CHCC RESEARCH BRIEF

Ketamine Shows Early Promise for Treatment-Resistant Depression
but Comes with Risks

October 2023

Ketamine is a drug receiving media attention as a potentially effective treatment for treatment-resistant depression and conditions such as chronic pain and post-traumatic stress disorder (PTSD). Ketamine is a dissociative anesthetic approved for sedation by the FDA over 50 years ago. Most ketamine used to treat mental health conditions is prescribed "off-label" (i.e., for a purpose or in a form or dose not approved by the FDA).

On October 23, 2023, the FDA issued a warning stating that "ketamine is not FDA approved for the treatment of any psychiatric disorder" and further noted that "FDA has not determined that ketamine is safe and effective for such uses."

A study published in *The New England Journal of Medicine* in 2023 reported results of a clinical trial comparing ketamine to electroconvulsive therapy (ECT) for drug-resistant depression found promising results for ketamine *compared* to ECT. The comparative effectiveness study, funded by the Patient-Centered Outcomes Research Institute (PCORI), follows other research suggesting benefits of ketamine for treatment-resistant depression.

Study methods, limitations

The trial randomized patients with treatment-resistant depression to either electroconvulsive therapy (ECT) or intravenous (IV) ketamine for 3 weeks. It evaluated clinical and quality of life responses to each treatment against harms and side effects. Using a statistical standard called "noninferiority" which researchers defined in advance to determine clinical significance, ketamine was found to be noninferior to ECT with fewer side effects for adults with treatment-resistant major depression. The study methods had strengths but also had limitations:

Strengths	Limitations
• Patients randomly assigned • Set standard for inferiority in advance • Published in peer-reviewed journal	• Patients not "blinded"; knew which treatment they received • Long term effectiveness not studied • Repeated use, associated safety not studied • Tested on narrowly defined clinical condition

Findings

The trial had an active treatment phase of three weeks. Researchers found IV ketamine was easier to administer and fewer patients dropped out. Ketamine's side effects were not as serious as ECT's, which include memory loss. Ketamine's side effects include dissociation, but this is "not usually an unpleasant experience for patients," according to a physician leading the study. Patients continued to take anti-depressant medications in both arms of the trial.

A higher proportion of the ketamine group (55%) reported a 50% or greater reduction in symptoms, compared to 41% of the ECT group. By the end of a 6-month follow-up period, relapse had occurred in 56% of the patients in the ECT group and in 34% of the ketamine group. Adverse effects of memory loss from ECT and dissociative symptoms from ketamine had decreased by the six-month mark, and patient-reported quality of life was similar in the two treatment groups. Researchers concluded ketamine was noninferior to ECT in treatment of moderately severe depression in this trial.

"For someone who is chronically ill with depression, three weeks of lightened mood is undoubtedly a gift. Many patients have reported ketamine therapy to be life-changing, and many clinicians are enthusiastic about bringing this gift to patients who otherwise seem unreachable. However, the results of this current trial suggest that the 3-week treatment was not life-changing. Ketamine treatment was effective, but by 6 months, a brief period in a lifetime of depression, quality of life was no better with the agent than with ECT." Robert Freedman, MD, who was not involved in the study.

What does research like this mean for purchasers?

As the "buzz" surrounding ketamine and psychedelics as potentially effective treatments for mental health conditions grows, expectations on plan sponsors to cover them may grow. Like other mental health treatments, a cash-based ketamine business is growing. Yet evidence for its long-term effectiveness and safety for major depressive disorder or for a broad set of mental health conditions is not well established.

Most drug therapy requires FDA approval, which is a threshold of evidence and safety used by pharmacy benefit managers (PBMs) for coverage on formularies. However, off-label prescribing is permitted by the FDA and is common. PBMs may require prior authorization on coverage of off-label usage. When ketamine is injected, which is the most common form of administration for on and off-label uses, it may fall under the plan medical benefit. Ketamine comes with serious risks, including adverse events and the potential for addiction and diversion. Long-term use of ketamine is understudied both from safety and effectiveness lens.

Key Takeaways

Ketamine is a dissociative anesthetic approved by the FDA decades ago for use in surgery. Its patent has expired.

FDA has yet to approve ketamine by injection for any mental health condition.

Ketamine is a controlled substance, has serious risks and must be administered under clinical supervision.

Results of a comparative effectiveness trial suggest ketamine may benefit patients with treatment-resistant depression.

A nasal version of esketamine, branded SPRAVATO, has been approved for adults with treatment-resistant depression.

Economic incentives to research ketamine's effectiveness for mental health conditions are limited due to its generic status.

FDA approval and the economics of drug development

The original patent for ketamine used for anesthesia has expired. As a result, the economic incentive to test, seek FDA approval, mass produce and market ketamine for treatment-resistant depression or other mental health conditions has diminished.

However, by focusing on the molecule esketamine and formulating it in a nasal spray, Johnson & Johnson created a drug that could be patented and succeeded in getting FDA approval in 2019 (brand name Spravato).

The FDA approved esketamine under a controversial pathway that required less evidence than a standard approval but required the drug only be administered under strict controls of a Risk Evaluation and Mitigation Strategy (REMS) to ensure the benefits of the drug outweigh its risks. It has a restricted pharmacy distribution channel, and the drug must be self-administered by the patient under direct observation of a health care provider for at least two hours.

How the FDA decides

The FDA compares benefits (i.e., efficacy) versus harms in evaluating whether a new drug is both safe and effective. The FDA generally requires at least two randomized clinical trials for the purpose sought in the application before approving a new drug or new use for a drug. Randomized clinical trials (blinded and using placebos in the control group) are considered the "gold standard" research method for demonstrating efficacy.

The difference between efficacy and effectiveness is that effectiveness is evaluated under "real world" conditions which may not be as ideal as those in most clinical trials but may reflect how the drug will perform. While the FDA will also look at other currently available treatments for the same condition, it does not typically require a direct comparison evaluation of two or more treatments (comparative effectiveness) for approval.

Off-Label Use

Physicians and other clinicians with prescribing authority are permitted to use a drug for off- label purposes. Most health plans and PBMs only cover drugs approved by the FDA, and may also cover off- label uses. One estimate indicates one in five prescriptions are for off-label use. The original FDA applicant may conduct formal tests for off-label purpose(s) and seek FDA approval for additional conditions or populations but is not required to.

The growing popularity of off-label uses of ketamine, and different forms of ketamine used clinically, highlight why the answer to the question, "is ketamine covered under your plan?" could be "maybe." Ketamine may be administered as an injectable in the veins or muscles, taken in pill form, or even as an FDA-approved nasal spray. Plan design and vendors may influence the form and setting of coverage.

TREATMENT	FDA APPROVED?
KETAMINE BY INJECTION	For sedation; original patent expired; now generic status
	Not yet approoved for depression, other MH conditions
ELECTROCONVULSIVE THERAPY (ECT)	FDA regulates ECT as medical device (does not require clinical trials for devices)