



A new
treatment
for
alcoholism
defies
the
recovery
movement

BY SUSAN SELIGSON

“It crept up on me.”

Lisa speaks softly as she sips spring water in a cafeteria at the BU Medical Campus. “My 5 o’clock drink got earlier and earlier, until I was filling a glass at 3:30.” Then one afternoon in the shadow of lunchtime, Lisa’s daughter asked her to babysit her children at their home just a few doors away. She knew right away that she had to say no. She was drunk.

Serendipity brought 59-year-old Lisa to the experimental alcoholism treatment clinic in the Doctors Office Building at the edge of the Medical Campus. (Names of the clinic’s patients have been changed.) The day after she told her daughter she was unable to babysit, she heard a radio announcement about a 16-week alcohol study headed by Domenic Ciraulo, a School of Medicine professor and chair of psychiatry and psychiatrist-in-chief at Boston Medical Center. The treatment, it turned out, was unlike Lisa’s notions about programs designed to help people beat an alcohol problem. It was also unlike programs that were endorsed by many in the recovery movement. For one thing, it attempts to treat alcoholism with long-term medication. For another, it allows those enrolled in the program to have an occasional drink.

During that first clinic visit, Lisa recalls, she was relieved to share the intimate details of her struggle with alcohol. “I’m a good news gal; I keep things private,” she says. Handed a 13-page consent form to review, Lisa was interviewed by a research coordinator, who asked how much she was drinking each week. (Participants in this study must be heavy drinkers. For males, this translates to 35 or more standard drinks a week—5 ounces of wine, 12 ounces of beer, or 1.5 shots of hard liquor. For women it’s 28 or more drinks a week.) Tallying the drinks in her head, Lisa came up with 30. At least 30. She was horrified.

“Most people, once they talk about it, realize they’ve been drinking much more than they thought,” says principal investigator Maryam Afshar, a MED assistant professor of psychiatry.

Ned, a wistful, mild-mannered, 55-year-old gay banker, considered

himself the epitome of the social drinker; he confined his alcohol consumption to martinis at a hole-in-the-wall pub near his home outside of Boston. Describing himself as “a boring guy,” Ned says that with each martini he lightens up and makes jokes, but is never “an obnoxious or mean drunk.” During the last year, it had become more difficult for Ned, who comes from a family of alcoholics, to convince himself his drinking was under control. By the time he found his way to the clinic, two days after seeing a television recruiting advertisement, he calculated that he was consuming at least 180 martinis or gin cocktails each month.

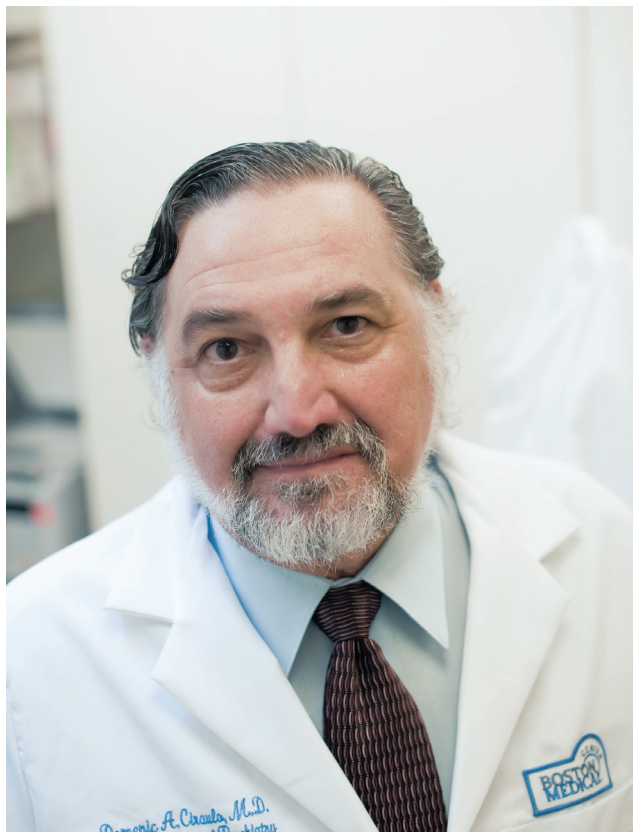
GOAL: BLOCK THE DESIRE TO DRINK

Ciraulo’s interest in addictions grew out of his college experience. He came of age in the drug-addled 1960s

and has been intrigued ever since by the effects on the brain of every abusable substance, from LSD to amphetamines. In medical school he was part of a group investigating the use of psychedelic drugs to relieve pain in cancer patients. Since then, he has devoted much of his career to answering questions about tolerance to alcohol, predisposition to alcoholism, and how the disease ties in with anxiety and depression.

“I wondered, what leads to alcoholism?” he says. “The first thing you notice is anxiety and depression, but I had it backwards. Depression doesn’t cause drinking; drinking causes depression.”

Ciraulo believes that both dependence on alcohol and the ability to stop drinking lie in the brain’s frontal lobe, ground zero of self-control. “The goal of all drug therapies for alcoholism is to block the desire to drink,” he says. What is known about that desire is that alcohol causes a chemical imbalance in the brain, apparently by sensitizing and ultimately wreaking havoc with the brain’s reward system, involving the neurotransmitters dopamine and serotonin, which are associated with pleasure and a sense of well-being. While alcohol initially leads to an increase in dopamine, chronic



Domenic Ciraulo wondered if it was true that depression caused people to drink. Perhaps it was drinking that made people depressed.



The Symptoms

consumption eventually causes dopamine levels to fall, leading to a more anxious craving for alcohol and requiring more alcohol to get the same pleasurable effects.

With backing from the National Institute on Alcohol Abuse and Alcoholism (NIAAA), Ciraulo, who has been chair of psychiatry since 1996, has joined with David Barlow, a College of Arts & Sciences professor of psychology and founding director of BU's Center for Anxiety and Related Disorders, to attempt to prove a controversial thesis: by adding drug therapy to the mix of short-term behavior therapy, and Alcoholics Anonymous (AA) if patients desire it, this program can help alcoholics like Lisa drink in moderation.

As chief investigator, Ciraulo presides over a team of psychiatrists, psychologists, pharmacologists, nurses, and research assistants who are recruiting subjects like Lisa and Ned to test the relative effectiveness of two antiseizure drugs—zonisamide and levetiracetam—in curbing alcohol cravings. Lisa signed on for a controlled, double-blind study comparing the drugs with each other and a placebo. It's a continuing study, requiring 160 subjects total, with 40 in each group.

WEB EXTRA
A video of Domenic Ciraulo talking about his work is at bu.edu/bostonia.

Many of the results of treating alcoholics with this class of drugs, approved by the FDA only to treat epilepsy and migraines, have been encouraging. Although the mechanism isn't completely understood, anticonvulsants appear to alter brain signals in a way that puts a significant dent in alcoholics' cravings. But the drug most studied, Topamax, has been associated with side effects such as burning or tingling sensations in as many as half of those who take it, along with a significant chance of dizziness, fatigue, and mental foggy. Ciraulo's team is hoping for conclusive evidence that one of the drugs being studied will prove as effective as Topamax.

"It's a race" is how Ciraulo describes the state of clinical alcoholism research in the United States. While per-

Also known as alcohol dependence, alcoholism the disease is not a subjective diagnosis. It is defined by a set of symptoms: a strong need, or urge, to drink; not being able to stop drinking once drinking has begun; alcohol withdrawal symptoms such as nausea, sweating, shakiness, and anxiety; and the need to drink greater amounts of alcohol to experience its effects, a phenomenon known in addiction parlance as tolerance.

vasive 12-step groups like AA, with an estimated membership of 1.2 million, are widely respected, nearly a third leave the program after the first month, with the attrition rate slowing gradually after the first year, according to AA's own informal statistics. And nearly all conventional treatment and rehabilitation centers are based on the 12-step model. Yet long-term abstinence is elusive, and alcoholism remains pandemic and increasingly costly to the nation's health and productivity. The NIAAA estimates that 14 million Americans either abuse or are dependent on alcohol. According to the institute, alcoholism and alcohol abuse are the third leading cause of preventable death in the United States and alcohol is a factor in nearly half of America's murders, suicides, and accidental deaths. Alcoholism costs the nation more than \$3 billion in lost wages each year. Approximately 90 percent of alcoholics are likely to experience at least one relapse over the four-year period following treatment, a dismal success rate that reflects only those who actually seek help.

Considering the influence of alcohol on our lives, says Ciraulo, whose funding for five projects includes more than \$13 million from the National Institute on Drug Abuse, \$12 million from the NIAAA, and \$3 million from private sources, there is surprisingly little understanding of how alcohol dependence works. Misconceptions abound, and the most common, says the researcher, is that quitting is simply "a matter of willpower."

The medical nature of why people start drinking and why they can't stop is hugely under-recognized, says Ciraulo, a plain-spoken, bearded man whose bearing would suit the set of a Puccini opera. "And the genetic influence that interacts with environmental stresses is a complex model that very few people understand fully," he adds. "We're just beginning to figure it out."

BIG PHARMA: DAMAGING THE BRAND

Using drugs to treat alcohol addiction dates back to the late 1800s and a misguided notion that alcoholics could be helped with opium. Today, only two drugs are FDA-approved to treat the disease. One, acamprosate, restores a healthy balance between glutamate and GABA, two of the chemicals that get jostled in the brains of alcoholics. The other, naltrexone, commonly used to treat heroin addiction, appears to help prevent abstaining alcoholics from relapsing. The FDA approved the use of naltrexone for alcoholism in 1995, to reduce both the desire for a drink and the craving following a first drink. An analysis of 20 studies found that naltrexone reduced the risk of relapse by 36 percent in abstaining alcoholics taking the drug every day, but the effect doesn't last for people who stop the drug or skip doses; one study of men only reported in the *New England Journal of Medicine* found that a year of naltrexone treatment didn't help hard-core alcoholics.

For the most part, says Ciraulo, when it comes to so-called addiction drugs, pharmaceutical giants like to keep their contributions low-key or steer clear of these applications altogether. "The drug companies fear that using their drugs to treat alcoholism would damage the brand," Ciraulo says. And Big Pharma also shies away from the notion of an "alcohol pill," he says. "Patients taking the drugs for their prescribed uses might feel stigmatized by, or otherwise averse to, taking it."

For Ciraulo and his team, the stigmatization of alcohol drugs is compounded by the controversy swirling around the notion that alcoholics can be healthy and high-functioning

without going cold turkey. BU Medical Campus alcohol and addiction researchers staff the Boston University Clinical Research Unit for Alcoholism Treatment, one of just five national centers established by the National Institute on Drug Abuse to investigate through a spectrum of studies whether addiction can be treated successfully with medication. Preliminary research has shown that the anticonvulsants don't seem to make that noon cocktail seem sickening or even shameful, but just easier to resist. At its heart, the research asks whether with some pharmacological help alcoholics can control what was once thought beyond control.

Alcoholics themselves are divided on the issue. "We have nothing against AA, but they have something against us," says Ciraulo, who believes that with a combination of counseling and drug therapy, it is possible for alcoholics to drink in moderation, an anathema to the prevailing 12-step creed of completely abstaining from alcohol, day after day, one day at a time. Although nothing in AA's *Big Book* specifically condemns or prohibits it, the bias against pharmaceuticals persists. Ciraulo acknowledges the important role AA can play for some of his patients. "Alcoholics have a lot of social problems, and they're still going to need mutual support groups," he says. "A pill may do it for

some people, but not all people."

Halfway into their respective studies, Lisa and Ned reported feeling a lessening of cravings—Lisa felt "more focused." Neither felt incapable of enjoying a drink. "What I first noticed was more clarity," says Lisa, who never experienced any physical side effects. She watched the morning news without getting distracted. "That was a great feeling, but it leveled off after a week," she adds.

By the end of her 16-week stint, Lisa was down to two or three drinks a week. But rather than trying to

abstain completely, she gave herself a different type of test—she went out and had a drink with friends. "It went fine," she says, but she's resolved not to repeat the test. She no longer feels obsessed with her next drink. But she is determined to work on whatever it is that drove her to drink in the first place.

Several weeks after going off the drug—or placebo, she'll never know—Lisa reported feeling increasingly bereft. She had managed to limit her drinking to a few vodka and sodas a week, but she felt her resolve wearing thin. But after just a few sessions with her old therapist, whom she'd seen years before the study, something happened. For three weeks and counting, she didn't drink at all.

And there's more. Lisa finally told her children about all of it: the stealthy vodka and sodas, the BU clinic, the return to therapy. She's been playing golf and basking in the new openness with her adult son and daughter, who have offered her their love and encouragement.

With his time in the study winding down, Ned reports feeling great. Part of him would like to stop drinking, but he admits that he's "just not ready," adding that if a pill were available to ease his cravings, "I'd go on it immediately, without batting an eye." In the meantime, he says, he has two priorities: "Number one: meet someone. Number two: enjoy my life." ■



Domenic Ciraulo uses transcranial magnetic stimulation to monitor activity in the prefrontal lobe of the brain, the ground zero of impulse control.



Your Brain on Martinis

At Domenic Ciraulo's clinic, researchers use an experimental machine to track brain activity in alcoholics who are drinking or craving a drink, and compare changes in patients' brains over time. The process is called transcranial magnetic stimulation, or TMS, and the device they use, approved by the FDA two years ago, combines a dentist's recliner with a wire-sprouting helmet. A special camera maps the frontal lobe activity recorded from the "optodes" protruding from the helmet, and can both monitor brain activity and stimulate the brain electromagnetically. If the prefrontal lobe—ground zero of impulse control—is also the key to alcohol and drug addiction, the researchers speculate that stimulating that section artificially may curb cravings the way a nonaddictive brain might.

Although the apparatus, developed in Tasmania and now used in New Zealand and India, conjures images of Dr. Frankenstein's lab, side effects are slight and usually involve some lingering facial discomfort. In addition to using TMS to treat addicts, Ciraulo is studying its effects on depressed patients who don't respond to antidepressants. SS