Lucy in the sky with ketamine

Psychoactive drugs have potential for a major breakthrough in treating depression

Katrin Weigmann

“I felt like being in a pod [...], like a little boat, going along through rooms [that had] white breathing walls.” This is how American standup comedian Neal Brennan described his experience with ketamine, a psychoactive drug also known as Special K in the club scene, in an interview with fellow comedian Joe Rogan. “I just couldn’t get over the fact that this was happening in a doctor’s office,” he said about taking ketamine as a medication against depression.

“One may argue that treating psychologically unstable patients with an addictive drug that has psychedelic side effects is not a good idea.”

Ketamine was introduced commercially in the United States in 1970 as an anesthetic. At lower doses, it causes dissociations, out-of-body experiences, and hallucinations, which explains its career as club drug. But during the past two decades, it has also gained attention as a fast-acting antidepressant. Its antidepressant effect was first noted by researchers at Yale University in the 1990s, and the effect was reproduced in a larger double-blind, placebo-controlled trial at the US National Institute of Mental Health, published in 2006. A number of studies have since shown the effectiveness of ketamine in treating patients with depression, suicidal ideation, and post-traumatic stress disorder [1]. Researchers have called it the biggest breakthrough in depression research in half a century. Ketamine is not yet approved by regulatory agencies, but is widely used off-label by private so-called ketamine clinics.

New medications to treat depression are urgently needed. The last significant innovation—Prozac, the first selective serotonin reuptake inhibitor (SSRI)—is now 30 years old, and SSRIs and many me-too drugs of similar structure and function still dominate the treatment of depression. They are, however, anything but satisfactory. It takes 6–8 weeks for their effect to kick in, and about 30% of the patients do not respond at all. The time lag and low response rate are particularly problematic for severely depressed patients who are at risk of suicide.

New drugs on the horizon

Ketamine could fill this gap and become a life-saver to those most in need. As its effect kicks in rapidly, it can relieve depression even in treatment-resistant patients and it has been shown to be effective for overcoming suicidal ideation. But although ketamine has been greeted with much enthusiasm, there have also been voices of concern. One disadvantage is that its effect is not lasting. A single dose can alleviate depression for a few days, and clinical data do not offer much information about the long-term outcomes of repeated use. The other main issue is its mind-altering effect. One may argue that treating psychologically unstable patients with an addictive drug that has psychedelic side effects is not a good idea.

“Psychedelic therapy” may hold the key to treating patients with depression, anxiety or obsessive compulsive disorder.

Interestingly, ketamine is not the only psychoactive substance that has been found to be effective in treating depression. Other substances most notably include psychedelics, a class of drugs that acts on the serotonin 2a receptor and includes lysergic acid diethylamide (LSD), psilocybin, which is naturally produced by magic mushrooms, and DMT, the key ingredient in ayahuasca. “Psychedelic therapy” may hold the key to treating patients with depression, anxiety, or obsessive compulsive disorder.

Yet, there are many open questions. What can be done to make the most of ketamine treatment and psychedelic therapy while minimizing the dangers of addiction and abuse? How can rules and regulations ensure that the good may prevail? To answer these questions, it will be important to better understand the neurobiological mechanisms behind their therapeutic effect. Although there is still much to learn, research in the past decades has provided some answers.

Obstacles to research

In 1943, Swiss chemist Albert Hofmann tested a substance he had synthesized 5 years earlier on himself: LSD. Its profound effects on behavior soon made it a tool used by psychologists and psychiatrists to better understand psychosis. In the 1950s and 1960s, psychedelics were extensively used in research and clinical practice to treat depression, anxiety, and addiction. However, therapeutic use and scientific research soon came to an end after the Controlled Substances Act was passed in 1970 in the United States [2]. “Why was LSD banned? Because young American men were starting to take it and stopped fighting in Vietnam. It was changing the whole

attitude of America to war and the government did not like that”, explained David Nutt, professor of neuropsychopharmacology at Imperial College in London, UK. Similar regulations were enforced in other countries, and in 1971, the UN Convention on Psychotropic Substances placed psychedelics into schedule 1, the most restrictive drug category. Together, national and international laws not only prohibited recreational use, but also made scientific research on a number of substances so difficult that Nutt calls it “the most outrageous censorship of research in the history of science”. Scientists need a special license to work with drugs classified as schedule 1, which is expensive, bureaucratically cumbersome, and time consuming to get. Another major obstacle is obtaining schedule 1 drugs for research, as there are only few companies worldwide that are licensed to produce and distribute these. Carrying out large clinical trials is almost impossible.

“... national and international laws not only prohibited recreational use, but also made scientific research on a number of substances so difficult that Nutt calls it “the most outrageous censorship of research in the history of science”.”

For about 25 years, even animal studies were rare, but the interest in psychedelics survived. The field awoke from hibernation in the 1990s with studies investigating their effect on the psychology of healthy subjects and the neurobiological mechanism behind it. Although regulations still impede research, scientists are restarting clinical trials to elucidate the therapeutic potential of these drugs. A number of early-phase clinical studies have provided evidence that psilocybin can alleviate depression and anxiety in cancer patients with end-of-life psychological distress. In addition, there is increasing evidence supporting the effectiveness of psilocybin for treatment-resistant depression. COMPASS pathways, a company specialized in developing psilocybin therapy, is currently starting large-scale clinical trials in Europe and the United States.

Furthermore, trials by a number of different research groups are addressing the impact of psychedelics on patients with obsessive compulsive disorder or addiction.

Nutt entered the field because he was particularly interested in the serotonin 2A receptor, the target of psychedelics. “There are so many of them, they must be some of the most important receptors in the brain”, he commented. Using functional magnetic resonance imaging, Nutt and colleagues found that LSD and psilocybin strongly reduce brain activity in regions that highly express the serotonin 2A receptor, such as the default mode network [3]. “Psychedelics decrease the integrity of the default mode network”, Nutt said.

Psychedelics and the default network

“The default network is highly associated with a sense of self, with self-referential processing, remembering about yourself in the past, projecting yourself into the future, defining your relation with the world”, explained Matthew Johnson, associate professor of psychiatry and behavioral sciences at Johns Hopkins University School of Medicine, Baltimore, MD, USA. Accordingly, disruptions of the network by psychedelics cause “a very altered sense of self”, as Johnson put it, “a sense of unity between self and the rest of the world”. Psychedelic drugs also cause a sense of transcending time and space. Together, these sensations cause what psychologists call a “mystical-type experience”.

As important as self-referential processing might be, it can get too much. “We think the default mode network is most likely involved in ruminative processes of disorders like depression or obsessive compulsive disorder”, Nutt said. “When depressed, people get locked into overthinking, they cannot escape from their thoughts”. According to this model, psychedelics would resolve this state through their effect on the default mode network. “You overcome the depression during the trip because you disrupt the thinking processes, which drives depression. If you are not depressed during the trip, this can give you hope and confidence that you can escape your depression”, Nutt explained.

Johnson also thinks there is a strong connection between the drug’s effect on the default mode network, the psychedelic experience it causes, and its therapeutic effect.

“My guess would be a mediation model where the brain change is related to the mystical-type experience, which is then related to the antidepressant effects”, he explained. Although speculative at this point, he suggests that similar mechanisms are at play when it comes to treating addiction. “All addictions – whether it is to a substance or to a certain pattern of thinking that comes with depression – can be seen as being stuck in a certain mental pattern. The radically altered experience of the self during the session can help to reframe a patient’s relationship with these patterns”, Johnson said.

Understanding ketamine’s mode of action

Ketamine, on the one hand, and psychedelics, on the other hand, have two different research histories. Researchers working on psychedelics have taken a more systemic approach while the ketamine field has focused more on the drug’s molecular and cellular mode of action. While the therapeutic effect of psychedelics has mainly been attributed to its impact on the default mode network, ketamine is thought to act by inducing synaptic plasticity. However, according to Johnson, “it also could be that the biological and psychological mechanisms are very similar. We need studies that directly compare them”. In fact, there is some evidence that ketamine also impacts on the default mode network [4]. Psychedelics, too, have been shown to induce synaptic plasticity. Different models may, at least in part, result from different research approaches [5].

“You overcome the depression during the trip because you disrupt the thinking processes, which drives depression.”

Research on ketamine was influenced by models explaining depression as a consequence of stress-induced atrophy of neurons in the prefrontal cortex and hippocampus [6]. Ketamine reverses neuronal atrophy by inducing synaptogenesis as it acts on the NMDA receptor, a neuronal ion-channel that responds to the neurotransmitter glutamate. “Shortly following the administration of the drug we see a large efflux of glutamate in several brain regions, including the

prefrontal cortex and the hippocampus”, said Gerard Sanacora, professor of psychiatry at Yale School of Medicine. Glutamate, in turn, induces a number of downstream events, ultimately stimulating synaptic plasticity. All these events take place within a few hours [1].

“Depression stems in part from the brain’s inability to form new connections. Neuroplasticity induced by ketamine allows to change state”, Sanacora explained. Hence, it is also very important to make sure the change is for the better. “The next logical step is to combine ketamine with non-pharmacological treatments such as psychotherapy to solidify positive changes”, Sanacora added. Indeed, one problem with ketamine treatments so far has been that their effect is relatively short-lived, with patients relapsing to depression after a few days following a single treatment or a few weeks after a short series of treatments. However, recent data from Sanacora’s research group suggest that combining ketamine with cognitive behavioral therapy can prolong its positive effect.

“Depression stems in part from the brain’s inability to form new connections. Neuroplasticity induced by ketamine allows to change state.”

While researchers studying LSD and psilocybin see a close connection between psychedelic experience and therapeutic effect, most scholars in the ketamine field do not. “I do not rule out there is any relationship, but we are talking about a correlation, not necessarily a causative effect”, said Sanacora. If ketamine exerts its antidepressant effect by inducing synaptic plasticity, there is, in fact, no reason to believe that the psychedelic experience is important for the therapeutic effect. Accordingly, researchers are putting efforts into developing new substances that maintain the antidepressant effect of ketamine, but without the dissociative and psychedelic side effects. “This has been the Holy Grail”, Sanacora said. There are, however, no attempts to separate psychedelic and antidepressant effects of LSD and psilocybin, for a simple reason. “I don’t think it will work with ketamine and I

don’t think it would work with LSD”, Nutt said.

A ketamine-like antidepressant without psychedelic side effects would be a game-changer. However, despite some initial promises, efforts to find ketamine-inspired substances with a better benefit-risk-profile have not yet led to the anticipated results in clinical trials. Of course, this does not mean that it will not work in future, and reasons for the absence of success might be technical. “People in the field have approached this with some level of nativity, thinking that a sustained blockade of the receptor would be a good thing. I think research is now suggesting that this might not be the case. This may be a unique situation where you want a short inhibition to induce the downstream effects, and then quickly return to a normal physiology”, Sanacora commented. A promising drug in development may be a partial agonist of the NMDA receptor—rather than an antagonist like ketamine. Rapastinel shows rapid antidepressant effects without the psychoactive properties of ketamine [7]. The drug is under development by Allergan and has been granted Fast Track designation by the FDA.

Ketamine in private clinics

The clinical development of ketamine itself has been hindered by the fact that the patent for ketamine has long expired, and therefore, there was little financial incentive for the pharmaceutical industry to invest in clinical research. Recently, however, The Janssen Pharmaceutical Companies of Johnson & Johnson have focused on a nasal spray version of esketamine, a ketamine enantiomer, which is eligible for patent protection. The company is conducting a number of phase 3 clinical trials required for FDA approval and the FDA has granted Breakthrough Therapy Designations for esketamine so that the drug can get to the market as quickly as possible. Esketamine, as ketamine, reduces suicidal thoughts and symptoms of depression. While its long-term effects are still being investigated, it may be particularly useful to manage suicidal risk until other antidepressants take effect.

For the time being, ketamine is used off-label and because the demand is high, the number of private ketamine clinics has exploded, particularly in the United States. “In my experience in interacting with many clinicians offering ketamine treatments, they

are generally well-meaning. I’m sure there are businesses out there that are looking at it for as profit making, but most of them are trying to do the right thing. They are frustrated by the limitations of our current treatment strategies and they are quite impressed by these rapid and robust effects of ketamine”, Sanacora said.

“... ketamine is used off-label and because the demand is high, the number of private ketamine clinics has exploded, particularly in the USA.”

But that does not mean that all is well. Ketamine has been approved for anesthesia, a one-time use. Since its effect against depression wears off after a few days, the treatment in ketamine clinics typically involves multiple injections over an extended period of time. “Even the most well-meaning clinicians do not have enough information to understand the long-term risks and benefits of the treatment”, commented Sanacora, who has been pushing for a registry of depression patients treated in private ketamine clinics. “There are at least 10,000 people that have been treated with ketamine, but almost none of this is being reported in the literature. We are not learning from the experience”, he said. “We don’t know what the optimal dose is, what the drug-drug interactions are, what the safety of long-term dosing is, just because we don’t have any coordinated effort to collect these data”.

Opinions on ketamine clinics are divided. “There is not enough evidence to say if this should or shouldn’t be done or how this should be done”, Sanacora commented. But there is enough evidence to be concerned about a few points, which Sanacora and his colleagues from the American Psychiatric Association summarized in a consensus statement [8]. It includes recommendations about patient selection, clinician training, dose and delivery procedure, and so on. And it warns against the idea of giving patients ketamine to take at home—currently, it is generally administered intravenously in the clinic. However, sounding a note of caution may not be enough to prevent diversion and ensure that clinics are not driving patients into addiction.

According to the ketamine advocacy network, ketamine clinics in the United States typically charge US\$400–800 per infusion. Costs are usually not covered by insurance. Cases have been reported where patients turn to other sources once they run out of funds [9].

With the current American opioid crisis as a warning example, it is important to ensure that the health system is not creating more problems for people suffering from depression than it actually solves. “How do we ensure that we don’t end up with another opioid epidemic?” Sanacora asked. “I think this is an issue of equal importance and it is really for the regulatory agencies to consider”.

Balancing risks and benefits

“Can a framework be established for the safe use of ketamine?” asked an editorial in the American Journal of Psychiatry [10] that accompanied a phase 2 trial of intranasal esketamine for the treatment of suicidal patients with depression. The authors raise concern about the potential detrimental effects of drug diversion and ketamine abuse and warn against an “epidemic of misuse”. “The mandate to individual physicians to prevent abuse has proven to be inadequate as the sole safeguard against the opioid epidemic, which has caused more morbidity and mortality than the postprocedure pain prevented by these medications”, they write. “A system similar to that used for methadone would offer an additional layer of protection. Limitation to authorized hospital pharmacies for inpatients and to authorized clinics for other patients would help prevent diversion by physicians and facilities unable to contain its use”.

Along similar lines, Johnson argues that LSD and psilocybin should be strictly regulated if they should be approved as therapeutics by regulatory agencies. He advocated that the FDA would apply a so-called Risk Evaluation and Mitigation Strategy (REMS), a drug safety program to help ensure the benefits of the medication outweigh its risks. “I would suggest that the REMS specifies that psilocybin can only be administered in a clinic that is very similar to those of the research studies, that there needs to be

psychiatric screening, preparation sessions, and that the drug needs to be administered in a setting with personal support and with follow-up discussions”, he commented. “I think it is important not to let the clinical use expand beyond the data” said Johnson, warning against a broad clinical use that is not supported by science. “Any careless use of the drugs could not only harm patients, but it may also may have a negative impact on the field itself. It could eventually stop the use of psychedelics by cautious clinicians who are doing it the right way”.

“Any careless use of the drugs could not only harm patients, but it may also may have a negative impact on the field itself.”

While it would be unethical to deny people in desperate need access to effective medication, exposing them to risks that may outweigh the benefits is also irresponsible. To find the optimal balance, more research into the benefits and risks of new rapid-acting depressants is required. However, research has been thwarted by different factors. The Controlled Substances Act in particular has created a catch22 for many of these substances: Schedule 1 substances are, by definition, without medical use. But as long as they are in schedule 1, research proving its medical use is almost impossible to carry out. Ketamine, on the other hand, has long been approved as a medication, albeit for a different use. While this makes basic research a lot easier, it also causes problems. The pharmaceutical industry has no incentive to develop a drug that is already on the market. Off-label treatment has developed a dynamic of its own while the long-term effects are still not understood. So far, the story of new antidepressants is also about how political and financial incentives retard science in a field where progress is urgently required.

References

1. Duman Ronald S (2018) Ketamine and rapid-acting antidepressants: a new era in the

battle against depression and suicide.

F1000Res 7: pii: F1000

2. Carhart-Harris RL, Goodwin GM (2017) The therapeutic potential of psychedelic drugs: past, present, and future. *Neuropsychopharmacology* 42: 2105–2113
3. Carhart-Harris RL, Muthukumaraswamy S, Roseman L, Kaelen M, Droog W, Murphy K, Tagliazucchi E, Schenberg EE, Nest T, Orban C *et al* (2016) Neural correlates of the LSD experience revealed by multimodal neuroimaging. *Proc Natl Acad Sci USA* 113: 4853–4858
4. Bonhomme V, Vanhaudenhuyse A, Demertzi A, Bruno MA, Jaquet O, Bahri MA, Plenevaux A, Boly M, Boveroux P, Soddu A *et al* (2016) Resting-state network-specific breakdown of functional connectivity during ketamine alteration of consciousness in volunteers. *Anesthesiology* 125: 873–888
5. Ly C, Greb AC, Cameron LP, Wong JM, Barragan EV, Wilson PC, Burbach KF, Soltanzadeh Zarandi S, Sood A, Paddy MR *et al* (2018) Psychedelics promote structural and functional neural plasticity. *Cell Rep* 23: 3170–3182
6. Duman RS, Aghajanian GK, Sanacora G, Krystal JH (2016) Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. *Nat Med* 22: 238–249
7. Zanos P, Thompson SM, Duman RS, Zarate CA, Gould TD (2018) Convergent mechanisms underlying rapid antidepressant action. *CNS Drugs* 32: 197–227
8. Sanacora G, Frye MA, McDonald W, Mathew SJ, Turner MS, Schatzberg AF, Summergrad P, Nemeroff CB, American Psychiatric Association (APA) Council of Research Task Force on Novel Biomarkers and Treatments (2017) A consensus statement on the use of ketamine in the treatment of mood disorders. *JAMA Psychiatry* 74: 399–405
9. Schak KM, Vande Voort JL, Johnson EK, Kung S, Leung JG, Rasmussen KG, Palmer BA, Frye MA (2016) Potential risks of poorly monitored ketamine use in depression treatment. *Am J Psychiatry* 173: 215–218
10. Freedman R, Brown AS, Cannon TD, Druss BG, Earls FJ, Escobar J, Hurd YL, Lewis DA, López-Jaramillo C, Luby J *et al* (2018) Can a framework be established for the safe use of ketamine? *Am J Psychiatry* 175: 587–589