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Medications Development Division Nurtures the Creation of New Addiction Treatments

NIDA At Work: NIDA's Division of Pharmacotherapies and Medical Consequences of Drug Abuse
Vol. 20, No. 6 (July 2006)

By Lori Whitten, *NIDA NOTES* Staff Writer

In the Anti-Drug Abuse Act of 1988, Congress mandated NIDA to promote the development of medications "to treat the symptoms and disease of drug abuse." Research by NIDA-supported scientists and others had by then made clear that drug abuse is a neurological disorder treatable by pharmacotherapy, but only three anti-addiction medications were available (disulfiram, methadone, and naltrexone), all developed in the 1960s and early 1970s. Congress recognized the need for Federal leadership and, because of NIDA's resources and expertise, entrusted the Institute with facilitating the development of pharmacotherapies to treat addiction.

With an initial appropriation of \$8 million, NIDA launched a Medications Development Program that same year and formally established the Medications Development Division in 1990. From its beginning, the Division has supported and coordinated academic and private sector scientists engaged in every stage of medications development—from the creation of new compounds in the laboratory to the testing of products in clinical trials. The Division's efforts have been instrumental in bringing buprenorphine and buprenorphine-naloxone—safe and effective treatments for opiate addiction, the latter suitable for office-based therapy—to the Nation's clinics and pharmacy shelves. Among other current priorities, the Division supports work to establish the safety and efficacy of the smoking-cessation aids nicotine replacement and bupropion for people with psychiatric conditions, pregnant women, and adolescents.

Under the leadership of Division Director Dr. Frank Vocci, Dr. Nora Chiang, Chief of the Chemistry and Pharmaceutics Branch, manages laboratory research grants designed to develop new compounds with therapeutic potential; Dr. Jane Acri, Director of the Addiction Treatment Discovery Program, leads a multidisciplinary team that screens compounds and advances those with therapeutic potential into testing for safety and efficacy; and Dr. Ahmed Elkashef, Chief of the Clinical/Medical Branch, coordinates the evaluation of data from clinical trials.

DUAL STRATEGY GUIDES NIDA's DRUG ABUSE MEDICATION DEVELOPMENT	
Test Existing Medications Researchers evaluate marketed medications whose chemical properties suggest they might reduce drug abuse.	
Characteristics Medications are already approved for marketing for other conditions. Known safety profile. Less expensive to develop than new compounds. Short time to gain approval for marketing.	Examples Methadone and buprenorphine, widely used for opiate addiction treatment, were first used as analgesics. Bupropion, prescribed for nicotine addiction, was first used for depression. Currently being evaluated for cocaine abuse: modafinil (narcolepsy), topiramate (seizures), disulfiram (alcohol dependence), bupropion. Currently being evaluated for cocaine and methamphetamine abuse: selegiline

	(Parkinson's disease), baclofen (muscle spasms), ondansetron (prevents chemotherapy-related nausea).
Develop New Medications	
Researchers investigate the therapeutic potential of new compounds.	
Characteristics	Examples
Lengthy process of discovery. Relies on behavioral, biochemical, and neuroimaging experiments with ultimate translation of laboratory findings to clinical studies.	Two compounds (GBR 12909, NS2359) that generate modest and long-lasting increases in dopamine have reached human safety evaluation. NIDA stopped testing of GBR 12909 because of cardiovascular concerns, but continues to evaluate NS2359.
Takes advantage of breakthrough discoveries in neuroscience. Potential for discovering medications that affect multiple addictions.	A compound (CP-154,526) that blocks the neurochemical corticotropin-releasing factor 1 attenuates stress-induced relapse to cocaine and heroin in animals.

The Division pursues a dual strategy that balances the need to advance scientific discovery and the need to find safe and effective treatments as rapidly as possible. On one track, NIDA intramural and funded scientists seek new medications. Researchers in the Cocaine Treatment Discovery Program have identified and evaluated more than 3,000 compounds whose molecular characteristics or performance in animal studies suggested they might reduce cocaine craving and prevent relapse. This process has, for example, identified a new compound called JD_{Tic}, which has anti-stress and antidepressant characteristics and prevents relapse in animals, and is developing the agent for potential clinical testing. Under the second approach, NIDA has established a network of clinical investigators to screen marketed medications with neurochemical effects that suggest a potential for reducing drug abuse (see [chart](#)). Among 65 medications examined so far, eight potential treatments for cocaine abuse—including topiramate, disulfiram, and modafinil—have advanced to the confirmatory stage of clinical trials in cocaine-dependent patients.

Throughout the 1990s, as well, the Division advanced research on vaccines that prevent drugs from reaching the brain. A vaccine to prevent cocaine addiction and another for nicotine abuse are now being tested for safety and efficacy.

Because medication development is an enormously complex and costly enterprise, the Division collaborates with other Government agencies, particularly the U.S. Food and Drug Administration (FDA), and the pharmaceutical industry. The relationship with FDA has been vital to overcoming scientific and regulatory barriers to evaluating new medications for opiate addiction and shepherding buprenorphine through the necessary approvals. The Division's relationships with industry frequently have been formalized as Cooperative Research and Development Agreements (CRADAs). In this type of arrangement, NIDA provides expertise, equipment, and facilities to test a corporate-owned compound as a potential pharmacotherapy; if the results are as hoped and a marketable medication results, the company maintains the commercial rights and NIDA retains a license to perform further research. Under a current CRADA, NIDA is working with Teva (formerly IVAX Corporation) to determine whether talampanel, a compound in clinical testing for treatment of epilepsy, may help cocaine abusers overcome their addiction.

Dr. Vocci says, "Our first 15 years have taught us the importance of developing treatments that patients will accept and readily use, and that medications are most effective in combination with psychotherapy or counseling. We now apply these lessons to all efforts." Looking ahead, Dr. Vocci lists Division goals for the next 5 years:

- Validate the effectiveness of promising medications for cocaine addiction;
- Advance compounds that have shown promise in animal research to clinical testing in people who are addicted to methamphetamine and marijuana;

- Advance a new smoking cessation aid into clinical trials (possibly selegiline, which has shown promise in preliminary studies);
- Determine optimal immunization schedules for nicotine and cocaine vaccines and obtain FDA approval;
- Identify medications to curb cognitive problems that limit patients' ability to benefit from behavioral therapies;
- Continue preliminary clinical studies of interactions between HIV infection, antiviral therapies, and anti-addiction pharmacotherapies and identify interventions that slow the progress of the infection in drug abusers; and
- Collaborate with other branches of NIH and industry partners to test a vaccine for hepatitis C among drug-abusing populations.

"Bringing a new medication to market is a lengthy and expensive endeavor, but physicians and patients need a choice of many treatment options. The progress in anti-addiction pharmacotherapies shows the strength of the dual strategy of medications development, which will continue to provide us with the best hope for novel approaches to treating addiction," says Dr. Vocci.

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Community-Based Treatment Benefits Methamphetamine Abusers

Research Findings
Vol. 20, No. 5 (April 2006)

A large California study finds favorable effects for inpatients and outpatients; women's gains are larger.

By Lori Whitten, NIDA NOTES Staff Writer

Methamphetamine abusers can achieve long-term abstinence with the help of standard community-based drug abuse treatment. Nine months after beginning therapy, 87 percent of patients treated for heavy or long-term methamphetamine abuse in California outpatient and residential programs were abstinent from all drugs, according to a NIDA-supported analysis. "In the public dialogue, and even among professionals in the field, one sometimes hears that meth abuse is 'not treatable.' But that view is not borne out by recent clinical trials or our study, which shows that community-based treatment reduces drug abuse and other problems," says lead investigator Dr. Yih-Ing Hser.

Dr. Hser and colleagues at the University of California, Los Angeles analyzed data from the California Treatment Outcome Project (CaTOP), an ongoing study that has followed the progress of adult substance abusers treated at 43 outpatient and residential programs throughout the State since April 2000. The researchers focused on 1,073 patients who reported that methamphetamine abuse was their primary drug problem (572) or that they had abused the stimulant regularly for at least 1 year before beginning treatment (501). Most were in their 30s or younger, White or Latino, unemployed, and on public assistance; most had an arrest history. They had abused methamphetamine for about 9 years, on average, and nearly one-quarter (22 percent) reported injecting drugs at least once. Although 64 percent had children aged 18 or younger, one-third of parents did not live with their children in the month before beginning treatment. One parent in five reported that a child protection court had ordered that his or her children live with someone else, and 6.3 percent had their parental rights terminated by the State.

The patients received the addiction treatment services routinely provided by each program. These usually included group therapy, with an average of 69 drug-related and 51 alcohol-related sessions during the first 3 months of treatment. On average, the patients also received 22 sessions on dealing with mental health symptoms and 13 addressing psychosocial problems, including family, parenting, and employment.

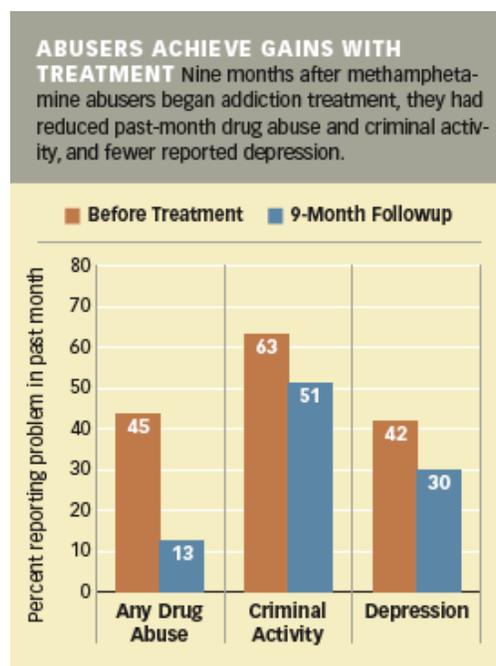
More than 60 percent of the patients completed 3 months of treatment. Among all the patients in the study—those who finished 3 months and those who did not—the average reported frequency of methamphetamine abuse fell from 2.7 to 0.5 days per month from the start of treatment to 9 months later. The portion who were abstinent from all drugs rose from 55 percent to 87 percent in the same interval, and 68 percent were abstinent and also not incarcerated. Patients improved in all areas—drug and alcohol abuse; mental health symptoms; and employment, family, and legal problems—except one: men's medical problems.

"Because methamphetamine abusers respond to treatment, getting them into therapy is a top priority. For women, there is added urgency to help them avoid exposing the children they may bear to the consequences of prenatal drug exposure."

Dr. Thomas Hilton of NIDA's Division of Epidemiology, Services and Prevention Research says these findings should reassure professionals working in the addiction, social services, and criminal justice fields that current therapies work for these troubled patients. "Dr. Hser's findings suggest that treatments available in the community help meth abusers reduce drug abuse and start to get their lives back on track, echoing prior research," he says.

WOMEN'S EXPERIENCES

Dr. Hser's findings confirm gender differences seen in other studies: Women began treatment with more severe psychosocial problems than men (see [chart](#)) and benefited more. Although treatment retention levels were similar for the two sexes, the women made greater gains in the areas of family relationships and medical problems, while achieving similar improvements in all other areas at the 9-month followup. The women's better outcomes may have resulted in part from more intensive services (see [chart](#)); as well, Dr. Hser says that many women in the study had a powerful motivator—family. "Many were trying to maintain or regain custody of their children by demonstrating improvement during treatment. Others had 'hit bottom,' saw how drug abuse was hurting their families, and decided to make a change," she says.



WOMEN RECEIVE MORE SERVICES IN SOME AREAS For some problems, women received more services than men during the first 3 months of treatment.

Services	Women (No. of interventions†)	Men (No. of interventions†)
Employment*	4.6	2.3
Family‡	6.5	4.6
Mental Health‡	23.6	19.9
Parenting*	4.2	1.7

†Includes counseling sessions, medical appointments, and prescriptions.
*Outpatients. ‡Outpatient and residential.

"Because methamphetamine abusers respond to treatment, getting them into therapy is a top priority. For women, there is added urgency to help them avoid exposing the children they may bear to the consequences of prenatal drug exposure," says Dr. Hser.

MEN, WOMEN EXPERIENCE DIFFERENT PROBLEMS Women beginning treatment for methamphetamine abuse reported more psychosocial problems, while men reported more crime and criminal justice involvement.

Family and Social Circumstances	Women, % (n=567)	Men, % (n=506)	Total, % (N=1073)
Children living with someone else by court order	29.3	9.9	20.1
Parental rights terminated	10.1	2.2	6.3
Family abused substances	21.7	10.5	16.4
Physically abused (past month)	5.5	1.8	3.7
Sexually abused (past month)	2.5	0.6	1.6

Employed	23.8	43.9	33.3
On public assistance	63.1	37.0	50.8
Criminal Justice System Involvement			
On parole	4.4	12.7	8.3
On probation	32.3	37.6	34.8
Ever arrested	76.7	88.3	82.2
Arrest in past year	36.7	45.1	40.6
Criminal activity (past month)	55.2	71.7	63.0
Psychiatric Symptoms (Past Month)			
Serious depression	38.8	29.8	34.6
Difficulties with understanding, concentrating, remembering	36.2	26.5	31.6
Suicidal thoughts	11.3	6.3	9.0
Prescribed psychiatric medicine	21.3	15.4	18.6

Dr. Hser and her colleagues continue to analyze CaTOP data, aiming to determine the longer-term impact of therapy and identify ways programs can improve outcomes. "Enhancing psychiatric, parenting, and employment services would better match patients' needs, and my team plans to study the relationship between help for these problems and longer-term outcomes," says Dr. Hser. They also plan to investigate whether women-only treatment is more effective for pregnant methamphetamine abusers than mixed-gender programs.

"The field needs more research following meth abusers over time to get a picture of the long-term outcomes of treatment, relapse episodes, and whether these patients require additional support to sustain gains made during therapy," says Dr. Hilton. "Because the availability of community health and social services varies across States, we cannot generalize the findings from one State, such as California. We need data from across the country," he adds.

Source

Hser, Y.-I.; Evans, E.; and Huang, Y.-C. Treatment outcomes among women and men methamphetamine abusers in California. *Journal of Substance Abuse Treatment* 28(1):77-85, 2005. [[Abstract](#)]

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Research Findings
Vol. 20, No. 5 (April 2006)

Bupropion Helps People With Schizophrenia Quit Smoking

Data address physicians' concerns about prescribing the medication for smokers with schizophrenia.

By Lori Whitten, NIDA NOTES Staff Writer

The smoking-cessation aid bupropion is safe and effective for people with schizophrenia, researchers at Massachusetts General Hospital and Harvard Medical School have found. In a NIDA-funded study of smokers with schizophrenia, those who took sustained-release bupropion were more likely to stop smoking by their quit date and to achieve continuous abstinence for a month than those who received placebo, and they also remained abstinent longer. The researchers did not observe any adverse interactions with the patients' antipsychotic medications or exacerbation of psychiatric symptoms.

The U.S. Food and Drug Administration (FDA) approved sustained-release bupropion as a treatment for depression in 1996 and as a smoking-cessation aid in 1997, but physicians have been reluctant to prescribe the medication for patients with schizophrenia. "Although 75 to 85 percent of people with schizophrenia smoke, we have lacked data on treatments for nicotine addiction in this population, resulting in many not receiving advice to quit," says Dr. A. Eden Evins, lead investigator of the study.

Dr. Evins and her colleagues treated 53 patients, aged 24 to 66, for nicotine dependence. When they began treatment, the patients smoked 30 cigarettes a day, on average, and typically had made two previous quit attempts. During the 12-week study, each participated in weekly sessions of group cognitive-behavioral therapy (CBT) and received either 300 milligrams a day of sustained-release bupropion or placebo. The CBT program was adapted for patients with schizophrenia from standard smoking-cessation therapy. Each patient visited the clinic once a week for evaluations of smoking (self-report confirmed by expired air carbon monoxide measurements), changes in psychiatric symptoms, medication compliance, and side effects.

Therapists encouraged all patients to set a quit date before the 4th week of treatment, and 36 percent of those taking bupropion—compared with 7 percent of those on placebo—achieved this goal, demonstrating abstinence at the 4-week assessment. Sixteen percent of patients in the bupropion group, but none taking placebo, achieved abstinence throughout the last month of treatment. Among patients who were not abstinent at the end of the study, those in the bupropion group reduced the average number of cigarettes smoked daily from 34 to 9, compared with a drop from 25 to 15 in the placebo group.

Bupropion was generally well tolerated and did not exacerbate the symptoms of schizophrenia. Depression and flat affect, as well as cognitive function, tended to improve among patients taking the medication. Common side effects experienced by people taking antipsychotic medications, such as muscle stiffness and shuffling gait, were not worsened by nicotine abstinence or bupropion. About 80 percent of patients in both the medication and placebo groups kept to their regimens throughout the study.

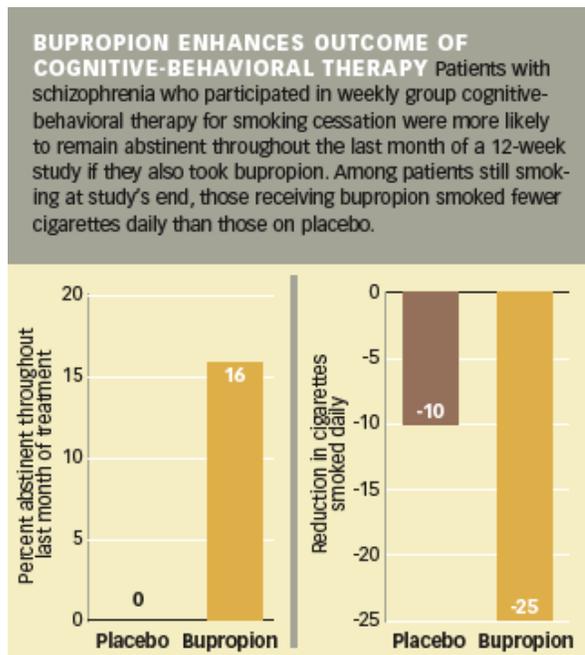
The findings confirm promising results from several smaller studies. Dr. Evins points out that the relapse rate was high after treatment discontinuation—75 percent of those who were abstinent at week 12 had relapsed to smoking at the 3-month followup. Only about 4 percent of patients in either group were abstinent in the week before the 3-month followup. Other studies of bupropion in the general population have shown that about half of patients tend to relapse after treatment

discontinuation. "Patients with schizophrenia may need a longer course of bupropion with CBT or a combination of bupropion and nicotine replacement therapy to avoid relapse," says Dr. Evins.

Source

Evins, A.E., et al. A double-blind placebo-controlled trial of bupropion sustained-release for smoking cessation in schizophrenia. *Journal of Clinical Psychopharmacology* 25(3):218-225, 2005. [Abstract]

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(April 2006)**



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