

Is ketamine the best hope for curing major depression?

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On the seventh floor of a building overlooking the Federal Reserve Bank in lower Manhattan, two medical clinics share an office. One is run by a podiatrist who's outfitted the waiting room with educational materials on foot problems such as hammer toes and bunions. The other clinic doesn't have pamphlets on display and offers a much less conventional service: For the advertised price of \$525, severely depressed and suicidal patients can get a 45-minute intravenous infusion of ketamine—better known as the illicit party drug Special K.

Glen Brooks, a 67-year-old anesthesiologist, opened NY Ketamine Infusions in 2012. "At least eight or nine of my patients have ended up making appointments with the podiatrist," he says. "But I haven't gotten any patients through him—I don't know why." Not that Brooks is lacking for business. He typically treats 65 patients a week. Most come in for an initial six infusions within a span of two weeks, then return every six to eight weeks for maintenance sessions. To keep up with demand, he often borrows rooms from the podiatrist on weekends so he can treat eight patients at once. His only help is a secretary at the front desk.

Patients don't need a prescription, but not just anyone can get an appointment. "You have to have the right story," Brooks says. "For ketamine to work, there needs to be some preexisting brain damage caused by post-traumatic stress. I'm looking for some indication of childhood trauma. If not overt pain, then fear, anxiety, loneliness, low self-esteem—or bullying, real or perceived." Patients receive a low dose of the drug: about one-tenth of what recreational abusers of ketamine take or about one-fifth of what might be used as a general anesthetic.

During the infusions, which are gradual rather than all at once, patients often experience strange sensations, such as seeing colors and patterns when they close their eyes. "The first time, I had a sense that the chair was rocketing upwards, just on and on and on ... a kind of weightlessness," a patient from a different clinic explains. The 51-year-old environmental engineer and university lecturer, who asked to remain anonymous for professional reasons, credits ketamine with reviving him from a near-catatonic depression. "During the treatment, I got this profound feeling of optimism," he says. "I told my family it's like getting hit by the freight train of happiness—they tease me about that now."

Brooks, who's about 5-foot-7, with kind brown eyes, gray hair, and a melancholic bedside manner, is among the first of a wave of doctors opening clinics specializing in ketamine infusions for depression. In 1999 one of his seven children committed suicide after battling depression and heroin addiction. "After my son died, my wife and I did what most parents would do—scholarship funds, charity organizations, those kinds of endeavors—but it was never really quite enough," Brooks says. In 2011 he founded a detox center for opiate addicts. He also started administering ketamine to treat patients with neuropathic pain. That led to calls from psychiatrists asking whether he'd treat their suicidal patients as well. "When I heard about the [therapy], I thought, Wow, this is exactly what I need to do," he says.

The U.S. Food and Drug Administration hasn't approved ketamine for the treatment of mood disorders, but dozens of medical studies show that it can quickly alleviate severe depression. There's no regulation to stop doctors like Brooks from administering ketamine for nonapproved uses—a practice known as "off-label" treatment—but insurers typically don't cover it.

Over the past three years, Brooks has treated about 700 patients, some who've traveled from as far away as Saudi Arabia, the Philippines, Israel, and Europe. He gets six to 10 daily inquiries from potential patients online. Of those Brooks treats, he estimates that about 70 percent show improvement. "For patients who are suicidal—and probably half of my patients are—they can get relief within an hour or two," he says. "For patients who aren't suicidal, it's a little more subtle. It could be six to eight hours."

Brooks plans to hire nurses and move into a bigger, private office this winter. He's also working with Kyle Lapidus, a professor of psychiatry at Stony Brook School of Medicine who studies ketamine, to open several more clinics across the U.S. within the next few years. At least two more doctors in the Northeast, including psychiatrist Keith Ablow—a frequent Fox News guest known for making inflammatory remarks about everything from Michelle Obama's weight to transgender people—have opened clinics and plan to launch chains and physician networks.

Meanwhile, pharmaceutical companies, which can't make money off generics such as ketamine, are spending millions to develop patentable derivatives and analogues. While they press ahead, some in the medical community have criticized doctors who use ketamine off-label, arguing that not enough is known about long-term effects. "They say we're in it for the money," Brooks says. "I just wish everyone would stop trashing ketamine and let those of us offering this treatment do our jobs without feeling like charlatans or something."

Ketamine was first developed in 1962 as a fast-acting anesthetic. It's still used widely in operating rooms and for pain management. Beginning in the 1970s ketamine became popular as a recreational drug, known for putting users in a "K-hole," likened to an out-of-body, near-death experience. In 1999 the U.S. Drug Enforcement Administration banned nonmedical uses for ketamine and designated it a Schedule III controlled substance, alongside drugs such as testosterone and anabolic steroids, meaning that it has moderate to low potential for physical or psychological dependence.

Around the same time, researchers at Yale, including Dennis Charney, who's now dean of the Icahn School of Medicine at Mount Sinai, stumbled upon the drug's promise as a mood stabilizer. They'd set out to study how depression is affected by glutamate, a neurotransmitter essential for brain functions including memory, learning, and the regulation of emotions. To do so, they gave seven clinically depressed patients ketamine, which is known to block certain glutamate receptors in the brain. "We were not thinking at the time that ketamine would be an antidepressant," Charney says. When patients started reporting that they suddenly felt better, the scientists were surprised.

The group's findings, published in *Biological Psychiatry* in 2000, were largely ignored. The study was tiny, and because of ketamine's reputation as a party drug, scientists were reluctant to follow up. "They didn't believe you could get better from depression in a few hours," Charney adds. "They'd never seen that before." Standard antidepressants such as Prozac and Wellbutrin take weeks or months to kick in. As many as 30 percent of depressed patients don't respond to conventional antidepressants, according to the National Institute of Mental Health.

Six years later, Charney, who'd gone on to work for the National Institutes of Health, initiated a replica study with 17 patients. "This was a population that had failed on average six different antidepressants, and some had also failed electroconvulsive therapy, which is generally regarded as a treatment of last resort," says Hussein Manji, one of Charney's co-authors, who's now the global head of neuroscience for Janssen Research & Development, a Johnson & Johnson company. Within a day of getting one ketamine infusion, 70 percent of the subjects went into remission. Since then, scientists at institutions

including Yale, Mount Sinai Hospital, and Baylor College of Medicine have performed dozens more studies that corroborate the findings. Additional studies show that ketamine works by producing long-lasting changes in the brain, reversing neural damage caused by stress and depression and potentially decreasing inflammation and cortisol levels.

“It’s settled—to my mind beyond a shadow of a doubt—that ketamine has a powerful antidepressant effect for as many as 50 percent of people where other medications haven’t been helpful,” says Michael Thase, a professor of psychiatry at the University of Pennsylvania who’s consulted for various drug companies developing ketamine-like products.

The FDA’s approval of ketamine for depression hinges on multiphase clinical studies, which are unlikely to happen. Pharmaceutical companies usually pay for clinical trials and can’t make money off a decades-old generic drug. “You can get a few years of exclusivity for a new use, but generally you need more than a few years to recoup the research and development costs of bringing a drug to market,” Thase says.

Dennis Hartman had already scheduled his suicide when he decided to try ketamine

Instead, companies are spending millions to develop similar, patentable drugs. Janssen is seeking approval for a nasal spray made from esketamine, a variation of the ketamine molecule that’s about 20 percent more potent, says Manji. The spray could come on the market in a few years. Cerecor, based in Baltimore, is developing a pill that replicates ketamine’s effects. In June, the startup filed to go public and raise as much as \$31.6 million. Pharmaceutical giant Allergan spent \$560 million in July to acquire Naurex, an Illinois-based biopharmaceutical company whose main products are two clinical-stage ketamine-like drugs called rapastinel and NRX-1074. Both are designed to modulate the same receptor as ketamine, alleviating depression without inducing hallucination.

One of Brooks’s early patients, Dennis Hartman, had already scheduled his suicide when he decided to try ketamine. At 46, Hartman had excelled professionally, working as a management consultant at Arthur Andersen and Deloitte before becoming president of a gaming company called Accel Entertainment. But he’d been masking depression for more than 30 years. “I became a good actor,” he says. “I never revealed to anyone the degree of my childhood abuse or my dysfunction.”

Hartman tried more than 15 antidepressants, none of which worked. He never married and mostly kept to himself. “When I would get social invitations, I would say, ‘Thanks, but I’m already busy,’ ” he says. “Really I was hiding at home because I needed to repair myself so I could get out of bed the next morning.” Eventually, Hartman decided that ending his life was the most humane option. Hoping to mitigate the trauma for his family, he set the date a couple of months into the future so a young relative could finish the school year.

On Oct. 26, 2012, at 3:15 a.m.—he still remembers the exact time—Hartman stumbled upon a news story about the benefits of ketamine. He then found that the NIH was enrolling patients in a study on the drug. “In the middle of the night I sent them an e-mail,” he says. Days later, he found himself in a hospital in Bethesda, Md., hooked up to an IV drip. “It was the moment of my life,” he says. “Within a few hours I could tell that my anxiety and depression were completely gone for the first time in my memory.”

After participating in the study for two months, Hartman found himself without access to ketamine. He contacted Brooks. “I do relapse—pretty much everyone does—though I haven’t had a single suicidal impulse since my first infusion,” Hartman says. “My baseline levels of misery and impairment aren’t as bad ... and I can view my symptoms as symptoms—they don’t send me back under the covers.”

Hartman is now a ketamine evangelist. He doesn’t have a job and lives off savings so he can focus on running the Ketamine Advocacy Network, a clearinghouse for research, media coverage, and clinics. He knows of 30 clinics in operation throughout the U.S. and estimates there are at least 20 more that don’t advertise.

Doctors running the clinics are typically either psychiatrists or anesthesiologists. Prices for a single infusion range from \$300 to \$1,000 and often aren’t covered by insurance. It depends on the dispenser and how they characterize the treatment. But for many customers, a lack of insurance isn’t a deal breaker. “If I had to go work a second job to pay for this, I would,” says Tamara Hartley, a 55-year-old accountant who struggled with treatment-resistant depression until she found ketamine. “Before, my life wasn’t a life—and I’m not going back.” She pays \$700 for each monthly maintenance session. Some academic centers, such as Yale, offer ketamine infusions to a small number of patients outside of studies, which are generally covered by insurance.

Steven Levine, an energetic, dapper, 37-year-old psychiatrist based in New Jersey, opened the Ketamine Treatment Centers of Princeton in 2011 before he knew of anyone else offering the treatment. “When I read the ketamine studies, they blew my mind. They almost spun my head around,” he says. “I decided I need to start using this even if other people aren’t—I can’t talk myself out of it, it makes too much sense.”

After researching the drug and consulting anesthesiologists about safety and dosing, Levine started treating patients from borrowed space at a local hospital. In March he hired an oncology nurse and opened a private treatment center outside downtown Princeton. The space is designed to be tranquil—Levine says patients respond best that way—with abstract paintings on the walls. Patients often bring their own headphones and listen to their choice of music, anything from James Taylor to electronic artists like Shpongle. Levine spends time talking with patients before and after their infusions and bills them \$450 for an extended psychiatry visit. He sees around 35 patients each week. He plans to open a second clinic, in Baltimore, next year, followed by a third in Philadelphia.

“For most people, ketamine does not induce happiness, and I always clarify that ahead of time,” he says. “Don’t expect to wake up tomorrow with a bluebird on your finger.” Instead of euphoria, patients tend to experience a lifting of their depressive symptoms and a gradual improvement with each successive dose. They report having an easier time with basic tasks like getting out of bed, brushing their teeth, or taking a shower. Some continue taking other mood stabilizers. Of course, it doesn’t work for everyone. “When it works, it’s tremendous, it’s wonderful,” Levine says. “When it doesn’t, it’s heartbreaking.”

Pharmaceutical companies tend to categorize the dissociative effect of ketamine as an unwanted side effect. But Levine—along with many other researchers exploring the promise of psychedelics in battling depression—argues that the hallucinations are likely harmless and may even be helpful. “Ultimately, it’s a dreamlike experience,” he says. “We don’t tell people not to sleep because they might dream.” Later this year, Levine plans to begin a study to evaluate whether patients who experience a stronger dissociative effect during ketamine infusions have better outcomes.

“We believe we can double the income of the average family physician or internist”

Some academics, including Charney of Mount Sinai, have concerns about ketamine clinics run by doctors prescribing the drug off-label. “They’re getting a little bit ahead of the science,” he says. “They’re kind of working on their own algorithms on how to maintain the response—and not in a controlled research setting.” Levine and Brooks dispute the claim that the science on ketamine is insufficient. The drug, Brooks points out, has long been used for anesthesia and pain management, at far higher doses, with no evidence of side effects. “I’ve been working with ketamine for 40 years. I know this drug,” he says.

Ablow, who runs a ketamine clinic in Boston and bills himself as “America’s most well-known psychiatrist,” is charging ahead. Instead of opening freestanding clinics, his fledgling company, Neuragain, hopes to raise \$1 million from investors this summer to start a network of “250 to 500” doctors who will offer ketamine treatments as a side business.

“We believe we can double the income of the average family physician or internist,” Ablow says. Neuragain, he explains, will keep up to 40 percent of the profits in exchange for providing marketing material, a physicians network, and a call center that will handle administrative tasks. “There are millions and millions of depressed people who can benefit,” says Ablow, who anticipates that a series of six sessions will cost patients \$3,000. “We’re treating everyone from cashiers to CEOs, because when you’re depressed, \$3,000 ... turns out not to be an impediment for the vast majority of people who have relatives who can help, health savings accounts, or who can otherwise procure the money or use a credit card, for that matter.”

Brooks almost went into business with Ablow five years ago but changed his mind. They remain good friends, but Brooks is concerned that Ablow’s plan isn’t right for patients. “This is 24/7 stuff—not something you can do on the side,” he says. “Unless you can do this full time and keep up with the literature, with the paperwork, the demands, you’ll never understand these patients. You’ll never really know what you’re doing.”

Brooks acknowledges that ketamine treatments can go wrong and that patients risk winding up with shoddy care. “Nobody in Florida knows what they’re doing,” he says, by way of example. That assessment is based on a patient who got a ketamine infusion from a family physician while she was on holiday. “It was a friggin’ disaster,” he says. “The dose was too high, it was going in too fast, she started to get hysterical. Meanwhile, the doctor is calling me asking what to do.”

On a Monday night in July, Brooks is seated on a leather chair in his cramped, windowless office. The wall is hung with diplomas, scientific diagrams, and a landscape print from Santa Fe, N.M. His bookshelf is filled with gifts, including books, a Slinky, and the knob of a 1965 Fender guitar. “Somebody brought me a cucumber from her garden last Sunday,” he says, pointing to the shriveled vegetable. “I didn’t quite know what to do with it, so it’s been kind of shrinking and looking less like a cucumber.”

Brooks’s patients range in background, but most are in their 30s and 40s. “Many people who suffer post-traumatic stress become overachievers,” he says. “They become very successful, rise very quickly, and then crash. They manage to get maybe to their early 40s, and then everything caves in.” About 20 percent of his patients are artists—writers, actors, musicians, and painters. “I get people who come in and say they haven’t picked up a paintbrush in three years, and after one ketamine treatment they’re up painting all night,” he says.

These days, Brooks is too busy to do much besides work. Recently, he treated a 16-year-old girl who'd been struggling with suicidal thoughts since she was 8. "She'd been hospitalized multiple times, self-mutilating, covered with scars," he says. After one ketamine infusion, she told Brooks that it was the first time she could remember not wanting to be dead.

He says it's hard to stay away from the office when there are so many people asking for help. "No one gets turned away, especially if they're suicidal," Brooks says. "It just gets more and more personal. I kind of see my son's face in everyone who comes in."

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