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Feature

Ketamine for depression: the highs and lows

Long used as an anaesthetic and analgesic, most people familiar with ketamine know of it for this purpose. Others know it as a party drug that can give users an out-of-body experience, leaving them completely disconnected from reality. Less well known is its growing off-label use in the USA for depression, in many cases when other options have been exhausted.

David Feifel, a professor of psychiatry at the University of California, San Diego, was one of the first clinicians to use ketamine off-label to treat depression at UCSD's Center for Advanced Treatment of Mood and Anxiety Disorders, which he recently founded. "Currently approved medications for depression all have about the same, very limited efficacy. A large percentage of patients with depression do not get an adequate level of relief from these antidepressants even when they have tried several different ones and even when other drugs known to augment their effects are added to them", Feifel tells *The Lancet Psychiatry*. "The stagnation in current antidepressant medication on the one hand, and the tremendous number of treatment-resistant patients, has propelled me to explore truly novel treatments like ketamine."

Compelling published study results and case reports exist of patients' depression—in some cases deeply entrenched depression that has lasted months or even years—alleviating within hours of use of ketamine. However, critics have warned that the drug has not been studied sufficiently (at least outside clinical trials), and also emphasised the cost. Patients can pay more than \$1000 per session for treatment that must usually be repeated several times. That cost is rarely covered by the patient's medical insurance.

The balance between prescribing ketamine off-label to patients with depression (who have exhausted other options) against making all patients wait until ketamine or a derivative is licensed for depression is the key ethical dilemma, says Dominic Sisti, an assistant professor in the Department of Medical Ethics and Health Policy at the Perelman School of Medicine, University of Pennsylvania, PA, USA. "I don't think patients who have exhausted all options should have to wait, but I worry that off-label use is not being properly monitored", says Sisti. "If patients are fully competent and informed, they should have the right to access ketamine—but we have to be sure they understand it is basically an experimental treatment. This is a vulnerable patient population."

Another criticism is that patients who have exhausted treatment options might be willing to try anything. "This implies that patients with treatment-resistant

depression (TRD) may be so desperate for relief that their ability to perform an appropriate calculation of the risks and benefits of trying ketamine is impaired. This insinuation infuriates many TRD patients in my experience", says Feifel. "The other assumption is an implicit one that somehow using ketamine for depression is highly risky or fraught with many side effects. Both are simply wrong."

Advocates of ketamine use in depression are excited because it has a different mechanism of action to standard antidepressants, which affect signalling by monoamine neurotransmitters such as serotonin, noradrenaline, or dopamine. Ketamine is thought to act by blocking N-methyl-D-aspartate (NMDA) receptors in the brain, which interact with the amino acid neurotransmitter glutamate. The resultant chemical changes in the brain caused by ketamine are not yet fully understood, but could involve ketamine-induced gene expression and signalling cascades that act long after the drug has been eliminated from the body. Meanwhile, critics say that the adverse effects of the drug, including the emergence reactions (hallucinations, dreams, and out-of-body experiences) sought after by recreational users, need further study before long-term use of ketamine can be approved for depression. Feifel states that he has patients who have been receiving ketamine treatments every 2–4 weeks for long periods, some for around 3 years, and has not yet seen any safety issues arise.

Pharmaceutical companies are entering this exciting arena by attempting to develop new drugs based on ketamine without similar side-effects. Naurex, situated in Evanston, IL, USA, recently reported results from a phase 2 study of its drug GLYX-13, which reduced depression in around half of the 400 patients in the study without any psychotic side-effects. The drug is given by injection once every 1–2 weeks, and should enter phase 3 trials later in 2015. Other pharmaceutical companies are developing drugs with other modes of administration. Johnson & Johnson (New Brunswick, NJ, USA) are developing a nasal spray containing a ketamine derivative, Crecicor (Baltimore, MD, USA) is developing a once-daily oral pill, and Naurex is also developing an oral version of GLYX-13. However, Feifel dismisses the notion that the dissociative so-called trip induced by ketamine is actually an important negative side-effect. "I have not had a single patient discontinue treatment due to the dissociative psychedelic experience", he explains. "Although I have had a couple patients have unpleasant 'trips', it's exceedingly rare, usually dose related, and very transitory due to ketamine's rapid metabolism."



Feifel says that, more often than not, patients find the trip to be positive, or even spiritual, and believe it is an important component of the antidepressant effect they experience afterwards. "There is no doubt the dissociative effect represents a logistical issue, requiring monitoring—and this should be addressed in any approval given for ketamine", he adds.

In the UK, ketamine has been used in two clinical trials for treating depression. Rupert McShane is the lead consultant for the local electroconvulsive therapy (ECT) service based at Oxford Health NHS Foundation Trust, Oxford, UK. His clinic took part in a UK National Institute for Health Research study (REDKITE) in which ketamine was administered for TRD in a series of 28 cases. These patients were largely referred by secondary care psychiatrists, but some contacted McShane's team following advertising or after reading about the study on the internet. Some patients had been actively looking for somewhere where they could receive ketamine treatment.

"Our team used one of the beds in the recovery bay of the ECT suite to administer ketamine during sessions where other patients—not those receiving ketamine infusions—were receiving ECT", explains McShane. "This had the advantage of having a team present which is familiar with treating resistant depression, and also an anaesthetist. Despite evidence of the efficacy of ECT, many patients are unwilling to try it. Thus, ketamine or similar compounds may have a role in those who would otherwise have had ECT."

McShane adds that his team is "exploring what options there may be for providing a ketamine service for people with treatment resistant depression". He explains that intravenous infusions seemed to clearly establish whether someone was a responder or not. "Our experience was that a second infusion was necessary in order to be able to decide whether someone was a responder, but if they have not responded by then, then they will not respond to further infusions at the same dose", explains McShane. "Its effect in those people who respond is dramatic. However, it is hardly surprising that a single dose does not usually have an enduring effect—one would not expect that of a single dose of any antidepressant." He adds, however, that "a few people seem to have much more prolonged responses—for several months. So far, the only way we know of to create a sustained effect in someone who has a brief response is to give it repeatedly, and also through co-prescription of conventional antidepressants which may also prolong the effect. I cannot see a future in which we will not be harnessing the use of ketamine in some way."

In terms of the safety profile of ketamine, McShane believes that adverse effects of long-term ketamine use on the bladder, which have been reported in people who

misuse it recreationally, are strongly dose and frequency related, and have not occurred in the context of medical use. "The dissociative side-effects are clearly dose related. Some patients will get benefit from ketamine at doses which do not cause them, but there is likely to be a trade-off", he explains. "Ketamine is safe enough, and there has been so much experience of it, that it is on the WHO essential drugs list. Tolerance may develop, especially if used very frequently, but this would only be problematic if *ad libitum* use was proposed. Routes such as intranasal, oral, intramuscular, and sublingual all have potential advantages and disadvantages in this regard. Yet whether alternative related compounds will have real safety advantages over ketamine would require formal study: it will be expensive to show that, for a dose of equivalent efficacy, their long-term safety is as good as ketamine."

Sisti cautions that any clinicians giving ketamine for depression should be fully trained in ketamine administration. "Many are but some may not be", he says. "Clinics should be outfitted with appropriate emergency equipment, and staff trained on its use. The FDA should set up a voluntary reporting system to track outcomes or adverse events so that some data can be gathered in the field on the safety and efficacy of ketamine for depression."

Feifel says that it is not for him, but for his patients to decide where the balance of risks and benefits lies in trying ketamine to treat their depression. "I live in a different world from my patients and each one of them in turn lives in a different world from each other", he explains. "We each place a different value on things, have different priorities, have differing notions of what makes life worthwhile but most importantly, unlike many of the people who come to see me, I am not experiencing the perpetual misery that makes every waking moment a struggle not to end my life. So it is much easier for me to place more weight on the unlikely negative possibilities of a treatment than the more likely potential benefits—this is the trap pundits who decry this off-label use are falling into. One could make a compelling argument that it's unethical to withhold ketamine treatments from someone who has chronic, severe treatment resistant depression. But I know this from the patients who tell me they would not be in this world right now if it were not for the ketamine."

Feifel concludes that it is straightforward to talk to TRD patients about ketamine. "I tell them all the relevant information. The efficacy rates, time to onset of benefits, duration limitations, alternatives, lack of insurance coverage, and other information. My job is to make sure they understand the parameters of the treatment, not to decide whether they should do it."

Tony Kirby