Hope in Treatment-Refractory Depression
Bret Stetka, MD, David Feifel, MD, PhD | Jan 10, 2013

Editor's Note: Severe, treatment-refractory depression is one of the most challenging conditions facing psychiatrists. And, unfortunately, it's very common. Now, an old drug -- ketamine -- is having a renaissance in psychiatry and is offering hope to patients unresponsive to standard antidepressant therapies. Medscape recently spoke with David Feifel, MD, PhD, Professor in the Department of Psychiatry at the University of California, San Diego, about his experience with using ketamine in the treatment of depression.

Ketamine: Old Drug, New Tricks

Medscape: We've been hearing a lot about ketamine's potential as a psychiatric medication lately. Can you give us some background on the medical and cultural history of the drug?

Dr. Feifel: Ketamine has been approved for veterinary and human use as an anesthetic agent for decades. It produces a type of anesthesia called a "dissociative anesthesia," meaning that it tends to dissociate or cut off the physical sensation of the body from the mind. Ketamine is used every day in medical centers around the world, including my institution, UCSD Medical Center, as an anesthetic and as an analgesic for intractable pain. However, the latter use is somewhat controversial, in terms of the potential long-term benefits.

Ketamine is also used illicitly for recreational purposes, typically as part of the club scene, and in this capacity it goes by various names, such as "Special K." Pharmacologically, ketamine is related to other known street drugs such as phencyclidine (PCP), also known as "angel dust."

Medscape: How is ketamine being used in psychiatry? And is this a relatively recent approach?

Dr. Feifel: Psychiatric use of ketamine is very recent and stems from research findings in patients with treatment-resistant depression. In such patients, infusional ketamine at a dose that is significantly lower than the anesthetic dose can produce a strong antidepressant response.

Not only do these challenging depressed patients respond, but the response is very rapid. Ketamine differs from anything we have with which to treat depression. The efficacy rate is higher than traditional antidepressant medications, and the onset of the antidepressant effect is almost immediate compared with conventional antidepressants, which have a latent efficacy that can take several weeks to fully manifest. This novel therapeutic profile is what has garnered so much attention for ketamine.

Medscape: Was ketamine's potential as a psychiatric drug an incidental finding?

Dr. Feifel: The recognition of its psychiatric potential came from a few seminal published research papers in which ketamine was tested as an antidepressant against placebo and shown to produce high rates of efficacy and very rapid effects. A couple of investigative groups conducted fairly rigorous research that, when published, generated a lot of attention and excitement and made the field aware of the potential of ketamine for depression.
Approved, but Not for Depression

Medscape: Is there approval potential for ketamine in depression?

Dr. Feifel: Though approved decades ago by the US Food and Drug Administration (FDA) for human use as an anesthetic, ketamine it is not FDA approved for depression, and I don't think it's likely ever to be approved for depression because the patent on ketamine has long expired.

Medscape: How might this affect its clinical use in this area?

Dr. Feifel: Typically, when we are presented with promising therapeutic data on a compound, it is a novel investigational agent that hasn't yet been approved by the FDA for any human use and is thus not in the hands of the medical community at large. As a potential "new" medication for depression, ketamine is unique because it is already approved for human use and has been used in humans for a long time with a very good safety record. This affords the opportunity of using it off-label in a clinical context for depression while the research into that indication continues on a parallel track.

Medscape: In your opinion, is there enough evidence to support using ketamine off-label for depression?

Dr. Feifel: There are many people with clinical depression who are in extreme distress right now. They have virtually no quality of life and are struggling to stay alive every day. They are often without hope because they have tried just about every conventional antidepressant treatment. For many of these people, ketamine may provide some relief of their depression. Therefore, as long as such a patient understands the limitations of ketamine, I don't see any reason to deny him or her the opportunity to benefit from this potential game-changing drug.

I selectively offer ketamine to appropriate patients in the context of full disclosure. At UCSD, we have developed a consent form that lets the patients know that ketamine is not FDA approved for depression, that it is still undergoing study for its antidepressant effect, that it may or may not effectively alleviate their depression, and that if it does, the benefits from a single administration will be transient. The consent form also makes it clear to the patient that this treatment is generally not covered by insurance, so there will be out-of-pocket costs. We let them know all of this upfront so there is no illusion of what we are offering. Most patients that I encounter already know these issues because they have extensively researched the use of ketamine for depression and have specifically sought out this treatment.

Desperate for Relief

Medscape: Are you finding that your depressed patients are satisfied with the results they're seeing from ketamine?

Dr. Feifel: Yes and no. The majority of patients, but not all, are very pleased with the acute effects of their ketamine treatments. The problem lies in the fact that nobody yet knows how to most effectively translate the acute benefits of ketamine into long-term benefits. Aside from a lack of response, the lack of sustainability is where patients may become disappointed.

Medscape: How widely is ketamine used around the country for psychiatric purposes?

Dr. Feifel: Since we first started offering ketamine for depression, we have seen a few other clinicians in both academic and private practice settings starting to offer it. Ketamine is slowly becoming clinically available.

Medscape: Do you reserve ketamine for the most treatment-refractory patients?
**Dr. Feifel:** At this point, the cost-benefit ratio justifies using ketamine, in my opinion, in highly treatment-refractory patients, a population which, unfortunately, is plentiful. It is disheartening how many patients with depression actually fall into a category where none of the current treatments give them significant relief.

Maybe in the future, as our experience and comfort with using ketamine in this population increase, it will justify gradually extending it to patients who are earlier in the process of finding a treatment that works for their depression.

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**How to Use It**

**Medscape:** How does your group administer ketamine?

**Dr. Feifel:** When we started offering ketamine, it was administered in an intensive monitoring environment -- the post-anesthesia care unit (PACU) at UCSD Medical Center -- and it was administered intravenously by anesthesiologists. The problems with that were 2-fold. Because of the involvement of the anesthesiologist and the intensive setting, the cost of an infusion was very high, and given that patients could require more than one infusion to continue to extract benefit, the treatment was cost prohibitive for many eligible patients. The second problem was the PACU was not a highly conducive setting for this treatment. So, we worked with our anesthesiology colleagues and the UCSD Medical Center and our Pharmacy and Therapeutics committee to develop a protocol that was specific for using low-dose ketamine to treat depression that did not require anesthesiologists to administer it. That has allowed us to move the ketamine infusions to an outpatient infusion center and lower the cost. It is still done in a hospital setting but a much more conducive environment for this type of treatment.

**Medscape:** Can you walk us through the typical patient experience? And how does dosing work?

**Dr. Feifel:** Well, keep in mind that our approach is evolving as we learn more about the drug and how best to use it to help patients. Typically, we start with the well-established infusion regimen of 0.5 mg/kg infused intravenously over 40 minutes. The efficacy rate we have been seeing from this single infusion is approximately 70%-80%.

**Medscape:** Is the response immediate?

**Dr. Feifel:** Almost all of the patients we have treated describe a dissociative experience that comes on fairly early during the infusion. Everyone experiencing this has generally retained an overarching sense of reality; that is to say, they recognized their dissociative experience for what it was: a drug-induced perceptual distortion. Most patients find it to be a bizarre but enjoyable experience. When we turn off the infusion, those dissociative sensations dissipate very quickly, typically within 30 minutes. However, the interruption of their oppressive depressive symptoms that occurred during the infusion typically persists.

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**The $64,000 Question**

**Medscape:** How long do the beneficial effects of ketamine tend to last?

**Dr. Feifel:** That is the most important question right now. Typically, we are seeing 4-10 days of benefit. A small group of patients did not respond at all, and in others, the antidepressant effects were gone within a day. The effects usually last a week, plus or minus 3 days.

**Medscape:** That’s a significant duration. For someone in such a bad state, I would think a week can be pretty meaningful.

**Dr. Feifel:** Exactly. Many patients are so desperate to experience some relief of their depression that they tell me beforehand that if the effects of ketamine last only a couple of hours, or even just the 40 minutes’ duration of the infusion, it would be worth the effort and cost. Having their depression turned off, even for a brief time, is a big deal to someone whose entire waking existence is unrelenting misery, hour after hour. It’s not just that they feel better for
an hour or two. For many patients, the remarkable recognition that their depression can be turned off, that they can feel good and remember what it is like to feel good, renews their hope for pursuing treatment.

The big challenge now is how to translate that short-term benefit into a lasting benefit to the patient. Our initial instinct was to administer an intense series of 2-3 ketamine infusions weekly, over several weeks, similar to the way electroconvulsive therapy is administered, with the idea that if you give an intense series, you may be able to convert a transitory effect into something more durable. However, I was dissuaded from taking this approach by emerging research findings that were not encouraging. One study showed a median 18-day sustainment of benefit after an intense infusion series. That might be a little bit longer than the duration of benefit following a single infusion, but it's not long enough to justify giving 6-9 infusions over a short period of time. Therefore, I don't believe this intense infusion series approach is going to be the answer to converting acute responses into more chronic improvements.

Right now, in the UCSD program, we are more oriented to a repeat treatment for maintenance approach. We look at a patient's first infusion to answer some important questions. Does ketamine work in this patient? If so, how long do the benefits last? If they last only a day, it is very challenging, and we focus our efforts on figuring out how to convert it into a longer effect. But for patients in whom the benefits of the ketamine infusion last at least a week, some sort of repeat treatment maintenance schedule can usually be developed. We now have a small group of patients who are on such a maintenance regimen. Although it is very early, so far, some of our patients have been on such a maintenance regimen for months, and it has profoundly changed their quality of life.

There is a cyclical aspect to ketamine infusions; patients feel better for a week or more, and then they go through the usual gradual dissipation of the effects. However, a second-level progression occurs over weeks to months, in which the baseline symptoms of depression seem to be improved. When the patients come in for their next treatments, they are not as depressed as they were before ever receiving ketamine. We don't know whether this improvement is a reflection of long-term pharmacologic effects of the drug slowly healing their depression or the result of psychosocial aspects -- they have more depression-free days and that experience in itself may be inducing a gradual improvement. They no longer expect to feel only misery; they expect to feel normal even when they are in the part of the treatment cycle where the overt benefits of ketamine have worn off. Over time, we are seeing that feeling better might be therapeutic in itself, and perhaps patients will need fewer ketamine treatments.

How Safe Is Ketamine?

**Medscape: Aside from the dissociative phenomena, does ketamine come with any serious potential adverse effects?**

**Dr. Feifel:** We have not seen any significant adverse events. There is, of course, a transient impairment in their cognitive abilities and sedation, so we do not let our patients drive themselves home, and we ask them not to plan any activities for the rest of the day. There is also typically mild elevation in blood pressure and heart rate during the infusion. We do know from the nondepression ketamine literature that a small percentage of patients can become dysphoric and agitated due to the dissociative experience, but we have not encountered that at all yet.

**Medscape: Is there potential for addiction?**

**Dr. Feifel:** That's a good question. A concern about ketamine as a treatment has been that it might not be viable because of a potential for addiction. We are, thus far, seeing no evidence of that at all. Although patients generally find the actual "trip" they experience during the treatment enjoyable, we have seen no evidence that they are seeking additional treatments for that experience. Rather, they are seeking additional treatments to reinstate or continue the relief from their depression that they have obtained. For example, we have had patients request to postpone their prescheduled maintenance ketamine treatments because their benefit from the prior treatment was still enduring.
Medscape: What is next for your institution’s ketamine research and usage?

Dr. Feifel: We are considering introducing some modifications to our current protocol; for example, a higher-dose infusion in patients who tolerate but don't respond to the 0.5-mg/kg dose. We don't know why some patients don't respond or have a very short duration of response, but some people may simply be less sensitive than others to the drug and require a higher dose.

Medscape: Do you have any final thoughts on ketamine’s role in psychiatry?

Dr. Feifel: I hope the exciting promise we are seeing from the research and from the early clinical application of ketamine persists. I have been disappointed with the currently available armamentarium to treat depression. It's humbling to see so many patients with severe depression who haven't responded to any conventional therapies. So it's very exciting to have a drug that seems to represent a whole new level of efficacy. My colleague and fellow UCSD psychiatrist, Dr. Scott Irwin, is using ketamine to treat depression in the hospice population and having similar success. As the use of ketamine evolves, it could usher in a new era in the treatment of depression.

References


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