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# An Anti-Addiction Pill?

**By BENOIT DENIZET-LEWIS**

Last month, the Picower Institute for Learning and Memory at the Massachusetts Institute of Technology was host to a conference about addiction for a small, invitation-only crowd of neuroscientists, clinicians and public policy makers. It was an unusual gathering. Addiction conferences are usually sober affairs, but M.I.T. offered a lavish cocktail reception (with an open bar, no less). More important, the conference was a celebration of the new ways scientists and addiction researchers are conceptualizing, and seeking to treat, addiction. While many in the treatment field have long called addiction a "disease," they've used the word in vague and metaphorical ways, meaning everything from a disease of the mind to a disease of the spirit. Many assumed that an addict suffers from a brain-chemistry problem, but scientists had not been able to peer into our heads to begin to prove it.

Now they can, using advances in brain-imaging technology. And they tend to agree on what they see, although not necessarily on how to fix it: addiction — whether to alcohol, to drugs or even to behaviors like gambling — appears to be a complicated disorder affecting brain processes responsible for motivation, decision making, pleasure seeking, inhibitory control and the way we learn and consolidate information and experiences. This new research, in turn, is fueling a vast effort by scientists and pharmaceutical companies to develop medications and vaccines to treat addiction. The National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism are studying, or financing studies on, more than 200 addiction medications.

The search for pharmacology to treat addiction is not new. The history of addiction treatment in America is rife with supposed miracle medications and "cures," most of which turned out to be useless. But there are a handful of drugs — some developed in the mid-1900's, others in the last decade or so — that are being used to help addicts quit. For heroin addiction, there's methadone and buprenorphine, both of which bind to and activate opioid receptors in the brain. Each essentially substitutes for heroin by activating the same brain receptors as the drug, but many addiction doctors prefer buprenorphine, which the Food and Drug Administration approved in 2002, because it causes less of a high and less dependence.

For alcohol, Antabuse, which makes people physically ill if they drink, has been on the market since 1948, although it isn't widely used. Addiction scientists are more hopeful about another anti-alcoholism drug, naltrexone, which was originally developed to treat opioid addiction but was approved for the treatment of alcoholism in 1994. Studies have found it can help some alcoholics abstain from or cut down on their drinking, and two pharmaceutical companies recently teamed up to produce Vivitrol, a long-acting, injectable form of naltrexone, which the F.D.A. approved in April. Some hope Vivitrol will sidestep a huge challenge facing those seeking pharmacological solutions

for addiction: unless they're getting high from it, most addicts aren't model medicine takers. (Vivitrol requires a monthly shot from a doctor.)

None of the medications currently approved to treat addiction are perfect, and in many ways they are the products of some of our earlier advances in neuroscience. In the last few years, though, scientists say they've learned a staggering amount about how addiction affects the brain, and neuroscientists and other addiction researchers are eagerly testing and developing a new generation of anti-addiction medications.

"In 5 or 10 years, we will be treating addiction very differently," predicts Nora Volkow, a psychiatrist and the director of the institute on drug abuse, who attended the M.I.T. conference and presented a lecture, "Addiction: The Neurobiology of Free Will Gone Awry," in an intense and rapid-fire speaking style. (Besides being a leading American thinker about addiction, Volkow is the great-granddaughter of Leon Trotsky.) What Volkow means is that in a decade or so, we may actually start treating addiction effectively. Addiction is one of the nation's biggest public health problems, costing $524 billion (including lost wages and costs to the public health care and criminal justice systems) each year. The majority of the estimated 20 million alcoholics and drug addicts in America (and millions more compulsive gamblers, overeaters and sex addicts, if you accept an expanded understanding of addiction) never get help. Those who do often relapse repeatedly, sometimes returning to treatment centers 5, 10 or 15 times (if they don't die first). And many of those who "recover" simply trade one addiction for another — addicts call this dance "switching seats on the Titanic."

The Dopamine Connection

For much of the past two decades, Volkow and other neuroscientists exploring the physiological basis of addiction have tried to explain it by studying the brain chemical dopamine, which functions as a neurotransmitter, sending signals between cells in the brain. Dopamine affects a variety of critical functions, including learning, memory, movement, emotional response and feelings of pleasure and pain.

Dopamine was originally thought to serve as a kind of pleasure signal in the brain, telling us when something feels good or rewarding. But scientists now believe that dopamine is more a predictor of salience — that is, it tells us, and then helps us to remember, what we should focus on. When you see a person you are strongly attracted to, scientists can now see a spike of dopamine in your brain. If you are hungry and smell a food you like, dopamine also increases. But even unpleasant experiences — like physical pain or the fear of an intruder in the house — can cause a dopamine spike. (Some hypothesize that different dopamine receptor cells are responsible for firing during rewarding or aversive situations.)

Drugs, particularly cocaine and methamphetamines, cause a large increase in the amount of dopamine secreted and pooling between brain cells, leading to feelings of euphoria. With regular, repeated "addictive" drug use, though, the brain eventually responds by reducing its normal release of dopamine. Studies also show a simultaneous decrease in the number of dopamine receptors created. That, in turn, makes the brain's reward system less likely to respond to behaviors

(romance, a good meal, the company of friends) that produce a normal dopamine surge. The addicted brain essentially becomes pathologically selective, dependent on bigger and bigger blasts of, say, cocaine to feel rewarded.

Perhaps most fascinating to addiction researchers is how an increase in dopamine creates a craving — and an expectation of a reward. In a study published earlier this month in The Journal of Neuroscience, Volkow used a brain scan to look at the dopamine releases in 18 cocaine addicts while they watched two videos: one of nature scenes, the other of people using cocaine. Volkow found that dopamine increased while the addicts watched the cocaine video and that the severity of the increase matched their self-reported level of craving for the drug. "For these people, their lives and experience had taught them that when they see others using cocaine, they're probably about to get rewarded with drugs, too," Volkow told me. "So even though they consciously knew that they weren't going to get cocaine after watching the video, their brains had learned to expect the reward."

Scientists posit that cue-induced dopamine spikes and craving essentially overpower the brain's well-meaning frontal cortex, which is responsible for planning and decision making. The institute on drug abuse is currently financing studies of medications that could potentially blunt that process, interfering with the release of dopamine when an addict sees a conditioned cue.

Dopamine also travels to the parts of the brain responsible for solidifying memory, like the amygdala, which learns and stores emotional memories (including the high of drugs). Some researchers hypothesize that through a combination of medicine and behavioral therapy, addicts could "unlearn" these powerful memories and associations, making them less likely to relapse when they see a cue. "Potentially, you could put an addict in a virtual-reality situation where you show them videotapes of friends they used to use drugs with, or whatever their strongest triggers are," Eric Nestler, a neuroscientist and addiction specialist at the University of Texas Southwestern Medical Center, told me earlier this month. "But now, the cue isn't associated with any kind of rewarding response. So then you can give a medication, which we're making progress on developing, that enhances memory formation. Essentially, you'd be teaching them something new — that a line of white powder means nothing special."

Dopamine may also make some people more vulnerable to addiction. Recent studies in both animals and humans have indicated that those with low levels of dopamine D2 receptors, which regulate the release of dopamine in the brain, are more likely to find the experience of taking drugs pleasurable. Some researchers, like Volkow, suggest that people with fewer D2 receptors experience a less intense reward signal, causing them to overindulge in order to feel satisfied.

In one experiment, Volkow increased the level of dopamine D2 receptors in rats that had low levels. After the increase, the rats significantly curtailed their intake of alcohol, which they had eagerly gulped down before. Unfortunately, we don't yet know how to safely increase the number of dopamine D2 receptors in humans.

In fact, we don't yet know how to do much when it comes to dopamine and addiction. Understanding how the neurotransmitter works may help us to understand addiction better, but it

hasn't led to any effective medications, the ultimate goal of many researchers. Because addiction seems to disrupt so many different brain regions, neuroscientists are now casting a wider net in their pursuit of effective medications. For some, the new frontier involves the brain's two major "workhorse" neurotransmitters: GABA and glutamate.

Getting the Brain's Brakes to Work

Walter Ling, a neurologist and the director of the Integrated Substance Abuse Programs at U.C.L.A., likes to explain complex brain processes using simple metaphors. GABA, he says, is to a brain what a braking system is to a car. "The brain works by inhibition," he told me recently. "At some point you realize that your car is a great car not because of its engine but because it has a great braking system. GABA is the brakes. If your brakes don't work well, you crash."

GABA (gamma-aminobutyric acid) is the brain's major inhibitory transmitter, and its role, in essence, is to keep glutamate, the main excitatory transmitter, from overwhelming us. In the extreme, too much glutamate can cause a seizure and too much GABA can put us in a coma. Researchers are particularly interested in the brain's critical balance of GABA and glutamate — some hypothesize that addictive craving is the result of too much glutamate or too little GABA. "We've been able to measure GABA in living brains for some time, but measuring glutamate in living human brains has just become feasible in the last few months," says Frank Vocci, the director of the division on pharmacotherapies and medical consequences at the institute on drug abuse. "What's been shown is that people with alcohol and cocaine problems have less GABA in their brains, and we do know that medications that increase GABA have shown some efficacy in treating addiction." (Vocci says that it isn't yet clear whether the absence of GABA is a cause of addiction or a result.) The seizure medication topiramate, for example, works on both GABA and glutamate and has helped some alcoholics in initial trials quit or cut back on their drinking. The muscle relaxant baclofen, which essentially mimics the effects of GABA, may also help some cocaine addicts quit. Both are being tested further by the institute.

Hythiam, a Los Angeles-based health care services management company that made national news in the spring when it plastered Chris Farley's face — with the words "It Wasn't All His Fault" — on a series of Los Angeles billboards, is particularly interested in GABA's role in addiction. The company is aggressively marketing its Prometa protocol for cocaine, alcohol and methamphetamine addiction, which involves therapy and medications, both oral and intravenously injected, not usually used to treat addiction: flumazenil, approved by the F.D.A. to treat overdoses of Valium and Xanax, and gabapentin, approved to relieve neuropathic pain. While no double-blind placebo studies have tested Prometa's effectiveness (two are under way), addiction-medicine doctors around the country who have administered the protocol report encouraging results. Prometa appears to reduce anxiety and craving by enhancing the brain's GABA receptors, says David Smith, the former president of the American Society of Addiction Medicine and now the director for medical affairs at Hythiam and the head of a Prometa treatment center in Los Angeles. Sanjay Sabnani, Hythiam's senior vice president for strategic development, says: "It's all hypothesis at this point, because we haven't sliced open anyone's brain yet, but it seems that normalizing the GABA receptor takes away the craving and anxiety that one would typically experience in the absence of the drug. And it

doesn't appear to be happening because of will power, love, God, discipline, family support or anything else. It seems to be happening because the protocol resets a faulty mechanism in the brain." Yet, several addiction scientists told me they were skeptical that Prometa works, and some criticized Hythiam for promoting it before it has been rigorously tested.

The Prescription Model

Hythiam was among a handful of companies publicizing their anti-addiction medications last month at the American Society of Addiction Medicine conference in San Diego. Several were armed with charts, graphs and clinical-study results (particularly the ones that found their medications most effective), and their eager young marketing and sales teams talked about doing for addiction what the pharmaceutical industry did for depression: medicalizing it, and destigmatizing it in the process.

They know it won't be easy. A series of recent surveys sponsored by the National Council on Alcoholism and Drug Dependence and by Faces and Voices of Recovery, a recovery advocacy group, found that half the public called addiction a personal weakness. Among those who did see addiction as a disease, most put it in a special category of diseases that people get by making poor choices. In a 2004 poll of the general public, two-thirds said they believed that a stigma — usually defined as a thing that disgraces a person or injures one's reputation — exists for people in recovery from addiction.

The pharmaceutical companies came to San Diego to argue that addiction is a chronic and recurring disease like diabetes or hypertension — and no one, they say, tells a diabetic to try to tough it out without insulin. They don't discount the importance of environment in inducing addictive behavior or psychosocial interventions as part of the recovery process; in fact, most stress therapy as an essential adjunct to their products. But they insist that medications will stabilize addicts and make the deeper therapeutic and spiritual work more effective.

In the exhibition hall, the prime booth location near the entrance belonged to Alkermes and Cephalon, the two pharmaceutical companies producing and marketing Vivitrol, the recently approved, injectable form of naltrexone, prescribed for alcoholics. Alkermes and Cephalon are initially focusing on doctors who specialize in addiction, but they plan eventually to market the drug directly to primary care physicians, most of whom are used to sending their addicted patients to treatment centers and groups like Alcoholics Anonymous. "It would require a complete paradigm shift," Doug Neale, a product director at Cephalon, told me, "but we'd like to see the day when a patient who is struggling with alcoholism can walk into their primary care doctor's office, say, 'Doc, I'm drinking too much and can't seem to stop,' and the doctor will have a handful of options for medications that he could prescribe."

But Ling, the U.C.L.A. researcher, cautions that we still have a way to go before we can effectively treat most addicts medically. "In general, we have a pretty good handle on dealing with opioid addiction," he says. But "if you look at the various studies of alcohol-abuse drugs, the results are mixed at best," he continues, adding: "These kinds of mixed findings mean that the drug maybe works for some people, but it's not working all that great. And we're still far off from having a

handle on treating people addicted to stimulants like cocaine and methamphetamine."

A Higher Power Versus Medicine

John Schwarzlose, the president of the Betty Ford Center, says he isn't convinced that treating alcoholics and drug addicts with more drugs — particularly if they aren't proved effective — is a good idea. He points out that millions of addicts around the world have recovered without the help of medication. "We're open to medications that will actually work, but the fact is that today 12-step treatment is still the best treatment there is," he told me. "Nothing even comes close. And until something does, we like to try to keep most of our patients as drug-free as possible."

Many addiction treatment centers share that view, which made for a strange scene in the exhibition hall at the society of addiction medicine conference. The treatment centers, most of which advocate a behavioral and spiritual solution to addiction, promoted their centers right next to pharmaceutical companies boasting novel medical solutions. "Why can't these two camps come together?" Smith, the medical director of Hythiam, said as he sat in front of the company's booth. "They need to come together. In medicine, if something isn't working, you try something new. In addiction, if someone goes to treatment and fails, for years we've just sent them back again and again and expected different results. That's insanity. And we're starting to realize that. The field of addiction treatment is changing right before our eyes, and it's only going to continue to change. Advances in neuroscience and pharmacology will change everything."

Those changes could lead to addiction vaccines. Several are already in development. The British company Xenova Group Plc has created what it says are effective vaccines for cocaine and nicotine addiction (NABI Biopharmaceuticals in Florida has also developed a nicotine vaccine). The vaccines, which the institute on drug abuse and others are testing, work by producing antibodies to a specific drug, binding to the drug when it enters the bloodstream and keeping it from entering the brain. An effective vaccine won't stop craving or treat any underlying pathology (making it an inadequate solution, some say), but it will make it nearly impossible for an addict to get high on that particular substance.

And if it is combined with medications that could blunt craving, some addiction specialists believe that we'll stop using the word "treat" and start using the word "cure." Matthew Torrington, an addiction-medicine doctor in Los Angeles who works with Smith at his Prometa center, attended the society's conference and told me that he believes we can essentially eliminate addiction in America.

"With the scientific advances we're making in understanding how the human brain works," he says, "there's no reason we can't eradicate addiction in the next 20 or 30 years. We can do it by fixing the part of the brain that turns on you during drug addiction and encourages you to kill yourself against your will. I think addiction is the most beatable of all the major problems we face. And I think we will."

The Stress Culture

It's not the first time a doctor has predicted the end of addiction. In his book "Slaying the Dragon: The History of Addiction Treatment and Recovery in America," William L. White recounts how in the 1800's, countless "medications" like Knights' Tonics for Inebriates promised to remove "the craving for a stimulant that those who have been addicted to the use of ardent spirits know so well." In the 1905 Sears, Roebuck & Company catalog, a person struggling with opium or morphine addiction could buy a bottled "cure" for 69 cents.

Most of these miracle potions were promoted as a result of important scientific and medical breakthroughs. Science, it seems, has always been just about to save us from addiction. "But it has never lived up to its promise," says Bruce Alexander, emeritus professor of psychology at Simon Fraser University in British Columbia, "and I don't believe the science will live up to its promise now, either. Addiction doesn't demand a scientific solution."

Alexander is among a vocal group of addiction researchers who argue that focusing on a pill to treat addicts fails to address the primary cause of becoming and staying hooked: our unhappy, disconnected lives. Beginning in the late 1970's, Alexander and his team of researchers at Simon Fraser set out to study the role of our environment on addictive behavior. Until that point, most scientists studying addiction put rats in small, individual cages and watched as they eagerly guzzled drug-laced solutions and ignored water and food, sometimes dying in the process. This phenomenon was noted — first by researchers, then drug czars, then parents trying to keep their children off drugs — as proof of the inherently addictive quality of drugs and of the inevitable addiction of any human who used them. This was false, of course. Most people who use drugs don't become addicted.

So what made all those lab rats lose their minds? Bruce Alexander and his research team had a rather simple hypothesis: The rats had awful lives. They were stressed, lonely, bored and looking to self-medicate. To prove it, Alexander created a lab-rat heaven he called Rat Park. The 200-square-foot residence featured bright balls and tin cans to play with, painted creeks and trees to look at and plenty of room for mating and socializing.

Alexander took 16 lucky rats and plopped them into Rat Park, where they were offered water or a sweet, morphine-based cocktail (rats love sweets). Alexander offered the same two drinks to the control group of rats he left isolated in cages. The results? The rat-parkers were apparently having too much fun to bother with artificial highs, because they hardly touched the morphine solution, no matter how sweet Alexander and his colleagues made it. The isolated and arguably depressed rats, on the other hand, eagerly got high, drinking more than a dozen times the amount of the morphine solution as the rats in paradise.

When I spoke with Alexander recently, he predicted that unless we undergo a "cultural renaissance" and all start living in a human version of his rat park (which he conceded isn't likely), we won't be eradicating addiction anytime soon. While Volkow of the institute on drug abuse doesn't agree with Alexander that developing addiction medications is a fruitless enterprise, she does say that a positive and nurturing environment, particularly during childhood and adolescence, is a strong protector against addiction. Volkow says that addicts are more likely to have been unnecessarily

stressed during childhood (from neglect; emotional, physical or sexual abuse; or poverty) and that they're less able to deal with stress as adults.

Studies show that animals who are stressed during early development are more likely to self-administer drugs later in life and that living in an enriched environment — one with a minimal amount of strain and anxiety, like Rat Park — appears to protect animals from developing addictive behavior.

And remember the dopamine D2 receptors that some hypothesize may protect us from abusing drugs? There is evidence that our environment can affect those, too. In 2003, researchers at the Wake Forest School of Medicine measured the levels of dopamine D2 receptors of 20 macaque monkeys while they were housed in isolation. They then assigned the monkeys to social groups of four monkeys each, letting natural social hierarchies develop. Three months later, they tested the levels of D2 receptors again.

The dominant monkeys — who, the theory goes, were much less stressed and anxious than the subordinate ones — had 20 percent higher D2 receptor function, while the submissive ones were unchanged. The monkeys were then taught how to self-administer cocaine by pressing a lever, with researchers finding that the dominant monkeys took significantly less cocaine than the subordinate ones.

Interestingly, though, when the animals that seemed to be protected from addiction were given cocaine repeatedly, the number of their D2 receptors eventually went down, and they then became addicted. The moral of the monkey story, Volkow says, is that environment — if good or bad enough — can sometimes trump genetics and biology.

"Some people may be naturally better protected against addiction than others," Volkow says, "but that's not enough to keep someone from becoming addicted. The same thing is true for those who are genetically predisposed. We know from twin and family studies that about 50 percent of a person's vulnerability to addiction is genetic. But if you're never exposed to illegal drugs, or if you grow up and live in an environment without trauma and too many stressors, you probably won't become addicted."

If It's Not One Addiction, It's Another

What Volkow and other researchers can't yet explain is why we choose one particular manifestation of addiction over another. Why do some of us become addicted to cocaine, while others are hooked on alcohol or cigarettes? Researchers hypothesize that environmental availability and genetic predisposition both play a part, but they don't know for sure.

Further complicating the question is that many people are addicted to more than one thing. Howard Shaffer, director of the division on addictions at the Cambridge Health Alliance, an affiliate of Harvard Medical School, suggests a "syndrome model" of addiction: each outwardly unique manifestation of addiction is actually part of the same underlying disorder. Shaffer's syndrome model argues that behavioral addictions (like gambling, sex and eating) can be just as powerful as

an addiction to heroin or crystal meth, and his belief is gaining acceptance among neuroscientists and addiction researchers, many of whom used to dismiss this idea as a product of an American culture that's addicted to calling everything an addiction.

But by studying the brain's reward and pleasure systems, researchers are discovering that drugs and powerfully rewarding behaviors like gambling and sex affect it in similar ways. Neurologists at the University Medical Center Hamburg-Eppendorf in Germany, for example, found that pathological gamblers, like drug addicts, have a sluggish reward system that doesn't react normally to pleasing stimuli. The scientists used an M.R.I. scanner to compare the brain responses of 12 gambling addicts and 12 nonaddicted people to a card-guessing game. Subjects were told to pick a playing card, and if the card turned out to be red, they won a euro.

The game activated the ventral striatum, an important part of the brain's reward system. Those nonaddicts who picked a winning card had increased blood flow to the striatum, but the gambling addicts who picked the right card had much less of it (their reward system was less active). It was as if their brains, which were accustomed to powerful rewards, were saying, "You call this silly prize a reward?" The same kind of indifference to basic rewards has been seen in the ventral striatum of cocaine addicts.

"People addicted to gambling and drugs look a lot alike," Shaffer told me when I visited him in his office in March. "Gamblers have to increase their bets to get the same level of excitement, just like someone addicted to drugs who has to keep using more to get an effect. When addicted gamblers cut back, they experience withdrawal symptoms that look like stimulant withdrawal. They get depressed, they're irritable and they have trouble sleeping. And if they gamble again, they can make the symptoms go away for the short run."

While Shaffer focuses much of his recent behavioral addiction research on gamblers, Volkow studies overeaters and also finds many similarities to drug addicts and alcoholics — including the fact that obese subjects have lower levels of dopamine D2 receptors than those who eat normally. "Because we know that many people are addicted to more than one thing and that many people switch addictions," she told me at the M.I.T. conference, "in my own research I'm mostly interested in developing medications that could work across a variety of addictions."

An Addict's Perspective

What do addicts think about all this focus on their brains? William C. Moyers, a recovery advocate (and the son of the journalist Bill Moyers) who for 12 years has been free of crack and alcohol, was invited to speak at the M.I.T. conference. In a room full of scientists and addiction researchers obsessed with the intricacies of the human brain, Moyers read a lecture that reminded them that treating addiction might be even more complicated than they thought.

"I have an illness with origins in the brain. . .but I also suffered with the other component of this illness," he told the gathered researchers and scientists, some of whom dutifully took notes. "I was born with what I like to call a hole in my soul.. . .A pain that came from the reality that I just wasn't good enough. That I wasn't deserving enough. That you weren't paying attention to me all the time.

That maybe you didn't like me enough."

The conference room was as quiet as it had been all day. "For us addicts," he continued, "recovery is more than just taking a pill or maybe getting a shot.. . .Recovery is also about the spirit, about dealing with that hole in the soul."

*Benoit Denizet-Lewis is a contributing writer for the magazine. He is working on a book about addiction in America.*