Depression is a common and debilitating mental disorder, with over 8% of Americans aged 20 and over suffering from the disease. There are significant burdens on patients, family members and society as a whole. Suicide rates have steadily increased since 1999, from 10.5 per 100,000 to 14.2 (a 35% increase). Treatment has been challenging, often consisting of multiple medications and modalities such as antidepressants, psychotherapy, transcranial magnetic stimulation (TMS) and electroconvulsive therapy (ECT).

The search for a new and novel treatment for depression was underway in the 1990s as many patients were resistant to common antidepressant medications. Researchers began investigating the use of ketamine, an anesthetic that was introduced into clinical use in the 1960s. Ketamine is a useful anesthetic because it affords cardiovascular and respiratory stability while allowing effective sedation and analgesia. It can be given through multiple routes, including intravenous (IV), intramuscular (IM), oral, nasal, rectal, subcutaneous and epidural. While its mechanisms of action are multifactorial, it primarily acts as an NMDA-receptor antagonist. Ketamine is considered a “dissociative” anesthetic, potentially causing an out-of-body experience. Other side effects include nausea, vomiting, hypertension, hallucinations and a feeling of “grogginess” or drowsiness. Some patients describe feeling numb.

HISTORY OF KETAMINE FOR TREATMENT RESISTANT DEPRESSION

In 2006, researchers at the National Institute of Mental Health found that ketamine produced rapid and relatively sustained antidepressant effects in patients with treatment-resistant depression. Since then, ketamine has shown benefits in treating bipolar depression and reducing suicidal thoughts. Newer studies have shown a ketamine metabolite (HNK) activates AMPA receptors essential to ketamine’s antidepressant effects.

While ketamine is not effective in all patients, the responders showed remarkable improvement in affect, daily functioning skills and interpersonal relationships.

While not yet FDA-approved for the treatment of depression, IV ketamine has been utilized widely across the U.S. over the past decade. Protocols vary, but generally a sub-anesthetic dose of 0.5 mg/kg infused over 40 minutes is administered to patients in a controlled setting such as a doctor’s office or hospital. Six to eight total doses are typically given over the course of several weeks, with additional infusions administered as needed for return of depression symptoms.

As IV ketamine use started to become more widespread and many articles appeared in the medical literature about its use for treatment-resistant depression, my anesthesia group decided to open a ketamine clinic in Kansas City in 2016. We formed a partnership with a psychiatry group to provide dual subspecialty expertise in the administration of this still relatively new treatment. We believed our patients would best be served by a physician anesthesiologist, an RN specializing in anesthesia care and their own psychiatrists. Our team administers the IV ketamine infusions in a monitored, yet comfortable and private, setting.

PATIENT FEEDBACK ON SYMPTOMATIC RELIEF

Right from the outset, we could see that this treatment produced very impressive symptomatic relief in certain patients. The Patient Health Questionnaire-9 (PHQ-9) was utilized to quantify depression symptoms before and after treatments. Scores range from minimal/none (0-4) to severe (20-27); we started seeing patients go from over 20 prior to starting therapy, to 5 and below after treatment. While ketamine is not effective in all patients (approximately 25-30% have not responded), the responders showed remarkable improvement in affect, daily functioning skills and interpersonal relationships. One anecdote that remains in mind from our beginning days...
came from a female patient in her 50s. She was a mother who loved to cook meals for her family, something depression rendered her unable to do. She came to our clinic after a series of treatments and told me, with tears in her eyes, that she went to the grocery store and cooked dinner for the first time in years.

**LESSONS LEARNED**

We have administered over 1,000 IV ketamine infusions since we opened our clinic. We have learned a great deal over the past few years, and here are some important pearls:

- Patients often come in expecting a “miracle drug.” It doesn’t work that way. Most patients will show slow, gradual improvement. Many patients describe it as keeping the depression symptoms at bay, helping them control the symptoms so they can maintain better daily function. It is often a significant other who is the first to notice small changes before the patient recognizes them in him/herself.

- Don’t get discouraged if improvement is not experienced right away. We have had a number of patients claim the ketamine simply wasn’t working, yet during follow-up several weeks after treatment completion, they started noticing positive changes. There are likely some “slow responders.” Other patients will figure out a pattern of recurrence of their symptoms and schedule maintenance infusions accordingly.

- Nausea and, to a lesser extent, vomiting are common. We now treat everyone prophylactically with an antiemetic.

- A detailed medical history and physical exam are absolutely necessary to screen for exclusion criteria. While ketamine has an excellent safety protocol, there are certain conditions that preclude its use. Additionally, not everyone is a candidate for office-based ketamine administration and would be better served in a hospital setting.

- Presently, the cost of ketamine treatment can be prohibitive for many patients. Until it is approved by the FDA, all costs are out-of-pocket. In March 2019, the FDA approved esketamine (Spravato), a ketamine nasal spray, for use for depression. Absorption is not as predictable in the nasal route compared to IV, and it still requires administration in a clinical, monitored setting.

- We still have much to learn about the long-term outcomes and potential side effects of ketamine therapy. There may be other conditions besides major depressive disorder that respond to ketamine, such as bipolar disorder and post-traumatic stress disorder (PTSD). Often, patients with mental health diseases have underlying substance abuse disorders, and this must be kept in mind as ketamine has the potential for abuse. We have been encouraged by our results over the past four years, and look with anticipation for future uses of ketamine.

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**REFERENCES**


