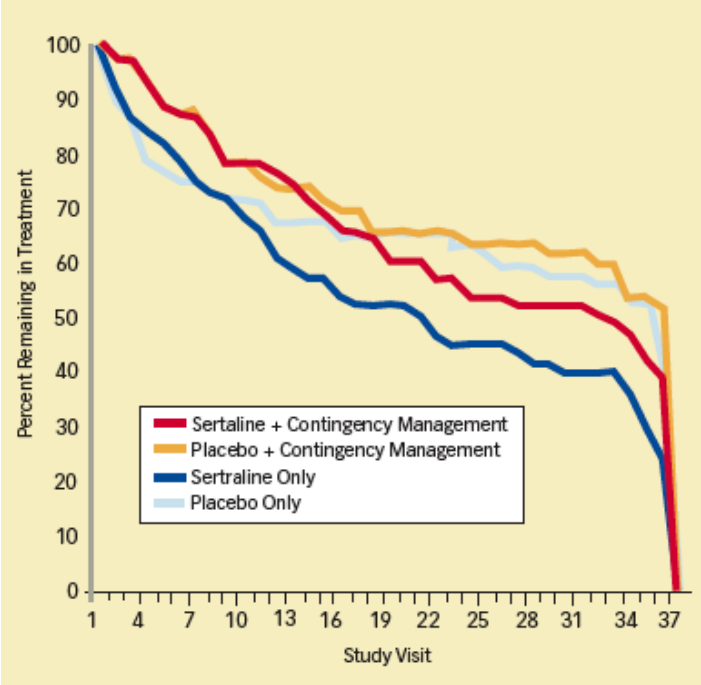
Dr. Steven Shoptaw, Dr. Alice Huber, Dr. Walter Ling, and their colleagues at the University of California, Los Angeles (UCLA) noted that methamphetamine abusers in withdrawal frequently complained of fatigue, lack of pleasure, sad mood, and persistent daytime sleepiness. The researchers hypothesized that the sertraline might alleviate these symptoms and promote abstinence because:

- methamphetamine is toxic to several pathways that produce the neurotransmitter serotonin;
- sertraline belongs to a class of antidepressant medications, the selective serotonin reuptake inhibitors (SSRI), that treat major depression by raising serotonin levels in the brain.

HYPOTHESIS DISPROVED

The team recruited 229 men and women who were addicted to methamphetamine. All were between the ages of 18 and 65, and all were seeking treatment. The trial began with a 2-week preparation process. The researchers performed baseline testing and encouraged the participants to stop taking methamphetamine with the help of twice-weekly recovery skills groups. At the end of 2 weeks, they randomly assigned the participants to one of four groups: sertraline with contingency management (CM), sertraline alone, placebo with CM, and placebo alone. All participants provided urine samples on Mondays, Wednesdays, and Fridays and attended a 90-minute psychological support group three times a week based on the Matrix Model relapse prevention program. This standardized, manual-driven model is evidence-based and incorporates social learning, behavioral and cognitive therapies, and psychological and HIV-risk education.

A TREATMENT FAILS THE TEST Participants receiving sertraline alone stayed in treatment for significantly less time than participants in all other treatment conditions.



The researchers evaluated methamphetamine use, time spent in the program, methamphetamine craving, and depressive symptoms. They found that:

- more participants in the CM program achieved 3 consecutive weeks of abstinence than participants who were not in the CM program (47 vs. 33 percent); all participants who received CM benefitted from this therapy, but its positive effects were blunted in the sertraline-with-CM group.
- fewer participants on sertraline alone, as compared with those on placebo alone (34 percent vs. 47 percent), achieved the goal of at least 3 consecutive drug-free urine samples during the study's 12-week treatment phase; participants on sertraline alone also attended fewer relapse prevention sessions and were more likely to drop out.
- craving and depressive symptoms were affected only by time since the last methamphetamine dose, and neither sertraline nor CM changed either of these two measures.

In addition, the sertraline group reported significantly more sexual, gastrointestinal (including nausea), and anticholinergic side effects.

RETHINKING WITHDRAWAL SUPPORT

The researchers concluded that treatment with sertraline did not relieve the depression associated with methamphetamine withdrawal or decrease methamphetamine use, and its side effects reduced the amount of time participants spent in treatment. Those who took sertraline also seemed to benefit less from behavioral interventions, and the researchers speculated that this might be due to the dampening effect of the medication since they had excluded all other possible factors in the statistical analysis.

The team recommends that clinicians not give SSRIs to people withdrawing from methamphetamine unless an underlying primary depressive disorder is definitively diagnosed. The recommendation reflects their own results and those of previous smaller studies with fluoxetine (Prozac) and paroxetine (Paxil), both of which were also found to have no effect on depressive symptoms during methamphetamine withdrawal. Together, these findings suggest that the etiology of mood disorder during methamphetamine withdrawal differs from that of primary depression.

The UCLA researchers suggest that clinicians offer people addicted to methamphetamine an effective behavioral intervention for depressive symptoms during the withdrawal process before prescribing any of the currently available pharmacotherapies for depression. If medication is needed, only non-SSRI antidepressants, such as bupropion, should be used.

"The SSRI sertraline is not only inefficacious for the treatment of methamphetamine dependence, but also produces a number of unprecedented side effects and has no effect on the secondary depression experienced during methamphetamine withdrawal," says Dr. Ivan Montoya, Clinical Director of NIDA's Pharmacotherapies and Medical Consequences of Drug Abuse Branch. "In addition, the negative effects of this SSRI in methamphetamine users are so powerful that they can dampen the strong therapeutic effects of contingency management. If these reactions can be traced to their source, they may help us understand the extent and duration of the effects of methamphetamine on the brain."

"We are trying to determine what people withdrawing from methamphetamine need to make withdrawal easier," Dr. Shoptaw says. "We've figured this out for other drugs, such as cocaine and heroin, but finding medications that counter the withdrawal symptoms of methamphetamine addiction is still a work in progress. We need this information so we can design treatment programs that help people get off and stay off this damaging drug."

SOURCE

Shoptaw, S., et al. Randomized, placebo-controlled trial of sertraline and contingency management for the treatment of methamphetamine dependence. *Drug and Alcohol Dependence* 85(1):12-18, 2006. [Abstract]

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NIDA's Newest Division Mines Clinical Applications From Basic Research

NIDA at Work
Vol. 21, No. 4 (October 2007)

NIDA's Division of Clinical Neuroscience and Behavioral Research

BY DEBRA P. DAVIS, *NIDA Notes* Staff Writer

NIDA's Division of Clinical Neuroscience and Behavioral Research (DCNBR) identifies, validates, and explores the clinical implications of basic science discoveries. Much of the Division's work consists of replicating results obtained in laboratory and animal studies in human subjects. A DCNBR project typically culminates in one of two outcomes: carrying a new discovery forward for development into actual interventions or referring it back to basic scientists for further investigation.

"We are uniquely positioned to uncover the factors in humans—neurobiologic, genetic, social-behavioral—that help explain the development and effects of drug abuse," says Director Dr. Joseph Frascella. "Being positioned between NIDA's basic research division and other more applied programs, our research programs inform basic science and promote the development and implementation of new medications and behavioral treatments across NIDA."

For example, building on basic research that linked nicotine acetylcholine receptors to the regulation of attention, DCNBR-sponsored researcher David Gilbert and colleagues at Southern Illinois University demonstrated that nicotine exposure and smoking cessation both influence the ability to pay attention. Now, NIDA's Division of Pharmacotherapies and Medical Consequences of Drug Abuse is exploring the clinical impact of these observations. They are testing whether bupropion and nicotine patches affect attention during smoking cessation, and whether such effects correlate with success in quitting.

In another DCNBR-supported study, Dr. Robert Risinger and colleagues at the Medical College of Wisconsin documented a pattern of fluctuating activation of the mesolimbic reward system as six cocaine-abusing men transitioned through cycles of cocaine craving, self-administration, and highs. The results, obtained with functional magnetic resonance imaging (fMRI), confirmed previous research linking those brain areas to drug self-administration in animals, and extended them by correlating them with drug abusers' subjective feelings and responses. (see "Cocaine Craving Activates Brain Reward Structures; Cocaine 'High' Dampens Them").

Neuroimaging studies comprise onethird of the Division's research portfolio. "Brain imaging has pushed drug abuse research in the last 15 to 20 years—allowing us to directly observe neural activity of awake and functioning people and obtain specific measures on how drugs affect the brain," Dr. Frascella says. Imaging studies indicate that the human brain undergoes major changes as a consequence of drug exposure and that the adolescent brain may be particularly pliant, "which may help explain why adolescence is the period when most new cases of drug addiction occur," Dr. Frascella adds. "Thus, we've become increasingly committed to using brain imaging to get a sharper picture of how

the brain changes with development and in response to active and passive exposure to drugs of abuse."

THREE BRANCHES OF CLINICAL RESEARCH

DCNBR, formed in May 2004, has three Branches:

Clinical Neuroscience: Under Dr. Steven Grant's leadership, the Clinical Neuroscience Branch focuses on how drug abuse affects the human central nervous system, including brain changes during different stages and states of abuse, such as addiction, withdrawal, abstinence, craving, and relapse. It also studies:

- The factors that make some individuals more vulnerable and others more resilient to drug abuse and addiction;
- The impact of drugs on learning, memory, judgment, and decision-making;
- Co-occurrence of drug addiction with other mental disorders;
- Neurobiological changes that result from behavioral and pharmacological treatments for drug abuse; and
- Interventions to ameliorate the negative health consequences of drugs, whether self-administered or incurred prenatally.

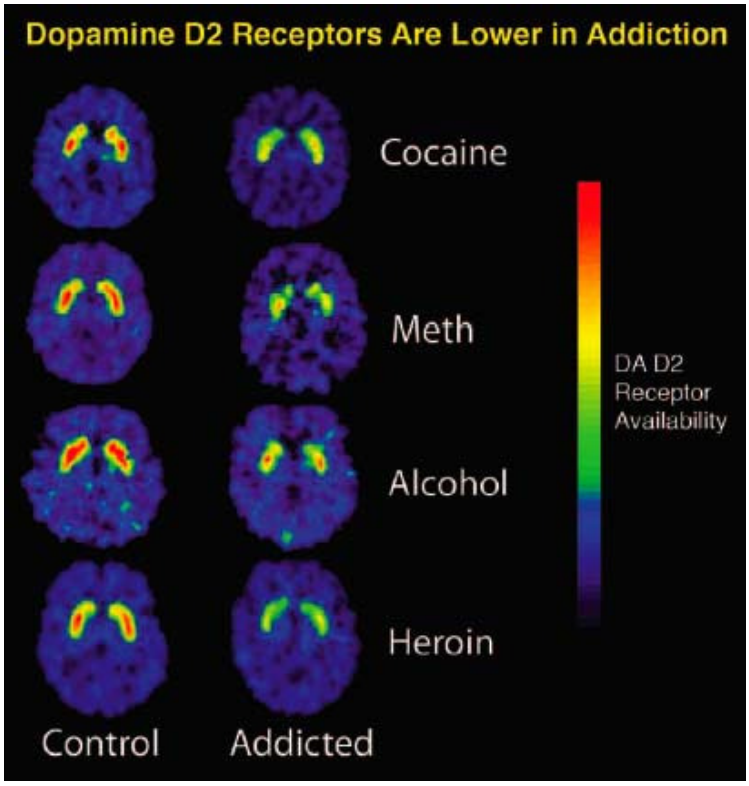
As an example of a recent Branch achievement, Dr. Grant points to a study by Dr. Martin Paulus and colleagues at the University of California, San Diego.

The researchers performed fMRI while 46 men who had been abstinent from methamphetamine for about a month took a decisionmaking test. The researchers found that patterns of activation in certain brain regions predicted with high accuracy which men would and would not relapse 1 year later (see "Brain Activity Patterns Signal Risk of Relapse to Methamphetamine"). "This use of fMRI, if replicated, could be adapted for treatment and preventive interventions," Dr. Frascella says.

Behavioral and Brain Development: Led by Dr. Vincent Smeriglio, this Branch examines drug exposure and abuse, and their health and social consequences, through the course of human development—from the prenatal period through childhood, adolescence, and young adulthood. Research focuses on:

- The effects of drugs on behavioral and brain development;
- The role of genetic, neurobiological, and environmental factors in youths' vulnerability to drug abuse and addiction; and
- The developmental effects of cooccurring exposure to drugs and infectious diseases as well as the impact of drug abuse on youths with mental illness.

BRAIN IMAGING IS A KEY TOOL IN STUDIES SPONSORED BY THE DIVISION OF CLINICAL NEUROSCIENCE AND BEHAVIORAL RESEARCH The images below—used in a recent Division presentation—show that repeated exposure to drugs depletes the brain's dopamine receptors, which are critical for one's ability to experience pleasure and reward.



One theme of the Branch's work is research to tailor drug abuse treatments to individual needs. As a recent example, a Branch-supported study by Dr. Leslie Jacobsen and colleagues at Yale University School of Medicine found that adolescent smokers experienced greater memory impairment during nicotine withdrawal if their mothers had smoked while pregnant. The study also produced fMRI evidence implicating particular brain regions in the deficits, which may be useful diagnostically as well as therapeutically.

Behavioral and Integrative Treatment: This Branch, under Dr. Lisa Onken's direction, aims to develop new and improved treatments for drug abuse and addiction, including behavioral, combined behavioral-pharmacological, and complementary and alternative treatments. The Branch designs new interventions, tests them for efficacy, and evaluates strategies to improve treatment engagement, adherence, and retention—key factors in success. The Branch also supports research that prepares treatments for use in community settings, where cost, training, and fit with existing services can be constraints.

"Behavioral therapies that work well in a research setting cannot necessarily be taken into the community. Oftentimes, they are too complicated and expensive, and require extensive training for clinicians," Dr. Frascella notes. One way of developing a community-friendly treatment is to identify the active ingredients of effective treatments, explains Dr. Onken. "In this way, we may be able to create more streamlined treatments that retain their potency. Another novel approach to making a treatment more community-friendly is to use computers to help counselors deliver treatment. For example, Dr. Kathleen Carroll at Yale University is testing the efficacy of computer-assisted cognitive-behavioral therapy in preventing cocaine relapse.

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