Ketamine Stirs Up Hope—and Controversy—as a Depression Drug

The next big depression treatment might be ketamine, but how best to use it remains unknown.

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Michael was on the 55th floor of a high rise in an Asian capital, in a conference room, when his world cracked open. His heart began to race and the building felt as if it were swaying. "I'm dying," he remembers thinking. He excused himself from his meeting and returned to his hotel room. His mind on fire, he wondered how to call for help, whether insurance would cover him, and what his wife and two daughters would think if he died here, half a world away from his home in Northern California. He tried lying down but it felt like he was rolling off the bed. He found that if he did jumping jacks while holding his breath, his chaotic mind calmed down.

Michael (who asked that his last name be withheld) didn't die. His psychiatrist back in California diagnosed him with panic attacks and prescribed Xanax. It helped, but

something had changed that day in Asia, and the panic attacks began to strike regularly—while driving his daughter to art class, at the office, at home. "Once I had broken that shell," he tells me, "it became spontaneous."

It was 2013. Michael, age 43, had suffered from psychiatric problems since he was a teenager—epic procrastination, binge drinking, and depression. He'd seen psychiatrists for 20 years and tried almost every antidepressant. What had helped him, at least temporarily, was a prescription for stimulants in the wake of a diagnosis of adult attention deficit disorder in his early thirties. The drugs immediately improved his mood, giving him energy and focus. His career had advanced steadily; he was in executive management at an IT firm. But now it seemed like the darkness he'd pushed aside for so long had come roaring back to claim him.

His wife, Lynn (who asked to be identified by her middle name), watched him spiral downward. Irritable and withdrawn, he'd often watch movies from Friday to Monday. He stopped doing chores. Lynn began parenting their two daughters mostly alone and, in some ways, became a caretaker to her husband as well.

Michael's wake-up call came when his eldest daughter, then 8, landed in therapy. She'd started throwing fiery tantrums and frequently succumbed to emotional meltdowns. Michael suspected that she wasn't just being a kid, she was

imitating his own erratic behavior. He indulged in profanity-laden fits for the most insignificant reasons—if he dropped something, say, or if he forgot to complete an errand. He needed to change for her sake.

Motivated by guilt and desperate for anything that might halt his own downward spiral, he scoured the internet for something new to try. He quickly came across headlines trumpeting a new treatment for depression. He didn't know it yet, but he'd just found the medicine that would change his life—ketamine.

Ketamine lozenges are gaining popularity as a treatment for patients with depression.

Samantha Cooper

Ketamine is an old medication; it was first synthesized in 1962 as a safer alternative to then-available anesthetics, which sometimes suppressed patients' breathing to the point of killing them. It's considered so safe by anesthesiologists that it's routinely used on children. But it has also become a popular club drug and can be addictive. Recreational users call it "special K," and the euphoric, hallucinatory experience it induces the "K-hole."

Research on ketamine as an antidepressant is in its infancy, but scientists speculate that it increases brain plasticity, the ability of the brain to change. To Michael, it made intuitive sense that augmenting your brain's malleability might help

you break out of what felt like an otherwise inescapable mental rut.

He started hunting for clinics willing to prescribe ketamine despite the unsettled science. Such clinics have been popping up in recent years, overseen by physicians willing to prescribe the drug off-label, meaning to treat conditions for which it is not FDA-approved, which is legal. But the places he found—in Portland, Oregon, and another in Freedom, California—seemed to take a dehumanizing approach, leaving patients alone as they received the drug intravenously, the liquid dripping into the bloodstream from a bag on a pole. He had a visceral aversion to this type of impersonal, hospital-like setting. The drug was infamous for causing a rupture with reality, and it seemed to him that patients receiving it should be tended to more closely.

Then he discovered a psychiatrist in a small town north of San Francisco. His name was Phil Wolfson, and with his partner Julane Andries, a therapist, he'd pioneered what he called ketamine-assisted psychotherapy. The couple didn't see the drug solely as an antidepressant, but as a vehicle for self-exploration and understanding. They drew inspiration from folk-healing traditions as well as traditional psychiatry. Instead of intravenous delivery, they used ketamine lozenges or a quick injection into a shoulder. Their less medicalized, more humanistic approach appealed to

Michael.

So one day in January 2016, Michael drove with his wife to meet Wolfson and Andries at the Pine Street Clinic in San Anselmo, where they rented space. There, water gurgled in a fountain, a bird twittered in a cage, and the smell of Chinese herbs filled the air. Wolfson, a big garrulous man with white, curly hair and a pronounced limp from several back surgeries, asked about Michael's medical history. As a teen, Michael had had a noncancerous tumor removed from his abdomen. The tumor was acting like an extra adrenal gland, secreting hormones that prevented him from growing and caused him to sweat profusely, often until his clothes were drenched. The surgery was successful, but recovery had been long and difficult, he told Wolfson. He'd been intubated in the intensive care unit for nearly a week.

Phil Wolfson at the clinic he and Julane Andries set up in San Anselmo to offer psychotherapy along with ketamine treatment.

Samantha Cooper

As Michael recalls, Wolfson told him, "You may be depressed, but I don't think that's the root of your problem. You have every glaring symptom of PTSD." Michael wasn't a veteran. He'd never been sexually abused. Wolfson's diagnosis felt off. He also knew that, years ago, Wolfson had lost a son to leukemia; the detail was on his website. In that moment, Michael diagnosed his therapist. "He's projecting,"

he thought.

Still, he felt comfortable enough with Wolfson to proceed. Ketamine can cause blood pressure to rise and the heart to race, so Michael began with a low-dose lozenge to see how he'd react. When nothing untoward happened, Wolfson gave him a shot in the shoulder. At subanesthetic doses, ketamine is considered a dissociative agent: You remain conscious but may lose awareness of your body and, depending on the dose, feel like you're traveling to other realms.

After the shot, Michael heard a buzzing noise that, as it pushed toward a crescendo, became almost intolerably loud. Then, all at once, the pressure of the noise seemed to release. He lost any sense of his body and felt completely at peace. No thoughts. No discrete sense of self. Just pure awareness. Behind the eyeshades Andries had given him, he saw a huge dome of sky, like a planetarium.

The session lasted maybe two hours. Afterward, the difference in Michael's mood was immediately apparent to Lynn. He was less irritable, more optimistic. She felt as if they'd been treading water for years in their marriage. But they started moving again—making plans, working on problems. Long estranged from his mother, Michael called her and reestablished the relationship.

"It's just been transformative," Lynn told me. She calls Wolfson and Andries "miracle workers." Michael is not, by his own admission, cured. He still has bad days, and he still needs occasional ketamine "booster" sessions to keep his mood up. But he credits ketamine with bringing him back to life and, ultimately, with saving his relationship with his wife. "It's probably the only reason I'm still married," he says.

Julane Andries at her and Phil Wolfson's California clinic.

Samantha Cooper

More than cancer, heart disease (with which it's linked), or diabetes, it's depression that disables people, eroding careers and ruining lives. Every year, 1 in 15 Americans experiences a severe depressive episode. Over a lifetime, 1 in 6 do. Some argue that the burden of depression has increased in recent decades, perhaps even amounting to an epidemic.

But the affliction has also been with us for millennia. The ancient Greeks dubbed it "melaina chole" or "black bile," from which we get the word "melancholy." The Greek physician Hippocrates thought it arose from a buildup of foul, black humors in the body. Later, Plato argued that because childhood shaped one's character, experience caused melancholy instead.

As the journalist Andrew Solomon points out in *The*

Noonday Demon: An Atlas of Depression, these two concepts of depression—one centered on biology, the other on how we're shaped by experience—have dueled ever since. "Hippocrates is, in effect, the grandfather of Prozac," Solomon writes. "Plato is the grandfather of psychodynamic therapy."

In the mid-20th century, the discovery of drugs that could alleviate depression pushed the scientific consensus toward Hippocrates and away from the Platonic idea and his famous standard bearer, Sigmund Freud. If biochemical dysfunction caused depression, and scientists could correct it with drugs, maybe talk therapy had been a big, unnecessary detour.

Today, drugs that increase serotonin levels—a neurotransmitter thought to underlie our sense of well-being—rank among the most prescribed of psychiatric medicines. These drugs, called SSRIs, were once considered revolutionary. But as time has worn on, SSRIs seem more like just another middling tool in the psychiatric armamentarium. They can have bothersome side effects, increasing the risk of suicide in some patients, diminishing libido in others, and they often take weeks to work. But the major problem with SSRIs and the other antidepressants is that, as a group, they fail to help about one-third of patients who try them. Meanwhile, research on new drugs for

depression has mostly stagnated for years, leaving a huge unmet need.

This is why there's so much excitement around ketamine. It offers relief to many patients who previously didn't respond to anything. When it works, the drug acts within hours, not weeks, which makes it especially promising for patients at risk of suicide. And because it targets a different neurotransmitter system—not serotonin but glutamate—it's giving scientists new insight into the biology of depression.

About half of patients respond to intravenous infusions of ketamine, and roughly half of those achieve full remission. The studies done so far are generally small, and the duration of the antidepressant effect is about one week. Yet because the therapy is experimental and only given to people who've failed other treatments, the patients treated are, by definition, the most difficult to treat.

Thomas Insel, former head of the National Institute of Mental Health, once called ketamine "the most important breakthrough in antidepressant treatment in decades"— a sentiment I heard repeatedly. Various drugs already exist that target the same type of glutamate receptors, called NMDA receptors, that ketamine tweaks, including nitrous oxide, the "laughing gas" dentists use to reduce anxiety and pain, and dextromethorphan, a decongestant found in over-the-counter cold medicines.

Inspired by ketamine, scientists are combing through these substances and testing their effectiveness on depression. Several ketamine-based and ketamine-like drugs are already in the FDA's approval pipeline. "Out of the modalities I've worked with in my career, this has certainly been the most dramatically effective and quick way to get someone out of a depression," Sanjay Mathew, a professor of psychiatry and behavior sciences at Baylor College of Medicine in Houston, tells me.

Large human trials showing that ketamine definitively works have yet to be published. As a result, no one knows, in a scientifically rigorous sense, how well it works or what the risks of using it to treat depression are. Even so, California-based healthcare organization Kaiser Permanente has begun covering ketamine infusions for certain patients with treatment-resistant depression. Private clinics often charge hundreds and sometimes thousands of dollars for treatment that patients pay out of pocket. Some people worry that, outside the academic setting, ketamine therapy is moving faster than what's supported by good evidence. Or, as one Yale scientist told *Scientific American* recently, "The nightmare is happening."

There's plenty to fret over. Weekly booster shots are often required to maintain remission, and the effects of repeated dosing remain unclear. Among chronic, recreational users,

ketamine has been linked with brain lesions, persistent hallucinations, and a strange inflammation of the bladder that, at its worst, requires removal of the organ. Addicts are extreme cases, of course. No one knows how much they've taken, for how long, and what else they've been imbibing. But given ketamine's addictive potential, most experts I spoke with urged caution. The last thing anyone wants is to accidentally spark another crisis like the opioid epidemic, they say, which began in part with the noble intent to treat people's pain.

Still, the desperate need for new treatments is making usually cautious scientists more willing to move quickly. "Two years ago, I would have said, 'We need more research,'" Carlos Zarate, lead author on a seminal NIMH ketamine study, says. But the risks of a not-fully-vetted treatment need to be weighed against the risks of untreated depression, he says. Depression injures the brain. The longer it drags on, the harder it becomes to dispel. "I still think we need more research," he says. "But there's tremendous suffering."

In 2017, the American Psychiatric Association issued recommendations on ketamine. The authors pushed for standardization of treatment, urging a protocol of 0.5 milligrams per kilogram of body weight given intravenously. Some clinic operators applaud this move. "We need to

adhere to what's evidence-guided," says Steven Levine, a Princeton, N.J.-based psychiatrist who heads a network of clinics that offer ketamine.

Others bristle at the idea of standardizing treatment. "What works best differs according to person," says Raquel Bennett, a psychologist in Berkeley, California. Bennett, who runs a yearly conference dedicated to all things ketamine, speaks from personal experience. After years of crippling depression, she accidentally discovered ketamine in 2002. She'd initially taken it for what she calls its "psychospiritual" effects, and was thrilled to find that her depression eased as well. For her, the drug works best at the higher, hallucinatory doses that push her into the "K-hole."

The proliferation of ketamine clinics alarms Bennett too, but her worry is that the experiential aspect of the drug is being ignored, to patients' detriment. She's heard stories of people hooked up to IVs and left alone in rooms with televisions blaring—or even with other patients screaming in terror as they wrestle with their own ketamine-induced visions.

Ketamine might emerge as the next big breakthrough in depression treatment. But many questions remain about how it should be administered.

Samantha Cooper

In these chaotic, early days of what could be an important new therapy, Bennett sees a tug of war between three

camps. One is the purely medical: Give the drug to patients and maybe preempt or treat the dissociative side effects with other drugs. In this model, the hallucinations are a nuisance, irrelevant to the therapy's effectiveness. Another approach is "shamanic:" What you see and experience while on the drug is important for healing. The third paradigm combines aspects of both. The goal isn't just to correct malfunctioning neurochemical pathways but, with the aid of a mental health professional, to gain insight into your psyche.

In the 1950s, a physician at Montefiore Medical Center in the Bronx made a prescient discovery. He found that a tuberculosis drug called cycloserine had the unanticipated side effect of lifting patients' moods. (It also caused convulsions and hallucinations in some.) The antibiotic, scientists would later discover, blocked glutamate receptors. This was perhaps the first evidence that the glutamate system might be important in depression.

Forty years later, scientists at the University of Mississippi found that people who'd committed suicide—arguably the end result of a battle with severe depression—had abnormalities in their NMDA receptors compared to controls of the same age. At the same time, researchers were zeroing in on this receptor subtype in rodent models of depression. In 1990, Phil Skolnick, a scientist at the National

Institutes of Health, discovered that when he treated animals with drugs that dampened NMDA receptor activity, they fared better in stressful tests, indicating an antidepressant-like effect.

SSRIs had just come on the market and while many hailed them as a godsend, it remained puzzling why they took so long to work. Skolnick's research again implicated the glutamate system. In animals treated with SSRIs, serotonin went up immediately, but it was only when the activity of their NMDA receptors became suppressed that the antidepressant effect emerged.

These observations suggested that maybe serotonin didn't matter in depression so much as glutamate. They also implied that SSRIs weren't working quite the way many scientists thought they did. Yes, they increase serotonin, "but that by itself is not sufficient. And it's not necessary either," says Skolnick, who's now chief scientific officer at Opiant Pharmaceuticals. Perhaps targeting the glutamate pathway directly could yield a faster-acting antidepressant.

What's remarkable about the story of ketamine is that, despite knowing that the glutamate system might be important in depression by the 1990s, and despite having drugs on hand, like ketamine, that targeted NMDA receptors, no one investigated the possibility in people for years. When scientists at Yale finally tested ketamine on

depressed people in the late 1990s, their primary goal was seeing how the drug might affect perception and the ability to think. Seven depressed patients received intravenous ketamine infusions. The researchers were surprised when every patient's mood improved quickly and dramatically.

The results seemed so over-the-top that even Dennis Charney, one of the study's senior scientists and now dean of the Icahn School of Medicine at Mt. Sinai in New York City, didn't quite believe them. Neither did anyone else, he thinks. No one replicated the research—until, in 2006, when Charney, by then at NIMH, teamed up with researcher Carlos Zarate and repeated it. Of 17 patients treated, 12 improved within a day compared to a placebo group, which saw no response. Five saw their depression completely disappear for the duration of the study.

This time, the field paid attention, and numerous studies followed. Mostly overlooked in this narrative of discovery is that, before bench scientists figured out how ketamine might work, a small community of therapists operating on the margins of science recognized its potential. Since the 1970s, they've accumulated knowledge about the drug that might have some bearing on how to best use it going forward.

A golden, laughing Buddha stands, arms folded across its fat torso, in front of Wolfson and Andries' house on a hilltop

near San Anselmo. When I visit, I find Wolfson, a weekend carpenter, in his driveway cutting a tile with a grinder. He looks up and says, "Do you know what 'pazzo' means?"

It's Italian for "crazy," he answers. He often felt a little pazzo, he adds, as he walks me to a stone patio under an enormous oak tree.

Decades after leaving New York City, Wolfson still emanates Queens, the borough where he spent his early years. He grew up in an observant Jewish household and in his youth regularly conversed with God. But one day during a snowstorm, his faith imploded. He wasn't talking to God, he realized, but to himself.

"In one moment, I lost all my conditioning," he says.

Wolfson dove headlong into the social ferment of the 1960s. He helped organize demonstrations against the Vietnam war and even got himself arrested once. He took LSD while in medical school, tripping with classmates on the roof of his NYU dorm.

These early adventures primed his later interest in using psychedelic drugs to help patients therapeutically. In the early 1980s, by then a psychiatrist, he began working with MDMA, also known as ecstasy and molly. What impressed him about MDMA, which can induce feelings of deep

emotional connection, was how it seemed to accelerate the therapeutic process, helping people achieve lasting transformation. (He and Andries are currently finishing up an FDA-approved trial on MDMA and anxiety in patients with life-threatening illnesses.) But after 1985, when it was classified as a "schedule I" substance, MDMA became illegal to prescribe.

Wolfson first tried ketamine in 1990 with friends. He ended up violently ill and vomiting—he probably received too high a dose—but the experience was transformative. He's a Tibetan Buddhist, and ketamine seemed to take him to places he'd only read about in Buddhist scriptures. A few years earlier, his eldest son had fallen ill with leukemia and, after a four-year battle, succumbed to the cancer. "I begged, 'Please take me and leave him,'" Wolfson told me. "That didn't work." He credited the ketamine experience with showing him how his own mortal form was connected to the timeless, primordial energy of the universe.

It wasn't until 2015, when the couple met a Tasmanian therapist named Stephen Hyde, that they brought ketamine into their practice. Hyde introduced them to ketamine lozenges, which made the treatment cheaper for patients and obviated the need for intravenous delivery with its attendant "medical mumbo jumbo," as Wolfson puts it.

Wolfson and Andries see themselves as pioneering a new

form of psychotherapy. They tend to describe ketamine not with the language of scientific articles but with more Buddhist-sounding phrasing, as giving patients a "time out from ordinary mind." They also send patients home with lozenges, something that the APA recommendations implicitly urge against. Wolfson disdains the recommendations, arguing that ketamine's safety record is far better than the APA authors imply, and pointing out that the ketamine-based drug that's probably closest to FDA approval—a nose spray made by the pharmaceutical giant Janssen—isn't delivered intravenously as the recommendations urge either.

Wolfson and Andries believe they are pioneering a new form of psychotherapy.

Samantha Cooper

Wolfson and Andries haven't published yet, so it's hard for others to evaluate their methods. In certain circles, they're held in high esteem. Clinicians interested in ketamine-assisted psychotherapy often seek them out for training. And Charles Raison, a professor of psychiatry at the University of Wisconsin-Madison, sees merit in the couple's approach. Parallel research on the hallucinogen psilocybin—aka magic mushrooms—for depression suggests as much, he points out. In those studies, patients work closely with therapists, and the ones who had more mystical experiences while on the drug saw a stronger antidepressant response.

But some psychiatrists instead see reckless doctoring. Writing in *JAMA Psychiatry*, three Austrian psychiatrists recently called the ketamine clinic phenomenon, to which Wolfson and Andries arguably belong, "unscientific and dangerous."

Wolfson is unapologetic. He thinks ketamine shouldn't be the last line of treatment, he told me, but among the first. And psychiatrists shouldn't ignore the therapeutic potential of the ketamine experience. "People come back different," he says.

About six months after beginning with Wolfson and Andries, Michael had a breakthrough. As he was coming out of a ketamine session, his mind's eye perceived a smooth, black object that reminded him of the monolith in the movie *2001: A Space Odyssey*. He remembers chuckling to himself, and thinking "What the heck?" Then the monolith morphed into a single word: anesthesia. Michael saw himself as 14 and lying on an operating table. Surgeons in white coats and masks bent over him. One turned to him and said, cheerfully, "Don't worry. You can't feel this. You're under anesthesia."

During a later session at home, with lozenges, the meaning of the vision became viscerally clear. Michael felt that man cut into his belly with a scalpel. He was overcome by a searing pain so unbearable that it seemed to expel him from

his body. He felt like he was floating above himself.

What Michael seemed to have remembered was that he'd woken up during surgery decades earlier—that he was conscious when doctors removed that tumor. It's impossible to know if the memory is real, although the phenomenon, called anesthesia awareness, is documented, and one of its consequences is PTSD. When I asked if Michael doubted the memory's veracity, he said that what led him to believe the memory was true were the details he wouldn't know to make up, like the oily plastic odor of the operating room and the cigarette smell on one nurse's breath.

Once that memory emerged, others surfaced as well. He recalled, for instance, that during his recovery in the ICU, the morphine often wore off, leaving him in agony over the 12-inch incision in his abdomen. Just when its analgesic effects waned, therapists would guide him through a series of coughing exercises to remove fluid in his lungs, which were excruciating because his abdominal muscles had been sliced open. "It was like being tortured several times a day," he says.

For Michael, these memories seemed to explain a lot. Here was the source of the PTSD that Wolfson had so confidently diagnosed that first day. Here was a reason for his panic attacks. At 14, he'd endured the unimaginable. Michael's recollection was cathartic for Lynn too, helping her get over

a long-held grudge. When Lynn was going into labor with their first daughter, at the hospital, Michael suffered back spasms so severe that he had to lie down and—completely inappropriately, in Lynn's view—seemed to doze off. Her 21-hour labor culminated in a C-section, but Michael not only slept through most of her ordeal, Lynn says, he seemed unable to help with the baby afterward. "Bad back, my ass," Lynn remembers thinking. "I just had surgery."

The episode had become a festering source of resentment. Now, though, she felt she understood the cause of Michael's odd behavior: the hospital. His body had reacted to the surroundings without his conscious awareness. Lynn forgave him. "That's been transformative for us," she says, "me letting go."

I repeatedly encountered stories like Michael's as I spoke with ketamine patients, tales of what sounded like cathartic insight followed by psychological healing, as if years of talk therapy were condensed into a few hours. A 40-something man, who'd spent nearly a decade in bed depressed and who'd been mercilessly bullied as a child, told me that ketamine helped him find his "core of obsidian." For years, when he looked in the mirror, he hated what he saw—as if he'd internalized his tormentors' view of himself. But after ketamine, he understood that the bullying wasn't his fault. "I felt empathy for that boy, sorry he had to go through that,"

he says.

Wolfson described this quality of ketamine as permitting patients to "go back and look at trauma without fear." It allowed people to fully face the terror and agony of their own distressing memories. The importance patients placed on these stories didn't entirely mesh with the notion that ketamine merely improved your mood. They suggested that the drug acted on other dimensions of the self as well.

Sometimes the visions people described seemed more allegorical than literal, but no less meaningful. One attorney who'd been sexually abused by her mother's boyfriend while young, and who became deeply depressed after the birth of her first child, told me how, while on ketamine, she'd perceived on her own back two brown and purple butterfly wings, with peacock-like markings, that then enfolded her in cocoon-like safety. She felt immense peace. "There's something really profound about having an otherworldly, spiritual experience to help you, give you something to reflect back on when things are difficult, something that anchors you to this life," she says.

A man in the San Diego area, who'd grown up in a conservative rural town, told me that when, as a teen in the 1970s, he'd revealed that he was gay, his family began treating him like a freak. People in his small town started heaping abuse on him. A few times, cars tried to run him

down.

In middle age, he became so despondent that he decided to end his life. He sent what he thought would be one of his final emails, to a ketamine clinic he'd heard about run by a psychiatrist named David Feifel. Feifel agreed to see him, and during his first session, the man had a vision of being embraced by Jesus. "God said, 'I love you just the way you are and you're fine,'" he told me in a phone call, weeping. "I felt like I was finally reconnected to the source of life."

Can sublime experiences dispel depression? The ketamine studies so far have not rigorously investigated that idea, although some researchers have begun to probe the possibility. Carlos Zarate has found that the quality of patients' ketamine experiences only weakly predict how well they respond. Some felt like they'd left their bodies but didn't improve; others had no such moments yet got better. Terrifying experiences on ketamine are also not unusual; patients sometimes think they're dying, and one clinician recounted how a patient screamed to be brought back to the land of the living. (That person ultimately responded well.) "One of the most common complaints I get is, 'Why in the world would anyone do this for fun?'" says Gerard Sanacora, a psychiatrist at Yale who studies ketamine.

But Wolfson and Andries aren't arguing that the ketamine trance is inherently beautiful, or that "tripping" is key for the

antidepressant effect. They're saying that with guidance, the hallucinogenic experience *can* be meaningful; that it presents another lever the therapist can pull in her quest to help the patient. If some currents of mainstream psychiatry tilt toward the Hippocratic understanding of depression—that it's an organic disease treatable with the right drugs—Wolfson is, in a way, defending the Platonic notion that one's personal history, the subjective experience, is also important.

Some evidence supports a related idea: that ketamine and talk therapy can work synergistically. In a small, preliminary study, Sanacora and his colleagues have found that patients who received cognitive behavioral therapy along with ketamine appeared to have an improved mood for longer than patients who received ketamine alone. Mason Turner, the former assistant director of regional mental health services at Kaiser Permanente Northern California, told me that in Kaiser's experience, while ketamine alone was helpful, patients who also did talk therapy saw greater improvement.

Ketamine augments the brain's ability to change, which could explain why talk therapy might be additive. You're nudging the brain through experience while ketamine, working directly on your neurons, has made it unusually receptive to being nudged. That enhanced malleability is

caused, scientists think, by elevated levels of a protein called brain-derived neurotrophic factor, or BDNF. Blockading NMDA receptors increases BDNF in certain regions of the brain. (Aerobic exercise, another antidepressant, also causes BDNF to rise.)

But why bother with NMDA receptors at all if elevating BDNF is what dispels depression? Two years ago, scientists at the University of Maryland discovered that, in mice, a byproduct of the body metabolizing ketamine was what really exerted the antidepressant effect, not ketamine itself. The metabolite increases BDNF in rodents, and could explain why ketamine seems to stave off depression long after the drug itself has disappeared from the body. Crucially, it doesn't affect NMDA receptors at all, the researchers claimed, meaning that it would likely not have ketamine's hallucinatory effects and addictive potential.

If the finding pans out (and it may not), the metabolite could serve as the basis for a fast-acting antidepressant without dissociative properties—a dream of many in the field. It would also imply that, contrary to Wolfson and Andries, the ketamine experience may not be terribly important for ketamine's antidepressant effect after all.

Last year, I tried ketamine myself. Wolfson and Andries offered it early in our conversations; I should know what I was writing about, they said. I initially declined. I wasn't, as

far as I knew, depressed. But as I interviewed more patients, I became intrigued by the ketamine experience. Where were these people going? How were they achieving their life-altering insights?

So one afternoon in May, in a room with a skylight at the Pine Street Clinic, I lay back on a bed with a red comforter, put a sharp-tasting tablet under my tongue, and pulled on black eyeshades.

Andries put on music—flutes and vocals without intelligible words or a beat. As the pill turned to goo in my mouth, I sank into a fluid warmth and felt as if I'd become a jellyfish-like blob. Behind my eyelids a vast space seemed to open up. Michael had called it the "planetarium," and it did feel like gazing up at an immense night sky. The usual stream of thoughts became more distant as I contemplated this inner universe.

After a second pill, Andries asked if there was anything I would like to talk about. Here's what poured out: my mother. It had been nearly 10 years since she died at a relatively young 63 from mesothelioma, a cancer almost entirely linked with asbestos exposure. She refused treatment—removal of one lung and half her diaphragm, and chemotherapy—which was unlikely to help in the long run anyway. I cared for her as she deteriorated over six months. Her pain had been difficult to control, and at one point

toward the end, she awoke from her delirium and whispered, "Help me." I understood that she was asking my sister and me to help her die. Distraught, we said we couldn't. She died a few days later, in the morning. I was sleeping next to her, holding her hand, and was awoken by her final, rattling breath.

Nearly a decade later, I was still haunted by the experience. I was broke when she fell ill, as was she. Being poor is always rough, but it seems particularly undignified when you're terminally ill. I'd always planned for her to eventually live with me, to give her the space to relax and enjoy life when I had a house and a family—which I now had.

I wept as I told Wolfson and Andries this. "She was supposed to be here," I said. Wolfson told me to "stop twisting the knife" so I could fully engage my memories of her. I'd done everything a good son could be expected to do.

"There wasn't enough time," Andries said. "There just wasn't enough time."

As they consoled me, I saw my mother as a young woman in my mind's eye, her dark hair in two long braids, and also the graying, handsome woman she aged into before she got sick. I embraced these phantoms, wrote "I love you" on scraps of paper in my mind, and tossed them into the space

of the planetarium, hoping they would find her, but also knowing they probably wouldn't because she was, I still understood, gone.

After the session I was emotionally raw, crying randomly, and unsure of what to do with an overwhelming feeling of tenderness. All that faded in a few days, but what didn't disappear was this: a monster headache.

Some doctors use ketamine to treat migraines, but in my case the drug triggered a headache that lasted, on and off, for nearly a month. Wolfson said he'd never seen anything like it in more than 100 patients treated, and he prescribed a migraine medication for me. Wary of more side effects, I ultimately declined to take it.

The headache made the treatment untenable for me, even if I could afford the $1,000 I paid for the session on a regular basis. But the experience was illuminating. Ketamine seemed to pry open the black box of the mind, remaking it as a universe filled with discrete memories and emotions that you could revisit and relive. And as Wolfson had said, it imparted an unusual serenity. In daily life, when grief threatened to emerge, I tended to cringe. But on ketamine, I watched calmly as sorrow welled up and subsumed my body like warm water filling a tub. And it was OK.

As I thought about my experience, I kept returning to

something Mason Turner of Kaiser Permanente, one of the authors on the APA recommendations, had said. Before Kaiser Permanente started its ketamine program, Turner's team had consulted with an extensive range of researchers and clinicians, including Wolfson.

Turner told me that the process had opened him to the possibility that, far from being unethical and dangerous, some of what was happening in practices like Wolfson's might represent innovation to be learned from and emulated.

When I asked for his takeaway on ketamine, he described it as the "most exciting treatment to come to the fore" during his career as a psychiatrist, and said depressed patients should have hope. But he had a more pointed message for scientists. The field was currently failing patients with treatment-resistant depression, he said. It needed all the help it could get. Scientists should "keep an open mind" and not dismiss, out of hand, knowledge accumulated at the grassroots level.

Usually, basic science filters down, he said. But in this case, useful techniques might filter up as well.