

# New Ways to Loosen Addiction's Grip -- NYTimes

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New Ways to Loosen Addiction's Grip  
By ANAHAD O'CONNOR

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When Aaron, a 33-year-old writer from New York, decided to get help for his five-year addiction to painkillers, there was really only one option.

Every morning, he visited a local clinic for a small cup of methadone, the standard treatment for addiction to heroin and other opiates since the 1960's. But his life soon revolved around the clinic's hours, he said, and the daily routine was humiliating.

"I had to stand in line with a bunch of people who were talking about getting high," and take a urine test for illicit drugs each week, said Aaron, who spoke on the condition that his last name be withheld.

Then, a year and a half ago, a quiet scientific advance gave Aaron – and 60,000 other Americans – a chance to break their dependence on drugs without shame.

Buprenorphine, made by Reckitt Benckiser and sold under the brand name Suboxone, became the first prescription medication for people addicted to heroin or painkillers.

The small orange tablet is available by prescription at any neighborhood pharmacy. It relieves symptoms of opiate withdrawal like agitation, nausea and insomnia.

But unlike methadone, buprenorphine (pronounced byoo-pre-NOR-feen) is only weakly addictive, and is thus less tightly regulated. Above a certain dosage, more will not produce a high, so it has a far lower risk of overdose than methadone. And once a patient has taken a pill, the effects last for about three days, greatly decreasing the chance of a relapse.

Serious drug addiction is a problem that afflicts more than 10 million Americans. The grip of hard-core drugs like heroin and cocaine is notoriously stubborn, and relapse rates are staggering. Rehabilitation programs have only limited success. Dropout rates are high, and even many addicts who do stay in rehab slide back into using drugs periodically.

But buprenorphine is the first of a new generation of prescription drugs that is changing the landscape of addiction treatment, providing new hope and moving addiction from clinics and rehab centers, long seen as magnets for junkies, pushers and gloom, into the comfort of the doctor's office.

In laboratories around the country, researchers are creating prescription medications to alleviate craving or blunt euphoria, and working on vaccines that can prevent people from getting high by mopping up a drug in the bloodstream. In some cases, the research is already bearing fruit: Campral, a new prescription drug to block cravings for alcohol, was approved by the Food and Drug Administration last week. Other medications are likely to enter the market within a few years.

At some point, experts say, the new treatments will allow addiction to be viewed – and treated – like any other chronic, relapsing disease.

"There has been a revolution in the way we view addiction," said Dr. Charles A. Dackis, chief of psychiatry at the University of Pennsylvania Medical Center–Presbyterian. "It's being seen now as a disease of the reward centers of the brain, much like pneumonia is seen as a disease of the lungs."

The new treatments arrive as scientists are beginning to unravel the underlying neurobiology of drug dependence.

Researchers have known for some time that all substances of abuse, including nicotine, alcohol, cocaine, marijuana and heroin, activate the same pleasure pathway in the brain. But they are now finding that many drugs cause subtle changes in brain activity that remain for weeks, months or years. Such alterations, studies have found, help unleash the cravings that can plunge recovered users back into the throes of addiction long after their last puff or snort.

"We now know the changes these drugs cause in the brain at the molecular level that lead to addiction," said Dr. Eric J. Nestler, chairman of the department of psychiatry at the University of Texas Southwestern medical center. "Because of imaging studies we know where to focus, and that's a brand new advance."

Although experts acknowledge that drug abuse begins as a voluntary behavior, many argue that at some point a perilous line is crossed. Brain cells that are repeatedly assaulted by addictive drugs change shape. The brain's reward pathway – the same, primitive system that by

evolutionary design makes basic drives like sex and eating pleasurable – is hijacked. The urge to get high is insatiable. In experiments, lab animals will press a lever for cocaine until it kills them.

Each drug manipulates the reward circuitry in a different way, but in brain scans every drug lights up a link in the neural pathway called the nucleus accumbens, the universal site of addiction. After repeated bombardment by drugs, the system loses sensitivity to more natural rewards.

"These drugs stimulate the reward circuitry so acutely that over time they disrupt it," said Dr. Dackis, adding that addiction is so lethal because it tricks the brain into acting as if the drugs were necessary for survival.

Over the years, chemical substitutes that mimic addictive drugs, activating the reward circuitry and reducing cravings, have had the most success in treating addiction. Methadone, a reddish liquid first used as a maintenance treatment for heroin addicts in 1964, has long been considered the gold standard. Chemically, it is not so different from heroin. It binds to the same receptors, gradually stimulating them. Patients say they experience a warm glow, though not the euphoric daze of heroin, the feeling of being wrapped in God's warmest blanket.

In its time, methadone was considered a breakthrough: It got people off heroin, reduced fatal overdoses and slowed the spread of infectious diseases through dirty needles. But it became clear that methadone had its own problems. Like heroin, it was strongly addictive. It was classified by the Drug Enforcement Administration as a Schedule 2 drug, in the same category as cocaine and PCP. And by law, it had to be distributed by special clinics that were so bathed in stigma that several states banned them. Former Mayor Rudolph W. Giuliani of New York declared five years ago, when he was in office, that methadone programs encouraged people to trade one addiction for another, and should be shut down.

Between 180,000 and 200,000 Americans are on methadone, said Dr. David M. McDowell, director of a program at Columbia University that helps people make the transition from methadone to buprenorphine, then refers them to other doctors for private care. In New York, 36,000 people are on methadone.

"The most stigmatized thing in this world is methadone," said Dr. Edwin A. Salsitz, director of Beth Israel Medical Center's methadone program in New York. "There is nothing people try to hide more than being on methadone. They don't want to be seen going into a clinic. They won't tell anyone they're taking it."

Methadone's limitations prompted experts to look for medications that were less likely to place recovering addicts in a stranglehold. What they found was buprenorphine. Like methadone, it is a chemical

substitute for heroin. But it activates receptors so weakly that it has a better safety profile and many users can be slowly weaned from it, leaving them drug-free.

"Buprenorphine is the most important advance certainly in heroin and opiate treatment if not all addiction treatments in the last 30 years," said Dr. Alan I. Leshner, a former director of the National Institutes of Drug Abuse.

In the brain, buprenorphine pries heroin from opiate receptors, binds tightly for two or three days, then produces just enough stimulation to relieve withdrawal symptoms. It is not perfect by any means. One drawback is that for some longtime heroin users, its effects are too weak, and methadone ends up as their only alternative. But for those who can take it, buprenorphine's effects last longer than methadone's, experts say, which drives the likelihood of relapse down sharply.

"If you get stressed out and decide you want to get high, you can go see your dealer but you're wasting your money because there's that three-day safety cushion where buprenorphine is blocking the receptors," Dr. McDowell said.

Last year, only 5 out of 43 patients at Dr. McDowell's center had relapsed after their first six months on buprenorphine, an 88 percent success rate; on methadone, treatment programs for most forms of drug addiction have less than a 50 percent success rate after six months, he said. In France, where buprenorphine has been on the market less than 10 years, fatal overdoses from heroin and other opiates have fallen almost 80 percent. "In the field of addiction treatment, those figures are just unbelievable," he said.

Doctors in the United States wrote 80,000 prescriptions for buprenorphine in 2003, a number that is expected to soar in the coming years. Lured by the prospect of privacy, many heroin and opiate abusers are seeking help for the first time. Others are switching from methadone.

Dr. Chadd A. Herrmann, a psychiatrist in Manhattan, said he has received about 20 telephone calls in the last three weeks from people looking for buprenorphine. He had to turn them away, he said, because he was still awaiting authorization to prescribe it. In New York, doctors who want to prescribe buprenorphine are required to take an eight-hour training course and then receive approval from the state.

Dr. Herrmann, whose practice is on Fifth Avenue, said many of the people who called did so "because of my address." He added, "They make it really clear that they don't want to be in a program or clinic in some other part of the city."

Perhaps buprenorphine's biggest draw, said Roberta P. Sales, a nurse coordinator at the Columbia program, is that it frees addicts from the

methadone clinic. With a prescription, they can get a month's supply of the medication at the pharmacy. The cost is about \$5 to \$10 a day.

"How can you possibly work or go to school when the primary focus of your day is going to a methadone program?" she said. "With buprenorphine, I've had patients literally break down and cry because they can travel to another state and see their family for the first time in years."

For all its promise, buprenorphine, whose use is confined to opiates, will help only a fraction of the Americans who abuse drugs. Researchers say their focus now is on finding new treatments for a wide variety of drugs. They hope to find medications that are not simply chemical substitutes but eliminate dependence altogether. In some laboratories, researchers are working on developing medications that do away with the cravings that make abstinence from any drug a struggle.

"It's never as simple as just washing the drug out of your body," said Dr. Anna Rose Childress, a research associate professor of psychology at the University of Pennsylvania medical school.

The shift toward treating cravings came largely from imaging studies. Researchers found that when a recovering addict was shown slight cues or reminders of an old drug habit – an antidrug advertisement, for example, a cigarette or a syringe – it set off intense activity in the brain's reward circuitry, and produced an urge to relapse.

"Often, this is what pulls people back in," Dr. Dackis said.

Campral, the anticraving medication, made by Merck and approved for alcoholism by the F.D.A. last week, appears to dampen that response by elevating levels of GABA, the brain's major inhibitory neurotransmitter. Dr. Childress believes that GABA helps rein in the reward circuitry that drives people to seek drugs and other pleasurable experiences. Campral has been used in Europe for several years.

At least two other drugs that increase GABA, topiramate and baclofen, seem to curb cravings for cocaine, heroin, cigarettes and alcohol. Dr. Childress, who is involved in clinical trials of baclofen for cocaine, said the medications may even help conquer compulsive behaviors like pathological gambling and sexual compulsion. Scientists have also found that the prescription medication modafinil, used for sleep disorders, can blunt the euphoria of cocaine.

Still other scientists are trying to solve two problems common among substance abusers: They often forget to take their medications, and even those who stay in recovery end up "slipping" periodically.

Vaccines, some researchers believe, may provide answers to these problems.

At Yale and Columbia, for example, researchers are testing a vaccine that uses molecules of cocaine bound to harmless pathogens. When the vaccine is injected into the body, the immune system responds by producing antibodies to the cocaine and to the pathogen it is paired with. After a handful of immunizations over the course of three months, the user has enough antibodies to prevent at least three times the typical dose of cocaine from reaching the brain.

"The people that make significant amounts of antibodies say that cocaine isn't what it used to be, and the people who make the highest levels of antibodies stop using it altogether," said Dr. Thomas Kosten, a professor of psychiatry and medicine at the Yale medical school.

In Australia, scientists are experimenting with a similar vaccine that blocks nicotine.

It may be years, experts concede, before the promise of vaccines, anticraving drugs and other new treatments can be fully realized. And if the prospect of a world without drug addiction seems too good to be true, it just might be. None of the drugs is a magic bullet. Psychotherapy will still be needed to help addicts repair frayed relationships and overcome psychological dependence. Moreover, an addict who is determined to get high, experts say, can counteract even the most effective medication – by not taking it.

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"Endeavor to persevere"  
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