Curr Psychiatry Rep (2014) 16:527
DOI 10.1007/s11920-014-0527-z

Proceed with Caution: Off-label Ketamine Treatment for Major Depressive Disorder

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Published online: 12 October 2014

Abstract Ketamine offers a promising new option for the treatment of depression, but its increasing off-label use is ethically and clinically inappropriate at the moment.

Keywords Ketamine · Depression · Ethics · Consent · Safety

Introduction

Research over the past two decades has shown that *N*-methyl-D-aspartate (NMDA) receptor antagonists have antidepressant properties [1]. One such NMDA antagonist is ketamine, which has been used as an anesthetic in veterinary and human medicine since the 1960s. Ketamine has been shown to stimulate new synaptic connections that may have been adversely affected by stress or trauma. These short circuits, in turn, have been implicated in clinical depression.

While there have been significant advances in antidepressant drugs over the past half century, all FDA-approved antidepressants target monoamine pathways and take a number of weeks to reliably separate from placebo. In contrast, ketamine activates the mammalian target of rapamycin (mTOR) pathway immediately stimulating synapse growth, plasticity, and signaling. Ketamine administration, typically done by infusion, creates a temporary dissociative state—1 or 2 h long—that is often followed by a distinct and clinically meaningful improvement in the patient's mood and in depressive symptoms [2]. This antidepressant effect usually lasts a few days and sometimes lasts as long as a few weeks. Importantly, the dose of ketamine that results in these dramatic clinical effects is much lower than the doses that are used by both anesthesiologists and people who abuse this drug for its psychoactive effects.

Clinicians, patients, and families have embraced enthusiastically the possibility that ketamine may offer patients with refractory mood disorders a viable treatment alternative. In fact, there are now dozens of providers nationwide who offer off-label ketamine infusions on an outpatient basis. While very promising, enthusiasm around ketamine should be tempered by a careful analysis of clinical, ethical, and policy questions related to its increasing off-label use (Table 1).

Clinical Issues

Patient Safety

Ketamine is approved for use as an anesthetic. It is not approved as a treatment of depression. As with off-label use of any other medicine, the use of ketamine as a treatment of depression should meet one basic standard—that the benefits to patients outweigh potential harms. Although ketamine has been shown to be safe as an anesthetic, it remains unclear whether this safety profile can be assumed for patients with depression and other psychiatric comorbidities. When used as an anesthetic, ketamine is administered by a trained anesthesiologist, who carefully monitors vital signs in a highly controlled operating room setting.

In contrast, many of the current providers of ketamine infusions for depression, as far as we can tell, are not anesthesiologists nor do they have particular expertise using intravenous infusion to deliver therapeutic regimens. Thus, although it is reassuring that the dose of ketamine typically used

This article is part of the Topical Collection on *Mood Disorders*

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Table 1 Summary of interrelated clinical, ethical, and policy issues arising from off-label, outpatient administration of ketamine to treat major depressive disorder

Clinical issues	
Patient safety and oversight	• Safety profile of ketamine has not been established in patients with MDD • Ketamine should be administered in a hospital setting by qualified anesthesiologist, not in an outpatient setting • Clinics should have emergency equipment and trained personnel • Lack of oversight exposes patients to risk of harm • Future research could be delayed due to irresponsible use of ketamine
Cognitive effects	• Long-term data on effects of serial use of ketamine on cognitive function are unavailable
Tolerance and dependence	• Ketamine is a schedule III controlled substance and may lead to physical or psychological dependence
Ethical issues	
Capacity and informed consent	• It is unclear that patients with MDD are fully capacitated to appreciate decisions concerning off-label ketamine treatment • It is unclear that outpatient consent processes are adequate to fully inform patients with MDD
Inducement	• Financial incentives for ketamine treatment may undermine patient voluntariness and consent • Risk of financial exploitation of vulnerable population
Access to alternatives	• Patients should be provided with information about clinical trials of ketamine as a potential alternative to off-label administration
Policy issues	
Approval and regulation	• Pending clinical trial results, ketamine may gain FDA approval, which would lead to greater regulation and broader access (e.g., insurance may cover the treatment)
Regulating ketamine clinics	• Require anesthesiologists to collaborate with psychiatrists to administer ketamine infusions • All adverse events should be reported promptly • Longitudinal monitoring of clinical progress and adverse events should be required, as longer-term consequences of multiple doses remain undetermined

to treat depression is well below that used as an anesthetic (e.g., about one fourth of the dose), one still wonders how many practitioners have handy the safety monitoring tools that would be considered standards of practice to anesthesiologists, including having immediate access to a crash cart and oxygen, or if treatment is always being administered by a physician with advanced cardiac life support training.

We also wonder how often these clinicians follow the standard treatment protocols used in clinical trials or if they determine treatment protocols themselves through trial and error or based on nonclinical research, blurring the line between treatment and ad hoc experimentation [3••]. Similarly, it is unclear whether they have carefully inquired about possible prior patterns of use or abuse of ketamine.

Without proper expertise, protocol design, and oversight, these clinics run the risk of harming their patients. If a patient experiences a severe adverse reaction or dies as a result of an unsanctioned ketamine treatment, public trust in this intervention will be compromised. The current promising research trajectory for ketamine may be detoured or delayed. A clinical mishap may increase policymaker concerns about the drug, which already has the reputation as a party drug. Known as Special K, Kit Kat, and Lady K, ketamine has been diverted and abused for decades for its hallucinogenic and analgesic properties. Also considered a rape drug, ketamine is included under the Drug-Induced Rape Prevention Act [4]. Off-label ketamine providers should consider these broader concerns and implications.

Cognitive Effects

Data on the cognitive effects of ketamine are equivocal. There is recent evidence that ketamine used to treat refractory depression may precipitate cognitive impairment. A 2013 study indicated that an inverse relationship exists between the cognitive effects of ketamine and antidepressant efficacy [5•]. Patients with treatment-resistant depression (TRD) who responded to ketamine within 24 h exhibited poorer baseline neurocognitive performance compared to nonresponders, with a slower processing speed and impairments in memory recall. However, in a comparison study between ketamine and triazolam for anesthetic use, ketamine was found to produce less cognitive impairment than triazolam at doses that produced a greater subjective response [6]. Therefore, compared to other drugs, ketamine may produce less unwanted cognitive effects and may offer greater potential for therapeutic gains.

The addition of ketamine as an anesthetic adjunctive to thiopentone during electroconvulsive therapy (ECT) did not elicit cognitive deficits beyond that seen with the use of thiopentone alone. Additionally, patients who underwent ECT with the ketamine-thiopentone combination, as opposed to thiopentone alone, exhibited greater therapeutic effects [7]. An earlier study examining the addition of ketamine as an

anesthetic for ECT found less short-term anterograde memory impairment compared to etomidate anesthesia [8]. Therefore, when used as an anesthetic for ECT, ketamine appears to mitigate cognitive impairments compared to other anesthetics, as well as enhance the therapeutic effects of the treatment. Baseline assessments of cognitive functioning prior to ketamine infusions remain relatively unstudied; before-and-after cognitive measures are indicated.

However, long-term, frequent use (more than four times a week) of ketamine produces cognitive deficits such as decreased working memory and recognition memory in nondepressed recreational drug users [9]. The long-term effects of ketamine use in patients with treatment-resistant depression, where serial treatments are staggered semiweekly, weekly, or biweekly, remain unexplored. There is minimal evidence thus far investigating the cognitive effects of ketamine when used as an infusion treatment for TRD.

Dissociative and Hallucinogenic Effects

The semantics around ketamine's psychedelic effects are clinically and ethically important, particularly when disclosing information about risks to patients during an informed consent discussion. Ketamine may be described as a dissociative agent, general anesthetic, or dissociative sedative in clinical and academic contexts. It is also described as a hallucinogen in recreational settings or other contexts of illicit use [10, 11].

It is unclear whether clinicians and patients in outpatient settings understand the use of ketamine as a moderately benign dissociative agent or potentially dangerous hallucinogen. Patients might be told they will experience a "bad dream" or "dissociation" and would generally consider ketamine to be safe. In contrast, frequent users report experiencing catatonia, memory loss, paranoia, anxiety, severe bladder cramps (k-cramps), and other psychological and somatic adverse effects [12]. The background understandings of both patient and clinician with regard to the nature of ketamine needs further study, so that risk and benefit information may be disclosed in an appropriate manner.

Tolerance and Dependence

In 1999, the US FDA classified ketamine as a schedule III controlled substance. The intoxicating effects of ketamine are dose dependent, and for most people, a dose of 1.0 to 2.0 mg/kg will produce a state of dissociation (people commonly report the sensation of floating in space), often coupled with euphoria, illusions, and/or hallucinations. Larger doses can induce a more sedated state, sometime called a "K-hole," which may represent the brink of an anesthetized state. Some people seek this level of intoxication for its "mind expanding" effects, though others experience it as a noxious state that is likened to a near-death experience. One reason for ketamine's popularity is that it is considered to be a "club" drug and it is said that the drug's effects can intensify environmental experiences.

As with other drugs that are taken for this purpose, such as ecstasy, ketamine is commonly used in concert with alcohol, cannabis, and—not infrequently—stimulants and opiates. Although not extensively studied, there is some evidence that repeated use of ketamine can result in the development of tolerance to the effects of the drug, and anecdotally, some heavy repeated users report that they stop experiencing the dissociative effects. In most cases, heavy use occurs within discrete binges, which may last hours or even several days. Anecdotal evidence suggests that some people will experience withdrawal symptoms when ketamine use is abruptly stopped after a heavy period of use. More data are needed on individual variations of the effects of ketamine on pharmacokinetic and pharmacodynamic metabolic patterns and drug-drug interactions.

Ethical Issues

Patient Capacity and Informed Consent

Serious ethical concerns arise when considering the degree to which severely depressed patients are able to consent to what is essentially an experimental procedure. Currently, there are no assurances that patients who sign up for off-label ketamine treatment—many of whom are undoubtedly desperate to find relief for the unremitting pain of depression—understand fully the experimental nature of the intervention and the potential risks of treatment.

This concern is particularly acute in patients with mental disorders that might undermine capacity. Capacity may be conceptualized as a trait or as a state [13]. When capacity is construed as a context-dependent state, a sliding scale to determine a baseline is often useful. The capacity standard for low-risk, high-benefit treatments would be less than that required for higher-risk treatments. Because the safety profile of ketamine for major depressive disorder (MDD) is currently being studied, it is difficult to determine the threshold of capacity that is appropriate for depressed patients. While it is true that empirical evidence indicates that patients with depression have the capacity to make decisions concerning consent to participate in research, it is less clear that patients with major depressive disorder or treatment-resistant depression retain capacity in the clinical setting, particularly when offered an inducement of some kind for treatment [14].

Inducement

If avoiding the pain of depression was not motivation enough, particular ketamine clinics currently offer financial incentives to patients for repeated treatment. For example, one clinic in Arizona offers infusions for $750 each for the first six, after which the patient is given a $500 rebate [15]. Variations of this financial incentive appear to be a common practice. We are concerned that such inducements are coercive at best and predatory at worst. They undoubtedly compound the complexity of an already ethically fraught informed consent process by raising questions about the true freedom and voluntariness of a particularly vulnerable patient population.

Access to Alternatives to Off-label Treatments

The above financial incentives seem to be structured toward inducing a particular socioeconomic patient population. Those who are able and eager to pay for services out of pocket will have access. This raises concerns about equity and fairness, given the disproportionate burden of depression in patients of lower economic status [16].

Clinical trials are underway to better study the risks and benefits of ketamine as a treatment for treatment-resistant depression. An alternative to the unregulated ketamine clinics is to enroll patients in these clinical trials, which take place in a safe and closely monitored environment, so they may reap the benefits of the initial evidence that point to ketamine as an effective treatment while minimizing potential risks.

Health Policy Issues

Regulating Clinics

Until the clinical trials are complete and clear guidelines on the most effective and safe administration of ketamine for TRD are determined, it is difficult to regulate the off-label use of ketamine in private clinics. These clinics are treating, and purportedly helping, severely depressed patients. As such, it would be unethical to pull the plug entirely on the off-label use of ketamine, since the drug has shown promise. One regulatory measure in the interim should be to require that anesthesiologists be on staff in these clinics to administer the actual ketamine infusion or at least that the clinicians have gone through training adequate to address risks that might emerge. Proper medical oversight or possibly training will mitigate some of the risks involved in delivering an off-label treatment.

Ketamine Approval

If the clinical trials produce results similar to the promising anecdotal evidence for ketamine as an alternative treatment for depression, proponents of the drug can vie for FDA approval so ketamine's usage in the treatment of depression would no longer be considered off-label. While gaining FDA approval is a lengthy process, it would mean greater available treatment options for severely depressed patients.

It should be noted that a number of pharmaceutical companies are working vigorously to develop oral preparations that would minimize or eliminate the dissociative effects and the potential for abuse while also being longer acting. Arguably, patients seeking the off-label treatments should be informed about these initiatives to aid their informed decision-making.

Insurance Coverage and Formulary Inclusion

FDA approval would greatly enhance access to ketamine for depression, as insurance companies could then weigh the option of expanding their prescription drug formularies to include coverage for ketamine infusion treatments. Insurance companies will not be required to cover the drug if it gains FDA approval, but they will certainly weigh the costs and benefits for a drug that has shown promise for high-use consumers who have failed multiple rounds of previous depression treatments. The financial cost of a series of effective ketamine infusions would be much less than continued prolonged ineffective treatment methods.

Conclusion

The results of controlled studies of ketamine have opened a new vista of hope for a novel class of mechanistically different medications for patients with treatment-resistant MDD. A recent commentary argued that clinicians should be wary of the "slippery ketamine slope" [17••]. We agree. Proper ethical oversight, clinical guidelines, and informed consent procedures should be developed before ketamine is used in the outpatient setting for treatment of depression. Concomitantly, because of the drug's reported promise and even potential life-saving impact of ketamine-like interventions for those who may have treatment resistance because of glutamatergic underpinnings, there should be vigorous and collective support from all directions to prioritize truly large-scale research efforts with longitudinal follow-up, to evaluate and accelerate the evolution of a safe and effective intervention.

Compliance with Ethics Guidelines

Conflict of Interest Dominic Sisti and Andrea G. Segal declare that they have no conflict of interest.

Michael Thase reports personal fees from Alkermes, AstraZeneca, Bristol-Myers Squibb Company, Gerson Lehman Group, GlaxoSmithKline, Guidepoint Global, H. Lundbeck A/S, MedAvante, Merck and Co., Neuronetics, Inc., Ortho-McNeil Pharmaceuticals, Pfizer, Roche, Shire US, Inc., Sunovion Pharmaceuticals, Inc., and Takeda. Dr. Thase also has received grants and personal fees from Eli Lilly & Co., Forest Laboratories, and Otsuka as well as royalties from the American Psychiatric Foundation, Guilford Publications, Herald House, W.W. Norton & Company, Inc., and Peloton Advantage.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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