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Ketamine clinics vary widely in pregnancy-related safeguards, study finds

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A patient receives a ketamine infusion for depression at the University of Michigan Health clinic, which requires pregnancy testing before treatment begins and weekly testing during treatment, as well as specifically recommending the use of highly reliable forms of contraception during the course of ketamine therapy, for all patients who could become pregnant. Credit: University of Michigan/Leisa Thompson

More hospitals and clinics now offer patients ketamine therapy for

severe depression, post-traumatic stress disorder and other mental health conditions that haven't responded to other treatments.

While ketamine is a safe medication when used with medical supervision , it does have a little-known complication: It may be very harmful to a developing fetus. It should not be used during pregnancy.

But a new study suggests that ketamine prescribers aren't paying enough attention to this risk and should do more to make sure that patients receiving ketamine aren't pregnant and are aware of the need to use contraception while undergoing a course of treatment over multiple months.

The new article in the *Journal of Clinical Psychiatry* was written by researchers from the University of Michigan's academic medical center, Michigan Medicine. It reports the results of a survey and document review conducted on ketamine clinics nationwide, and a review of records from the ketamine clinic for depression at U-M Health.

In all, the team found a wide variation in policies, practices and warnings about ketamine use related to pregnancy and reproduction. This is despite the fact that the 119 clinics that answered the survey report treating a total of more than 7,000 patients with ketamine per month, and estimate that a third of patients they serve are female and pre-menopausal.

Key findings

More than 75% of responding clinics said they have a formal pregnancy screening process, but only 20% actually require a pregnancy test at least once prior to or during treatment.

More than 90% of clinics said they note that pregnancy is a

contraindication to ketamine treatment in their informed consent documents and/or conversations. But less than half of clinics reported discussing specific potential risks with patients.

The researchers also looked at informed consent documents on the websites of 70 other ketamine clinics. In all, 39% did not include language about pregnancy in their documents, and those that did were generally vague.

When it came to contraception counseling, only 26% of the clinics that answered the survey said they discuss the potential need for contraception with ketamine patients. Less than 15% of the clinics specifically recommend or require contraception use during treatment.

This is especially striking, the authors say, because more than 80% of clinics reported prescribing long-term maintenance ketamine, with nearly 70% of these saying their patients receive care for more than six months and many saying patients receive ketamine for a year or more.

The review of records from 24 patients treated with ketamine at U-M's clinic in the past showed all had taken a pregnancy test before beginning treatment and weekly during treatment, and but only half had documentation in their records that they were using contraception.

Inspiration for the study

Lead author Rachel Pacilio, M.D., a psychiatrist who recently joined Michigan Medicine as a clinical assistant professor after completing her residency at U-M Health, said the idea for the study came to her during a rotation in the perinatal psychiatry clinic.

Patients who were pregnant or had recently given birth asked her about ketamine as an option for their treatment-resistant depression. They had

heard of the potential positive impact of the drug when given intravenously as an off-label use of a common anesthetic, or as an intranasal spray of esketamine that's marketed as Spravato and approved by the U.S. Food and Drug Administration.

"There was little guidance available to prescribers other than the general recommendation to avoid ketamine in patients who are pregnant, because of the unknown potential impact on a fetus or a breastfeeding newborn," says Pacilio. "That sparked our interest in surveying clinics to see how they were handling this during their intake processes, initial treatment courses, and during the maintenance therapy phase. As far as we know, this is the first time this has been looked into."

Variation in oversight

Clinics offering intravenous ketamine require specialized staff and post-administration monitoring for each session. And the FDA specifically requires at least two hours of in-person observation after dosing of intranasal Spravato to ensure safety and monitor for complications.

By contrast, other formulations of ketamine can be administered outside the clinical setting with minimal oversight. Some clinics surveyed reported prescribing sublingual ketamine for at-home use.

The new study did not include online, direct-to-consumer ketamine providers that offer treatment exclusively via telehealth consultations. It is unknown how these companies address reproductive and other safety concerns despite their growing popularity among patients.

"These data suggest that a large population of patients could be pregnant, or could become pregnant, while receiving ketamine treatment via multiple routes of administration. This risk increases with the duration of therapy, which can last weeks for the initial course and a year or more

for maintenance," said Pacilio. "Many patients do not know that they're pregnant in the first weeks, and animal studies of ketamine are very concerning for potential harm to the fetus during this time."

She noted that while many psychotropic medications have been studied extensively and found to be safe for use in pregnancy, including a variety of antidepressants, antipsychotics and other psychiatric drugs, there is no data to support the use of ketamine for psychiatric illness in pregnancy.

Pacilio pointed out that the FDA's risk mitigation program for Spravato, the nasal form of ketamine, does not include any provisions about pregnancy. A warning issued by the FDA last fall about the risks of compounded forms of ketamine available online also does not mention precautions about pregnancy.

"The variability in practice that we see among clinics in the community in this study is stark," said Pacilio. "The field is really in need of standardization around reproductive counseling, pregnancy testing and the recommendation for contraception during ketamine treatment."

If someone becomes pregnant while undergoing ketamine treatment, and has to stop receiving the drug for the remainder of the pregnancy, they are at risk for a depression relapse that could continue after the baby is born. Perinatal and postpartum depression are major risk factors for a range of issues in both the birthing parent and the infant.

Need for standard guidance

After sharing their findings about U-M patients in the new study with leaders of the U-M Health ketamine clinic, Pacilio said that the clinic began recommending the use of highly-reliable forms of contraception to patients who could become pregnant while receiving ketamine treatment.

Small standalone community clinics offering ketamine therapy may not have the same resources that a large clinic like U-M's does, so standard guidance could especially benefit them.

Interventions including improved patient education with an emphasis on the requirement for pregnancy prevention for the duration of ketamine treatment during the informed consent process, routine pregnancy testing before and during treatment for appropriate patients, and effective contraceptive counseling are needed. Many of these could be easily implemented and have the potential to positively impact public health.

"Ketamine is a really effective, potentially lifesaving, treatment for the right patients, but not everyone is a good candidate for it," she said. "As psychiatrists, we need to ensure this treatment is being delivered in a way that benefits patients while preventing harm."

In a commentary in the journal about the U-M team's findings, psychiatrist and journal editor Marlene Freeman, M.D., wrote that based on the new findings, "It is imperative that best practices for women of reproductive age for the use of ketamine and esketamine are determined and utilized." She added that this is especially important in light of the changing landscape of abortion-related laws.

Freeman also noted that those who have used ketamine in any form during pregnancy, as well as other psychotropic medications, can join the National Pregnancy Registry for Psychiatric Medications during pregnancy and help provide much-needed information on the impacts of these medications.

In addition to Pacilio, the study's authors include Jamarie Geller, M.D., M.A., a psychiatry fellow at U-M, and faculty members Juan F. Lopez, M.D.; Sagar V. Parikh, M.D. and Paresh D. Patel, M.D., Ph.D.

More information: Study: Rachel M. Pacilio et al, Safe Ketamine Use and Pregnancy, *The Journal of Clinical Psychiatry* (2024). DOI: 10.4088/JCP.24m15293

Commentary: Marlene P. Freeman, Reproductive Pharmacovigilance and Best Practices, *The Journal of Clinical Psychiatry* (2024). DOI: 10.4088/JCP.24com15473

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