

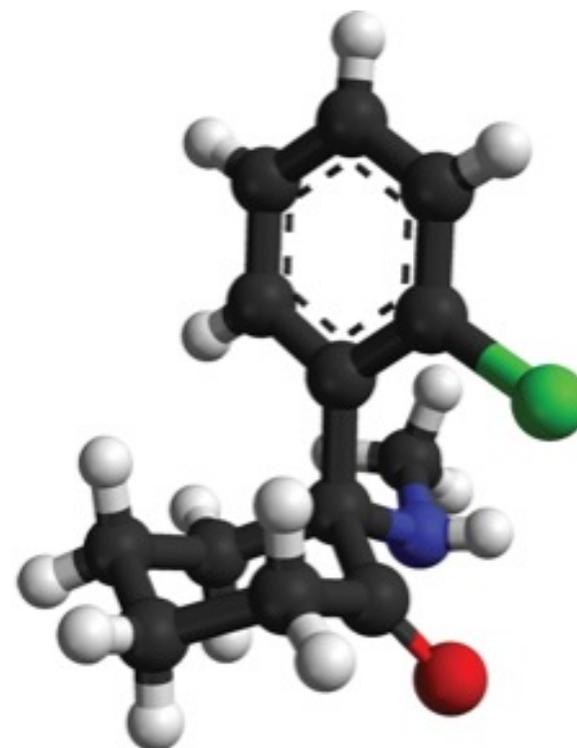
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Anesthesiologists Take Lead As Ketamine Clinics Proliferate

A growing number of anesthesiologists are opening private clinics that provide off-label infusions of ketamine to patients suffering from treatment-resistant unipolar and bipolar depression, post-traumatic stress disorder (PTSD), anxiety, suicidality and other disorders. Psychiatrists and other physicians have also recently opened clinics.

The cost per infusion ranges from \$400 to \$1700, with most clinics charging about \$500. Patients pay out-of-pocket since most health insurance plans do not cover the off-label procedure.

Despite the cost, patients seek the treatments after their antidepressants and other therapies prove ineffective. Proponents claim that, when administered as an IV infusion in a subanesthetic dose (typically 0.5 mg/kg body weight) over 40 to 45 minutes, ketamine begins reversing symptoms of depression for two of three patients in less than 24 hours, with effects persisting for a week or more. Nearly three of four patients suffering from suicidality experience an almost immediate reversal in thinking.



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“The results are amazing,” said anesthesiologist Glen Z. Brooks, MD, founder and medical director of New York Ketamine Infusions LLC, in New York City, and one of the pioneers in the field. His success rate averages about 65% when measured by standardized mood and function surveys, and is even greater for younger adults, he said. The typical course of treatment is six infusions administered every other day for two weeks followed by “maintenance” or “booster” infusions as needed, typically every six weeks afterward.

“The procedure is very well tolerated. We have seen no complications during or after the 45-minute infusions in now close to 8,000 treatments,” Dr. Brooks told *Anesthesiology News*. “I have been treating some patients for as long as three years with ongoing remission of their symptoms, so efficacy can be very long term.”

Ketamine Can Work Quickly

Ketamine was synthesized in the early 1960s and approved for human anesthesia a decade later. It has been administered to millions of patients worldwide, and continues to be an anesthetic of choice for pediatric patients who may experience adverse reactions to other agents. It also is used in pain clinics and when changing dressings of severe burn victims.

For treating depression, it only takes two ketamine infusions to determine whether a patient will respond favorably, whereas traditional antidepressants can take four to six weeks and will work about 30% of the time. During the ketamine infusion, patients remain awake or in a twilight state. Dizziness or a sensation of dissociation is common, and generally disappears shortly after the infusion. “We notice a 50% improvement in depression scores within the first three infusions, which take six days,” said anesthesiologist Enrique Abreu, MD, medical director at Portland Ketamine Clinic in Oregon. “Overall, 75% to 80% of patients see improvement in depression, mood and anxiety after six treatments,” he told *Anesthesiology News*.

Some experts in depression research have called ketamine’s “rapid and robust” antidepressant properties “arguably the most important discovery in half a century” (*Science* 2012;338:68-72). Others urge caution, citing concerns over long-term side effects and potential for abuse. The latter concern stems from ketamine being an illicit “rave” drug (nicknamed “Special K” or “Vitamin K”) that creates intense, short-term hallucinations, dissociation and psychotomimetic effects. Ketamine also is pharmacologically similar to PCP (phencyclidine), a powerful psychotomimetic drug.

While the World Health Organization has long included ketamine on its model list of essential medicines for anesthesia, the drug also has been placed under national control in more than 60 countries, especially in Asia, where abuse is common. Bladder problems and cognitive declines have been observed in long-term recreational ketamine abusers, but none of these effects has been observed in clinical trials.

The anesthesiologists and psychiatrists who administer ketamine infusions for severe depression report overwhelmingly positive outcomes. New Jersey psychiatrist Steven Levine, MD, decided to explore ketamine after reading reports of clinical studies conducted at the National Institute of Mental Health (NIMH). "The results were unlike anything we had seen before, with positive outcomes emerging within days or weeks," Dr. Levine said. "Some really sick people were getting significantly better within hours. I couldn't convince myself to *not* do it."



Dr. Levine quizzed several anesthesiologist friends about potential dangers before opening his clinic. "They were totally nonplussed about the low dosage used in the infusion, unconcerned about any potential for bad side effects," Dr. Levine told *Anesthesiology News*. "They were used to giving it in much higher doses for anesthesia and even higher doses in burn units when changing dressings." Dr. Levine opened Ketamine Treatment Centers of Princeton LLC, in New Jersey, in 2011 and has since treated about 500 patients. He plans to open clinics in Baltimore, Florida and Denver in early 2016.

Mechanisms of Action

Typical FDA-approved antidepressants target neurons that inhibit the reuptake of serotonin, norepinephrine and dopamine. Ketamine works more broadly by blocking the *N*-methyl-D-aspartate (NMDA) receptor, a component of the fast-signaling glutamate system that affects nearly all neurons. Brain scans reveal that ketamine rapidly induces synaptogenesis, repairing damage caused by chronic stress.

Many clinical trials of ketamine for depression have been, and continue to be, conducted at NIMH. A seminal study published in 2006 was a randomized, placebo-controlled, double-blind crossover trial led by Carlos A. Zarate Jr., MD, chief of NIMH's neurobiology and mood disorders treatment section. In this year-long study, patients receiving ketamine showed significant improvement in depression compared with placebo after 24 hours, with effects remaining "moderate to large" after one week (*Arch Gen Psych* 2006;63:856-864). "This line of research holds considerable promise for developing new treatments for depression with the potential to alleviate much of the morbidity and mortality associated with the delayed onset of action of traditional antidepressants," Dr. Zarate and colleagues wrote, citing the need to improve the drug's long-term effectiveness.

Since then, studies at NIMH and elsewhere have demonstrated ketamine's efficacy for rapidly diminishing suicidal ideation (*Drugs R D* 2015;15:37-43), unipolar and bipolar depression (*Cochrane Database Syst Rev* 2015;23:CD011612; *Cochrane Database Syst Rev* 2015;29:CD-011611), and for PTSD and other anxiety disorders (*JAMA Psychiatry* 2014;71:681-688).

The American Psychiatric Association's Task Force on Novel Biomarkers and Treatments urges caution when it comes to clinical use of ketamine. In a systematic review and meta-analysis of randomized clinical trials of ketamine and other NMDA receptor antagonists (*Am J Psych* 2015;172:950-966), the task force concluded: "The antidepressant efficacy of ketamine ... holds promise for future glutamate-modulating strategies." However, the "fleeting nature of ketamine's therapeutic benefit, coupled with its potential for abuse and neurotoxicity, suggest that its use in the clinical setting warrants caution."

When asked to comment on anesthesiologists performing off-label ketamine infusions, the American Society of Anesthesiologists (ASA) provided this statement to *Anesthesiology News*: "The American Society of Anesthesiologists is committed to promoting the highest standards of care for the patients they serve. This new practice area has been brought to ASA's attention and will be carefully reviewed."

Gaining Legitimacy

According to ketamine advocate Dennis Hartman, at least 60 private clinics in the United States offer off-label infusions, and the number is growing. The former business executive says ketamine infusions rescued him from suicide in 2012, and ongoing treatments have brought his depression into remission. As founder and CEO of the nonprofit Ketamine Advocacy Network, Mr. Hartman now works full time with practitioners and patients to help gain legitimacy for the field. His website lists 18 ketamine practitioners in the United States, most of them anesthesiologists, with a smaller number of psychiatrists and neurologists, plus one emergency medicine physician and one family physician.

“There are others that we have not vetted and others that we’ve purposefully chosen not to include,” Mr. Hartman explained, most often because they charge too much money or require expensive additional tests or medical procedures for which clinical evidence is lacking. “There are still others who offer the treatment but want to be under the radar,” Mr. Hartman told *Anesthesiology News*.

Anesthesiologists generally believe they are uniquely qualified to administer ketamine infusions because of their expertise with anesthetics. “I want this to stay as something for anesthesiologists,” said Steven Mandel, MD, founder of Ketamine Clinics of Los Angeles. “Nevertheless, I don’t want there to be a conflict between anesthesiology and psychiatry, because ketamine definitely needs an anesthesiologist to administer it and definitely needs a psychiatrist or psychologist involved because they know about psychopathology,” he said. But ketamine does take “considerable vigilance and finesse” to infuse properly, he added, even for those with years of operating room experience. “This is different because the ‘sweet spot’ for treatment is this side of unconsciousness in the moderate- to deep-sedation range,” Dr. Mandel explained.

Many psychiatrists, on the other hand, believe they are best suited to oversee ketamine therapy because of their expertise in treating patients with depression, PTSD and other conditions. In those ketamine clinics run by psychiatrists, the IV insertion is generally performed by a nurse, not an anesthesiologist, and the infusion is overseen by a psychiatrist and a nurse. Clinics led by anesthesiologists generally do not employ a staff psychiatrist but coordinate with the patients’ mental health practitioners.

Virtually all practitioners—anesthesiologists and psychiatrists alike—recognize the importance of cooperation. Nearly all ketamine clinics require a referral from a psychiatrist or other mental health professional, with few accepting walk-ins. “Three years ago, the relationships [between psychiatrists and anesthesiologists] were difficult, to say the least,” said anesthesiologist Mark Murphy, MD, who established Ketamine Wellness Centers in Phoenix, in 2013. “However, the momentum is shifting. Now we regularly receive referrals from mental health professionals.”

Those patients who do best tend to have psychiatrists or therapists supporting them throughout the treatment course and are engaged in a team approach, said anesthesiologist Isabel Legarda, MD, medical director at Boston MindCare LLC. "I believe anesthesiologists and psychiatrists must work collaboratively when it comes to ketamine infusion therapy; anything less shortchanges patients," she said.

Insurance Coverage?

Because ketamine is generic, pharmaceutical companies have no financial incentive to sponsor the costly clinical trials needed to win FDA approval, generally a prerequisite for insurance coverage. Recognizing this, there is a movement in the ketamine community to gather and publish retrospective chart data and promulgate best practice guidelines. "There's never going to be an FDA label for ketamine to treat depression," said Dr. Levine. "But once more guidelines and protocols for using ketamine in clinical practice are published, it is very likely that insurers will consider covering it," he predicted.

At least two drug companies are developing new ketamine variants that might be easier to administer and which lack some of the generic's less-favorable short-term side effects, such as dissociation, and which insurers may be willing to cover. Johnson & Johnson's subsidiary Janssen Pharmaceuticals is conducting late-stage clinical trials of esketamine, a variant that can be administered via a nasal spray. The FDA granted the drug "breakthrough" status in 2013, which streamlines the regulatory approval process. Allergan's subsidiary Naurex Inc. is testing GLYX-13, an IV NMDA receptor variant that reportedly is effective in about half of patients in 24 hours, but without ketamine's dissociative side effects. NeuroRx Inc. is testing a drug, Cyclurad, whose ingredients include D-cycloserine, an NMDA receptor modulator.

Dr. Levine and other physicians caution colleagues against starting a ketamine clinic to make quick money. "If someone is thinking of doing this part time to pad their income, there could be bad outcomes because these patients are very vulnerable," Dr. Levine said. "This is an area that could use some regulation and standardization so that patients don't get hurt, and what is a very important treatment becomes lost."

Most ketamine practitioners say their motivation stems from having had patients or family members who were treatment resistant and, in some cases, even committed suicide. For them, money is secondary to the satisfaction they gain. "For me, this has been a much more demanding and professionally rewarding practice than being in a hospital operating room," said Dr. Brooks. "It requires a special dedication and availability."

