COMMENTARY

Is Ketamine Living Up to the Promise for Depression?

Lloyd I. Sederer, MD; J. John Mann, MD

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After years of dormancy, psychiatric drug development is showing signs of life. There is the novel antipsychotic lumateperone, recently approved for adults with schizophrenia. Brexanolone was approved last year for postpartum depression. And perhaps generating the most attention lately among psychiatrists — and people with depression — is the use of ketamine and esketamine for depression.

Columbia psychiatrist J. John Mann, MD, a professor of translational neuroscience and a mood disorder specialist, has been involved in several notable studies of ketamine in patients with depression. He and his colleagues' recent research efforts include a randomized study into ketamine's ability to reduce suicidal thoughts in bipolar depression and an MRI analysis illuminating the role that dosing plays in antidepressant effects.

Mann sat down with his Columbia colleague Lloyd I. Sederer, MD, to discuss how, nearly a year after its approval, ketamine fits into mental health care.

Lloyd I Sederer, MD: Nearly 20 million people in this country alone suffer from clinical depression every year. That means they have a functional impairment in addition to their suffering and are at risk of taking their own lives. Depression is a very prevalent, painful, and disabling condition. The psychopharmacologic treatments we've had have been more or less the same for the past 20 or 30 years.

We've asked Dr Mann to come here today and talk to us about ketamine and its nasal preparation esketamine, which is a novel psychopharmacologic treatment. Dr Mann, please tell us about ketamine, its utility, and the yet-to-be-answered questions.

J. John Mann, MD: Ketamine and esketamine, which is a component of ketamine itself, is different from traditional antidepressant medications in three fundamental ways.

The first is that it acts very quickly. Traditional antidepressants take 4, 6, 8 weeks to work. This means that the patient has to put up with a great deal of suffering while waiting for a response. And the probability of the medication working isn't that high. About 50%-70% of individuals will respond *eventually* at the end of this ride. But ketamine, when it works, does so in 2 hours. That's a totally different timescale.

The second aspect is that when it does work, it often works very robustly, even though it's a quick-acting antidepressant. The patient often quickly feels distinctly better.

Very often when you're using traditional antidepressants, it takes a while for the improvement to reach the point that the patient is confident that they are clearly better, and too often that does not happen.

Sederer: As the treating doctor, you're trying to keep that patient's hope alive, even though we don't have substantial evidence that they're going to respond.

Mann: Exactly. One of the difficulties of keeping patients on track with traditional antidepressants is that after the first dose or two, they have all the side effects and yet no benefit has emerged. In many ways patients sometimes feel that they're going backwards. They have all of their depression *plus* the side effects of the medication.

But with ketamine, it's rather different. You come in, you have the treatment, and many patients feel improved in a couple of hours. And not just a bit improved, but in many cases distinctly improved.

It's very important for clinicians to appreciate that ketamine will work in patients who have a classically described treatment-resistant depression, meaning they've tried several other types of antidepressant medications that haven't worked.

A prerequisite for treatment with ketamine is that they have had a number of treatment failures. The labeling for the intranasal esketamine states that you should try the other antidepressants first and then use this if they don't work. The fact that ketamine can work even when the other medications have failed is a huge advantage.

Sederer: There is another feature of ketamine, in that it also has a pronounced benefit for suicidal ideation, which your research has reported on.

Mann: Yes, we've learned over the years that depression and suicidality are in some ways comorbid conditions. That *both* have to be addressed in order to keep somebody alive so that they can respond to treatment.

That's a very important point. If the patient is suffering from depression and the antidepressant takes weeks to work, they may lose hope during that time. They may become overwhelmed by the suicidal ideation, no longer able to control or resist the impulse to take their life. A lot of the management is therefore to try to help support the patient (and family) so that these thoughts never become too compelling. Often we have to consider hospitalization to protect these patients so that they can stay alive long enough in order for the antidepressant to work. But ketamine not only has this very rapid effect for their depression; it also has a partly *independent* effect on suicidal ideation that is equally rapid and robust, which can render the patient safer.

Sederer: In other words, it's effective and rapidly so for depression, with a bonus of reducing suicidality? This sounds almost too good to be true.

Mann: There are some limitations that we have to keep in mind. One limitation is that a single administration of ketamine will produce this robust improvement but it will only persist for most people for 5-7 days.

Sederer: Is the same duration true for scheduling the next treatment as well?

Mann: Yes, it is. The patient will gradually begin to deteriorate if you do not repeat the treatment. But as we showed in our randomized controlled clinical study with ketamine for suicidal ideation, if you continue to deliver the medication, you can sustain the benefit.

Sederer: Can a person receive both ketamine and a conventional antidepressant at the same time?

Mann: Yes. In this study, half of the patients were actually continued on their previous medication while we added the ketamine on top of that. It worked very well.

In practice, people use two approaches. One approach used by most ketamine clinics is to give six doses of ketamine at a frequency of about two per week. Then they will reduce the frequency down to once a week for a few more doses and then once a month.

Sederer: And this is a ketamine infusion?

Mann: Yes; this generally has been a ketamine infusion. This approach seems to work quite well. But that may not be necessary.

Another strategy is to give one, two, or three doses of ketamine. If the patient doesn't respond robustly to two or three doses, they're not going to respond to subsequent doses.

Sederer: So, initial responses are a predictor of future response?

Mann: Exactly. Now, if they haven't done well with two or three doses, then you've got to use other treatments. But if they do well with the two or three, then you've got a choice: You can either complete the treatment course with ketamine and then continue them on antidepressant medications, or simply treat them with ketamine alone. What we tend to do is to only treat with antidepressant medications after a small number of ketamine treatments. We also use ketamine as a kind of "rescue medication" if they relapse into severe depression, though this is only true for a minority of patients.

Sederer: One of the things that we've learned is that antidepressants have a very beneficial effect for some people, but then they wear out and the person starts to relapse. Should ketamine be studied as an intervention for people who are no longer responding to the antidepressant(s) that they are on?

Mann: We do not really know the answer to that question. My experience treating very seriously ill patients is that sometimes the ketamine will work very well the first time or the second time, but then in the future, if you try to use it as a rescue medication, it might not work that well. There is some clinical experience that suggests that that may be true for some people. But we have no idea about the frequency or timing with which this might happen. That's all uncertain.

Moreover, most of our control clinical trial data come from either one dose of ketamine or from a few trials where people have received multiple doses of ketamine, followed by a bit of a taper. But there are very, very few of those types of studies. We're still learning about the use of this medication.

Sederer: Importantly, you referenced the side effects of antidepressants. What are the side effects and risks of ketamine?

Mann: We know a lot more about the immediate short-term side effects of a single dose or a few doses of ketamine. Most people will get a kind of tripping experience. They'll feel a bit unreal, or their circumstances or experiences of the world feel a bit distorted.

Some patients develop strange ideas. Most patients don't enjoy those symptoms, even though I know ketamine is used as a party drug, and so on and so forth.

Sederer: It seems that the context is what matters.

Mann: Yes. And in a clinic context, most patients simply don't enjoy these types of dissociative experiences, but they put up with them. They're not severe, in general.

Sederer: Is part of the preparation of the patient telling them that this may happen?

Mann: Yes. We try to explain the potential for these symptoms and that most people get them. These side effects almost invariably terminate with the cessation of the administration.

Sederer: What's the typical duration of the infusion you use?

Mann: Traditionally, infusion is 40 minutes and always in a clinic setting.

Sederer: And that's because of the concern that a patient may have these symptoms?

Mann: Exactly. They may have dissociative effects that they're disturbed by, and we need to monitor that. They're probably going to remain under observation in the clinic for about the same amount of time because it takes about the same time for these effects to wear off.

The other consideration is that some people get a little nausea. In our experience with the intravenous ketamine, there's also a problematic side effect that their blood pressure will be slightly raised. Therefore, it's good to know that the person's blood pressure is under control before they begin the treatments and that you're monitoring it during administration.

Sederer: What are the differences you're discovering between esketamine and ketamine?

Mann: It is a bit different. We've just completed a very important National Institutes of Health–funded clinical trial here at Columbia showing that with esketamine or ketamine itself, the dose and the blood levels are very closely related to the robustness of the clinical response.

When you give a drug intravenously, you give a very reliable dose. When you give the drug over 40 minutes, you're spreading the dose administration over a period of time so that it doesn't peak very high. The side effects appear to be proportional to the peak dose.

When you give it intranasally, you give the drug over a much shorter period of time. Even if you use more than one intranasal administration to give the whole dose, it's still a relatively shorter time compared with the 40 minutes.

Sederer: This means that to get the equivalent dose intranasally, the patient is going to have to experience a higher peak. Can you predict that those patients who are treated intranasally are going to have more side effects?

Mann: Right. And that should be explained to the patient. You will not need an intravenous line inserted, which some people might find highly appealing and advantageous, but you will probably have more side effects.

Also, in general, intranasal absorption of drugs is more variable. The predictability of the blood level and, therefore, the degree of antidepressant effect is not as good intranasally as intravenously.

Now, all of this is anecdotal clinical experience, based on theoretical pharmacology, because nobody has actually done a head-to-head control comparison.

Sederer: What about the cost of both of these preparations?

Mann: There is a bit of a range in pricing between ketamine clinics around the country. It's always important to find out what they charge per administration. And then it makes a difference whether you have two or three administrations vs six plus further tapered administration. Clearly, the cost can vary a great deal.

Sederer: But it's generally not covered by insurance, so most people are paying out of pocket.

Mann: Yes. The intranasal ketamine is still in a matter of negotiation at the moment, but it should be resolved before it's fully marketed.

Sederer: Ketamine is used for major depression. Does it have utility in bipolar depression?

Mann: We and some others have done initial studies in bipolar depression. In our view, it's probably going to be as effective in bipolar disorder as it is in major depressive disorder, unipolar depression.

We haven't seen any manic episodes triggered, but we don't give repeated doses. We allow research patients to stay on anticonvulsants or mood stabilizers, so that's helpful. Generally, people with bipolar disorder who come for ketamine treatment for their depression are coming on a mood stabilizer, because that and perhaps other conventional antidepressants have not proven to be effective. So, I think that ketamine plus mood stabilizers seems to be very promising.

Sederer: I want to return to the antisuicidal properties that you had previously mentioned. I heard from a colleague about a patient who had been admitted to a psychiatric inpatient unit. The patient was in her 20s; she did not have major depression but was persistently suicidal, constantly trying to hurt herself in any way she could. But that seemed to be more product of borderline personality disorder, with its impulsive and self-destructive problems.

In the end, they tried intranasal ketamine. The response was, just as you described, robust. Her self-injurious behavior dropped in a very pronounced way within a day or two. But she then did require administrations a couple of times a week in order to keep that suicidality at bay.

Based on that example, I'm wondering whether there is an application here for people who are suicidal yet who may not have features of major depression or bipolar depression.

Mann: It's a very interesting suggestion for which we have no data-based answer. However, we have a clue from the study that we published in the *American Journal of Psychiatry* and have since published further analyses on.

The reasons that people die by suicide, or make suicide attempts, are not entirely due to the fact that they suffer from a mood disorder.

Sederer: Yes, because only a minority of individuals with a mood disorder ever make suicide attempts. But there is a subgroup at risk.

Mann: Here at Columbia, we've promulgated the stress-diathesis model for suicidal behavior. A stressor could be external life events, but the internal stressor would be something like an acute episode of depression.

But predisposition also plays an important role, which has several elements to it. One is decision-making. These are patients with a propensity to go for a short-term, quick relief. In other words, a patient would be seeking immediate relief rather than waiting for the delayed improvement from an antidepressant. They're more prone to act on the pain of the depression and terminate their lives — to try to end their pain — rather than wait and hope that, in time, there's a chance that the antidepressant will work.

Sederer: What else do you want to share with our viewers about this medication and how it's used?

Mann: My goal in treating patients is to try to use the least amount of medication possible. We do not really know yet the long-term safety of ketamine treatment.

It's been used for many decades in anesthesia, but people don't get repeated anesthetic doses of ketamine. And higher doses of ketamine given repeatedly have been shown in preclinical studies to produce little lesions in the brain, which is not good. But we're using much lower doses.

As we potentially move into a time when we could be giving multiple doses of ketamine to patients, we should remember that we need to be cautious about that. If we don't need to give them more doses, we shouldn't. We should know that there is a potential downside that we don't fully understand yet about giving ketamine repeatedly.

And that's aside from its abuse potential. We know that people have employed ketamine for physical and emotional pain, and when they administer it themselves, they tend to get dependent on it. In a clinic setting it's given in a very formal and structured fashion, a bit like the administration of opioids. In that setting, it is much safer and the risk for abuse and diversion is minimized. But we need to remember that this drug does have abuse potential and perhaps not yet fully measurable and neurotoxic effects.

Sederer: If physicians, nurses, and other professional clinicians want to learn more about this medication, what are the accurate, reliable sources of information to which you suggest they turn?

Mann: The National Institute of Mental Health's website offers good and reliable information for patients and their families. It is an unbiased, scientific, and thoughtful source of information, and better than just trolling the internet for information.

People are much more sophisticated now than they were 20 years ago in these matters, and scientific papers are much more accessible to the public. Reading papers in recognized journals is also a useful way to gain information.

For example, one of the major papers that we published in the *American Journal of Psychiatry* is available to anybody on the internet to read. So, I encourage people to make their own inquiries and talk to more than one doctor. Informed patients and families are the best partners a doctor can ever have. We encourage that in all of our patients.

Sederer: I want to thank you very much, Dr Mann, for your work in this area and for joining us here at Medscape and Columbia Psychiatry to teach us so much about what is truly a novel psychopharmacologic agent, yet one where we still have a lot more to learn.

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