Ibogaine Therapy: A 'Vast, Uncontrolled Experiment'

Despite potentially harsh side effects, an African plant extract is being tested in two public clinical trials—and many clandestine ones

On a snowy President's Day, an odd group of activists and scientists devoted to treating addiction gathered in an art gallery in the Chelsea warehouse district of New York City. As an all-night, all-day rave throbbed next door, panelists outlined the latest developments in a decades-long movement to mainstream a West African plant alkaloid, ibogaine, that purportedly interrupts addiction and eliminates withdrawal.

Sustained by true believers who operate largely outside the academic medical world, research on the vision-inducing drug is gaining attention, despite its U.S. status as a banned substance. The Food and Drug Administration (FDA) approved a clinical trial in 1993, but the National Institute on Drug Abuse (NIDA) decided not to fund it after consultants raised questions about safety.

Traditional high. Ibogaine is derived from a root bark used in the West African Bwiti religion as a way to "visit the ancestors."

CREDIT: LAURENT SAZY

The plant extract can be neurotoxic at high doses and can slow the heart. Yet a handful of scientists continue to study it for its potential in treating addiction. The enthusiasts who gathered in New York reviewed efforts to tease apart its antiaddictive and hallucinatory components.

Although a PubMed search for "ibogaine" pulls up some 200 articles on laboratory studies, clinical reports cover just a few dozen patients. That's because patients seek treatment clandestinely. "Whether the FDA likes it or not, the fact of the matter is that … hundreds, probably thousands of people … have been treated with ibogaine," said Stanley Glick, a physician and pharmacologist at the Albany Medical Center in New York who has documented ibogaine's antiaddictive potential in rodents. At the meeting, Kenneth Alper, a Columbia University assistant professor of psychiatry, estimated that more than 5000 people have taken ibogaine since an organized (but unregulated) clinic opened in Amsterdam in the late 1980s. Boaz Wachtel, an ibogaine advocate in Israel, believes that 30 to 40 clinics operate worldwide. Listed alongside heroin, LSD, and marijuana on the U.S. Drug Enforcement Administration's schedule I of banned substances, ibogaine is nevertheless legal in most of the world.

"There's basically a vast, uncontrolled experiment going on out there," said Frank Vocci, director of antiaddiction drug development at NIDA. The agency spent several million dollars on preclinical ibogaine work in the 1990s before dropping it.

Ibogaine's promoters yearn for the legitimacy that a successful clinical trial can bring. They may soon get their wish. Later this spring, neuroscientist Deborah Mash of the University of Miami in Coral Gables, Florida, will launch a phase I safety trial in Miami. A second safety and efficacy trial, of 12 heroin-addicted individuals, is slated to begin this fall at the Beer Yaakov Mental Health Center in Tel Aviv. Both are being funded in an unusual fashion: by anonymous donations—$250,000 for Mash, a smaller amount for the Israeli study.

Restarting

For Mash, a tenured professor who runs an Alzheimer's brain bank and won attention in the 1980s for research on how mixing alcohol and cocaine damages the brain, the donation marks a victory. The holder of a patent claim on ibogaine, she has been trying for 12 years to give the drug a scientific hearing. FDA approved Mash's phase I study in 1993, but she abruptly halted the trial when NIDA rejected her funding application.

Three years later, she moved offshore, opening a fee-for-service clinic on the Caribbean island of St. Kitt's. The standard fee per patient of several thousand dollars is adjusted based on ability to pay, according to Mash. Critics derided the unorthodox move as a money grab, but Mash maintains that her motivations were scientific. "You know, somebody ought to test it. Either the damn thing works or it doesn't," she said in a telephone interview.

At the New York meeting, Mash's physician colleague Jeffrey Kamlet presented snippets of data from the 400 patients he and Mash helped treat at St. Kitt's. (Patients took a single dose of ibogaine titrated to body weight and other factors.) He said that for up to 90 days posttreatment, patients reported "feeling wonderful"; physician evaluations also showed improvement in depression and drug-craving scores. The results mirror those from 27 cocaine- and heroin-addicted individuals treated with ibogaine at St. Kitt's published by Mash in 2000 in the *Annals of the New York Academy of Sciences*.

However, Mash has not published the bulk of her data. Her explanation: She does not want to stir up long-running controversies, including a patent dispute with Howard Lotsof, who discovered ibogaine's antiaddiction value as a young heroin addict in 1962.

Multiple effects

There is no consensus on precisely how ibogaine works, although researchers have shown that it inhibits the reuptake of the neurotransmitter serotonin, among other actions. In this way, "it's like supersticky, long-acting Prozac," said Kamlet, president of the Florida Society of Addiction Medicine in Pensacola.

It can also have effects similar to those of LSD or PCP. Like them, it jolts serotonin and glutamate systems and can cause hallucina-

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tions and feelings of depersonalization. In Gabon, the Bwiti religion revolves around "visits to the ancestors" induced by eating root bark from the shrub *Tabernanthe iboga*, the source of ibogaine. Many patients in the West also report emotionally intense, sometimes frightening visions: scenes from childhood, or past mistakes and regrets replayed and somehow released. Debate rages over whether these experiences are key to ibogaine's antiaddictive potential or simply a psychedelic side effect.

Not every patient experiences visions, but animal and human pharmacokinetic data reveal a common physiological response: The liver converts ibogaine into its primary metabolite, noribogaine, which fills opiate receptors hungry for heroin or morphine. Mash believes that this dramatically reduces or eliminates withdrawal symptoms, and "that's why [addicts] don't feel dope sick anymore." Ibogaine also stimulates nicotinic receptors in the cerebellum, an action that, according to Glick, contributes to ibogaine's long-lasting antiaddictive properties by modulating the dopamine reward circuit in the midbrain.

Besides tweaking neurotransmitters, rodent studies suggest that ibogaine increases quantities of a protein in the brain called glial cell line–derived neurotrophic factor (GDNF). Researchers at the University of California, San Francisco, recently observed this effect in the brain's dopamine-producing areas. Dorit Ron and colleagues reported in the January issue of the *Journal of Neuroscience* that addicted rodents lose interest in opiates when given either ibogaine or GDNF. But after injecting an anti-GDNF antibody that scoops the growth factor out of play, the team found that the animals go dope-crazy again.

Ron goes further, suggesting that GDNF maintains and possibly even repairs frazzled dopamine receptors. She reported last year in the *Journal of Neuroscience* that genetically modified mice producing excess GDNF grow up to have denser dopamine connections in the ventral tegmental area, where the dopamine reward pathway begins.

Mash and others suggest that the effects of the St. Kitt's therapy lasted up to 3 months because unmetabolized ibogaine deposits in fat, creating a slow-release reservoir, and because metabolized ibogaine can stay in circulation for weeks. But government agencies are wary of ibogaine, in part because of its myriad effects. It slows the heart and, at very high doses, can destroy neurons in the cerebellum. FDA and NIDA cited these toxicity risks repeatedly in the 1990s.

Glick has been trying to develop cleaner-acting derivatives. The best-studied, 18-methoxycoronaridine (18-MC), exhibits strong action at nicotinic receptors but "seems to lack all of the actions that make ibogaine undesirable," said Glick. Mash and other ibogaine supporters claim that the neurotoxicity risks have been hyped. But the St. Kitt's team closely monitors heart activity of volunteers, excluding any with irregular rhythms.

While Glick tries to line up funding for clinical studies of 18-MC, Mash is betting on a formulation of the metabolite noribogaine. She and the University of Miami won patent rights to noribogaine in 2002 after a long-running dispute with Lotsof, who holds a patent claim on ibogaine. Mash hopes that, like 18-MC, noribogaine may offer antiaddictive effects without the scary trip.

Meanwhile, Vocci is disappointed that Mash has not published her data from St. Kitt's. "This big case series, no one knows what to make of it," he said. "I would expect to see a spectrum of responses. Even though it's not a controlled study, it would still give us some idea whether or not she has anything worth looking at." If Mash's new trial does produce promising data, ibogaine advocates will have a token of legitimacy to point to. But the circle of true believers seems to be expanding, Wachtel says, because users insist that ibogaine works.

–BRIAN VASTAG

Brian Vastag, a writer in Washington, D.C., is working on a book about ibogaine.

Ecology

Experimental Drought Predicts Grim Future for Rainforest

An extraordinary research effort in the Amazon starved a tropical forest of rain and provides a glimpse of the potential effects of climate change

For 5 years, Daniel Nepstad has been slowly killing trees throughout a hectare of his beloved Amazonian rainforest. In an elaborate experiment akin to an installation by the artist Christo, Nepstad's team set up a 1-hectare array of 5600 large plastic panels that diverted the rain and created an artificial drought. The point of the $1.4 million experiment is to provide the most detailed look ever at how tropical forests respond to such stress.

The good news, as Nepstad, an ecologist at the Woods Hole Research Center (WHRC) in Massachusetts, and colleagues have reported in recent papers, is that the forest is quite tough. Although that's no great surprise—forests in the eastern Amazon have long experienced regular droughts from El Niño events—the team is discovering clever tricks that the trees use to survive when the soil becomes parched.

What's worrisome is that when drought lasts more than a year or two, the all-important canopy trees are decimated. Everyone knows that a lack of water eventually kills plants. But by pushing the tropical forest to its breaking point, researchers now have a better idea of exactly how much punishment these forests can withstand.

These kinds of data will be indispensable for predicting how future droughts might change the ecological structure of the forest, the risk of fire, and how the forest functions as a carbon sink, experts say. Given that droughts in the Amazon are projected to increase in several climate models, the implications for these rich ecosystems is grim, says ecologist Deborah Clark of the University of Missouri, St. Louis, who works at La Selva Biological Station in Costa Rica. The forests are "headed in a terrible direction," she says. What's more, the picture includes a loss of carbon storage that might exacerbate global warming.

Parched. Thousands of panels prevented most rain from reaching the forest floor.

CREDIT: WOODS HOLE RESEARCH CENTER

Basement to attic

Nepstad got the idea for the experiment while working in the eastern Amazon in 1992 during