Therapeutic Potential of Ketamine in Treating Depression

By Hayfa Feroz

Depression as a mental illness

Depression is a serious and widespread mental illness that affects people all over the world. According to the World Health Organization (WHO), depression affects over 264 million people worldwide, making it one of the most common mental health disorders. It is a common mental illness characterised by a persistent and pervasive sense of sadness, hopelessness, and worthlessness. Individuals suffering from depression may lose interest in previously enjoyed activities, have difficulty sleeping or eating, and struggle to concentrate or make decisions. Physical symptoms such as headaches or fatigue may also occur. It affects people of all ages, genders, and backgrounds and can have serious consequences for a person's quality of life, relationships, and ability to function in daily activities. It is also a leading cause of disability globally, and it is linked to an increased risk of suicide. It can also cause a variety of physical health issues, including chronic pain, sleep disturbances, and heart diseases. Depression is caused by a variety of genetic, environmental, and psychological factors have been identified as contributing to the development of depression. These include genetic predisposition, childhood trauma, stress, and chemical changes in the brain. Although depression is often treatable with a combination of therapy, medication, and lifestyle changes, many people do not receive adequate care due to stigma, lack of resources, or other barriers to treatment. Despite the availability of treatment, many people suffering from depression do not receive adequate care, emphasising the importance of increased awareness, screening, and access to mental health services. Recognizing depression as a serious mental health issue includes increased efforts in order to raise awareness, reduce stigma, and improve access to effective treatment. Depression research, prevention, and treatment are all ongoing, and new interventions are being developed to address this critical public health issue. Moreover, depression is a serious mental illness that affects millions of people worldwide. Understanding the complexities of depression's causes and effects is critical to improving diagnosis, treatment, and support for those suffering from this condition.

Ketamine as a potential treatment for Depression

Ketamine, also known as K, Ket, KitKat, Special-K, Vitamin K, Super K, Donkey dust, and even horse tranquilizer is a dissociative anaesthetic which was initially used by vets as a sedative on horses, donkey, cats, dogs and various other domestic animals when they're doing surgery on them, but in the current situation, it's a more widely available recreational drug than one to fulfil pharmaceutical purposes. It's known as a dissociative drug as it causes a feeling of separation from your environment, and also a separation from your body. At low doses, Ketamine can cause a feeling of mind and body separation along with seeing trails, a sense of floating and numbness, blurred vision and even hallucinations. When Ketamine is taken in higher doses, it can make your legs feel very weak and wobbly and make your heart race causing breathing to be really difficult. When you fall into the "K hole" (as they like to call it), i.e the state of complete disconnection from the world, where you sort of have an out of body experience, floating through space or experiencing all of eternity at a single point in time. The world becomes increasingly distorted and distant, time is suspended, and hallunications may occur along with a sense of disorientation and derealization. I've heard people describe it as like putting your brain on airplane mode, and that means basically you don't get any inputs from outside. People don't notice, for instance, that they're freezing to death if they're out in the winter or they don't notice if they're drowning when they're taking ketamine in the bath. Although, falling into the K hole can also lead to a near death experience where you feel completely powerless and totally confused. Research is currently being conducted to determine whether Ketamine can be used for treatment resistant depression i.e particularly depression that is unaffected by 2 or more different antidepressants. Ketamine administered by doctors to patients has been shown to have a rapid antidepressant effect that can last for several days, they also believe that this is because the Ketamine is promoting a complex signalling cascade which is resulting in more synapses and increased neuronal connectivity particularly in the Prefrontal Cortex of the brain. Ketamine is popular because of the interesting mental state it produces. It's also used after parties to help people come down from being overactive, overstimulated. It is an anesthetic; it calms down the brain, dampens down activity, and lets people sort of chill out in a chemical way. The

most interesting thing about ketamine today, though, isn't that it's used to anesthetize pets or help stressed out hedonists or pleasure-seekers get wonky. It's that more and more doctors and psychologists across the world are heralding ketamine as a life-changing and potentially life-saving treatment for otherwise unshakeable cases of depression. Although, for years, ketamine has been available as a last-ditch treatment for depression sufferers in low-key, off-label drip clinics. In these controlled conditions, it seems to be especially effective for an estimated third of depression patients, for whom all other methods have failed. Often these are people who see ketamine as their final hope. Most currently available treatments for depression, they're mostly based upon the seratonin hypothesis of depression and the idea of not having enough serotonin, or enough of feel-good hormones in the brain, and if it's replaced with medicines that increase those levels, is when you feel better and they work moderately well. Based on research and understanding, Ketamine, according to me, was unique in some very important ways and the results of it being used as a medicine to treat mental disorders were dramatic. Until now, in psychiatry, there was no drug which would act so fast and which would save lives so fast, with such an immediate effect. So ketamine is a life-saving drug, according to me. Now, K is also taking its first steps out of these clinics to more widespread therapeutic use. In 2019, the FDA approved a ketamine nasal spray for Americans suffering severe depression. Ketamine therapy has shown positive effects when used to treat other conditions too, like PTSD and alcoholism.

Pharmacology of Ketamine

Ketamine hydrochloride is a synthetic dissociative anaesthetic. Ketamine was introduced in 1956 at a pharmaceuticals company in the United States. Researchers found that a new drug called phencyclidine or PCP made a wonderful anesthetic for small mammals. But while this was a red letter day for all the little monkeys and rats waiting for life-saving medical procedures, PCP didn't provide as an anesthetic for humans. It made them weird and angry when they woke up, sometimes for hours on end. So, a bunch of PCP derivatives were synthesized to produce one compound in particular, developed by a chemist named Calvin Stevens in 1962 at Parke Davis Laboratories, was a revelation, a short-lasting anesthetic called CI-581. This is the compound now known to you and I as Special K, K, Ket or ketamine. It was first synthesized in the 1960s for medical purpose, and was first used medicinally during the Vietnam war.
Recreationally, it is usually consumed by snorting a white crystalline powder, and at lower doses than when it's used as an anaesthetic. However it can also be injected, or smoked. It started being used for veterinary purposes in Belgium and in 1964 was proven that compared to PCP, it produced minor hallucinogenic effects and shorter psychotomimetic effects. It was FDA approved in 1970, and from there, it has been used as an anesthetic for children or patients undergoing minor surgeries but mainly for veterinary purposes. It was scheduled in the United States in 1999 and classified under the UK's misuse of drugs act in 2006. It remains to be the most famed and popular dissociative. Ketamine's mechanism of action involves its interaction with a type of glutamate receptor in the brain known as the N-methyl-D-aspartate (NMDA) receptor. The NMDA receptor regulates a number of vital neurotransmitter systems, including glutamate and gamma-aminobutyric acid (GABA). Ketamine binds to the NMDA receptor and blocks its activity, causing glutamate release to increase and GABA release to decrease. This imbalance in neurotransmitter release raises activity in several brain regions, including the prefrontal cortex, amygdala, and hippocampus, all of which are involved in mood regulation.

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raises activity in several brain regions, including the prefrontal cortex, amygdala, and hippocampus, all of which are involved in mood regulation. Ketamine also activates other neurotransmitter systems, including monoaminergic systems involved in mood regulation, such as serotonin, dopamine, and norepinephrine. Research suggests that ketamine's impact on the NMDA receptor causes a rapid and sustained increase in synaptic plasticity, which is the brain's capacity to change and adapt in response to environmental stimuli. The precise mechanism by which ketamine produces its antidepressant effects is still under investigation.
Overall, research indicates that the NMDA receptor may be a novel target for the creation of new antidepressant medications due to ketamine's distinct mechanism of action.

Evidence for Ketamine in the Treatment of Depression

Major depressive disorder (MDD) patients make up about one-third of those who do not respond to antidepressants currently on the market, and those who do typically take weeks to months to have a noticeable impact. A definite unmet need exists for quicker acting, more potent treatments. We'll talk about recent developments in the study of ketamine, a traditional anaesthetic that has shown a lot of promise in clinical trials as a potent, quickly acting antidepressant. patients with unipolar MDD who are resistant to treatment, with an emphasis on clinically significant elements like dose, route of administration, and duration of effect. Additional research suggests that ketamine may be helpful for patients with bipolar depression, posttraumatic stress disorder, and acute suicidal ideation. The safety of ketamine is then discussed, with the observation that the majority of neuropsychiatric, neurocognitive, and cardiovascular disturbances are temporary; on the other hand, ketamine's long-term effects are still unknown. As evidence for ketamine's potential use in clinical settings keeps surfacing, underscoring the need for more research into its effects, we conclude with crucial ketamine information for primary and secondary care doctors.

The first study to emphasise ketamine as an antidepressant was a cross-over study done in 2000 on 7 patients with major depressive disorder. Six years later, a study of 17 treatmentresistant Major Depressive Disorder patients showed that ketamine (0.5 mg/kg iv infusion over 40 min) caused a greater than 50% reduction in depressive symptoms in 71% of the participants within 24 hours, whereas the same participants showed almost no change in symptoms after receiving the saline injection used as a placebo. Additionally, throughout the 1-week follow-up, about one-third of the participants' responses were still present. Ketamine was found to be associated with higher rates of clinical response and remission at 24 hours, 3 days, and 7 days compared to the comparator (saline or midazolam) in a recent systematic review that included nine ketamine trials. Ketamine does not work on all patients, and the antidepressant effect lasts for varying amounts of time in different people. It has been demonstrated that ketamine reduces suicidal thoughts in depressed patients. Additional research is evaluating the potential use of ketamine in palliative care settings, where its pain-relieving effects may complement its antidepressant effects.

One subanesthetic dose of (R,S)-ketamine (0.5 mg/kg for 40 min) could have a strong antidepressant effect on patients with major depressive disorder (MDD), according to a doubleblind, placebo-controlled study carried out at Yale University in 2000 by Berman et al. After that, (R,S)-ketamine gained considerable attention in MDD studies and received backing from a number of research teams, with ketamine exhibiting palpable antidepressant effects. In contrast to traditional antidepressants, (R,S)-ketamine had effects that could last up to 7 days and relieved depression within 2 hours. Over the past 20 years, ketamine research has expanded to include a wide range of disorders, such as bipolar disorder, post-traumatic stress disorder, obsessive-compulsive disorder, and many others. In addition to its immediate and long-lasting antidepressant effects, increasing evidence suggests that (R,S)-ketamine can reduce the risk of suicide in patients experiencing depressive episodes (Witt et al., 2020; Witt et al., 2020). This powerful and long-lasting antidepressant effect unquestionably meets the requirements for the ideal antidepressant. Despite significant progress, there is still a need to address widespread concerns about ketamine's negative effects, such as its psychotomimetic and dissociative effects as well as its addictive qualities. The use of ketamine in medicine has been constrained by these side effects and addictive qualities. In contrast, these restrictions have prompted research into the mechanisms underlying ketamine's antidepressant effects in order to determine these effects' special antidepressant properties while avoiding side effects like addictive qualities and dissociative symptoms.

Ketamine is what scientists call a dirty drug. That means it doesn't just target one system in your brain, but dozens. It has a weak effect on opiate receptors in the dopamine system, which drugs like heroine and cocaine target. But most importantly, ketamine manipulates a neurotransmitter called glutamate, earning it the attention of psychiatrists nationwide. Glutamate is what many of the neurons in your brain use to communicate with each other, and without it, well, your brain would essentially shut down like a city grid without power. Now, at high doses, ketamine seems to block glutamate. That's why it's such an effective anesthetic. But in low doses, like what you might find at a club or in a spray of the FDA-approved drug esketamine, it actually ramps up glutamate production, and that comes with all kinds of side effects. It can make you hallucinate or feel as though you're losing touch with reality. And it might also help build new connections or synapses between neurons, electrifying new parts of that city grid. When people are stressed for a long time or when they suffer from depression for a while, they start losing these connections, and when we give them ketamine 24 hours, they reverse. Now they look like more a normal brain. So we believe that perhaps ketamine is working by regenerating these connections that are needed for normal brain functioning. And that could make ketamine one of the best drugs out there for treating depression. This isn't how other antidepressants work. Medications like Prozac and Zoloft take weeks if not months to kick in, and they regulate serotonin, another chemical

in the brain, which scientists have long tied to depression. These more traditional drugs may work for some people, but not for everyone. In fact, as many as 4 million American adults have treatment-resistant depression. And for them, well, ketamine might be the only drug out there that can provide relief. That's according to Doctor Andre Atoian. Doctor Andre Atoian, the founder of Ketamine Specialists, a clinic where he administers ketamine to patients with mood disorders, pain, and addiction. He tells that 'Ketamine is the agent that works when most others have failed. It is something that really allows us to give patients a sort of new hope 'cause a lot of people that I treat have basically already tried everything, and they're in this situation where nothing's really working, and they're suffering, they're miserable.' So it's hard to deny that ketamine's effect on depression sounds promising, and, clearly, it's a useful sedative. While, Doctor Nolan Williams, an assistant professor of psychiatry at the Stanford University Medical Center. He says that 'because ketamine manipulates so many different receptors in the brain, it's been hard to nail down all of them. So it's still unclear how it might affect different patients both short- and long-term, and researchers still haven't figured out how to preserve its benefits as an antidepressant.

Why I chose this topic

Recently, I have come across many people in college quit their prescribed antidepressants resorting to microdosing LSD and mushrooms. Most of these people are skeptical of the pharmaceutical industry and are desperate to find more pleasure in life for cheap; for some, coding substance use as an antidepressant routine, and ingesting very tiny doses has been seeming to work just fine for the treatment of certain mental disorders, even though it's temporary. During my visit to the UK in 2021 is when I was enlightened by the number of teenagers using Ketamine. There's a whole ketamine culture in the UK. Even the way people dance has changed due to ketamine and it's influence. Fortunately, I was able to connect with few of my cousin's friends from the university of exeter who were regular users of the drug for recreational purposes. What got me hooked was the story of how a horse tranquilizer has turned into a staple drug of choice for raves and parties. Through an acquaintance of my cousin's, who'd like to remain anonymous, I was also lucky enough to talk to a local ketamine dealer who helped me gain insights on some of the history of ketamine and how it was supplied to texas prisoners initially which was situated next to a horse parade, where ketamine was being used as a sedative in case of injuries. He told me that the usage of ketamine recreationally began in the 80s when some Bristol hippies were backpacking around India and realized that they could buy it over the counter there, and make tons of money if they brought it back to the UK. And now it's one of the most popular drugs in the free party scene over there. Bristol has also become of the spiritual homes for ketamine. Despite it being torturously difficult to make, some drug gangs have cracked the chemical code. It's not just doctors who lap it up, it's psychonauts and club kids, too. In the four years that followed its UK ban, use of K among 16-to-24-year-olds did not drop off, it doubled. In 2018, the amount of ketamine seized by the police had risen by 30 percent, and more young Brits were taking it than ever before. For decades, Ketamine has been quietly winning battles in the war on drugs worldwide, thwarting bans and cultural concerns about horses and nappies convincing medical experts to extend its empire through every populated continent. When China asked the UN to ban it, ketamine won. What's fascinating is also that where it has been outlawed by governments, recreational users almost invariably sustained or increased. Despite the barriers put up by the war on drugs, ketamine's therapeutic potential is finally being realized. And the next few years could usher in its third act as a legal tool for therapists seeking to save the lives of countless depressed people.

Side Effects from the use of Ketamine

Ketamine abuse has been linked to several harmful long-term side effects, most of which, according to studies, are only experienced by regular users. Ketamine-induced ulcerative cystitis, also known as "ketamine bladder," is the most severe of these side effects. This recently discovered condition, which is characterised by excruciatingly painful frequent urination, appears to have serious and potentially lifelong effects on the patient. One in four people who use ketamine even once a month have some kind of bladder symptom. When ketamine enters the bladder, it damages the epithelial cells of the bladder lining. These umbrella-shaped cells are designed to contain urine. But if they become too damaged, urine can seep through, damaging the inner layers of the bladder wall. This can scar the bladder's muscles, reducing its ability to expand. Symptoms can include frequent peeing, pain, and blood in urine. Because ketamine is a painkiller, though, heavy users often don't notice. While many people believe cooking the ketamine reduces bladder damage, your kidneys don't care if it's crystal, powder, or liquid. If you stop using it frequently, the bladder will almost always repair itself, but a small minority will need their bladders removed. Drug users who use ketamine less frequently than daily, however, have not reported or demonstrated a 'ketamine bladder'. The dosage and

frequency of ketamine use differ significantly between clinical and recreational use. Rapid ketamine tolerance development is known as tachyphylaxis in anaesthesia practise. In order to make up for this, frequent recreational users will gradually increase their dosage until they are consuming several grammes per day rather than milligrammes. These doses are typically 'snorted' through the nose like cocaine. Contrarily, a single 35mg intravenous dose for an adult of average weight would typically be prescribed for medical use in depression and could be administered again at the same dosage days or weeks later.,.Hepatotoxicity risk is correlated with dose level and frequency, with longer infusion times or frequent dosing in therapeutic contexts carrying a higher risk. This is why, even though the FDA approval is considered a victory for the millions of people with treatment-resistant depression, doctors cannot give it every day, due to substance of abuse which will harm the brain eventually, doctors still caution that ketamine should only be used as a last resort.

At doses ranging from 1 to 3 mg/kg, ketamine has been proven to be both a safe and effective anaesthetic in both children and adults. Ketamine has been used to treat depression and pain at doses as low as 0.1 mg/kg and as high as 1 mg/kg. These subanesthetic doses may cause transient neuropsychiatric effects such as dissociation, sensory-motor disturbances, and neurocognitive disturbances. They may also cause temporary increases in blood pressure and heart rate. Common side effects may occur up to 4 hours after ketamine administration and may include nausea, vomiting, headaches, dry mouth, agitation, and coordination and attention deficits.8 Ketamine for depression studies have shown some mild side effects, including dry mouth, tachycardia, an increase in blood pressure, and dissociation during the 40 minutes of ketamine administration and for a short time after. Patients with a history of cardiovascular disease would need to be closely watched, though, as transient increases in blood pressure could be dangerous.9 Because ketamine has historically been used recreationally,15 the possibility of abuse is a medical concern and a crucial area for research. It is crucial to be aware of the unresearched long-term effects in relation to dosage and administration frequency because this medication is still in the experimental stage. Potential side effects from long-term ketamine use, like urinary cystitis and mild cognitive impairment, would need to be closely monitored. Understanding the evidence of cognitive impairments among ketamine abusers is crucial given the uncertainty surrounding the long-term effects of the drug (while keeping in mind that these participants frequently combine multiple drugs of abuse). Over the course of a year, chronic ketamine users exhibit memory impairment; in contrast, participants with TRD who received IV ketamine less frequently and at lower doses displayed improved cognitive function.

It’s important to remember that it always starts as a fun drug, it always starts as an after party drug or a rave drug. It’s really hard to tell when that recreational habit is going to turn into a serious problem, and it can happen to anyone. If you don’t speak to someone, then that problem can end up taking your bladder and possibly your life. And if you’re using ketamine to achieve a euphoric state of mind, come down off of ecstasy after a rave, or make the world temporarily hilarious, that’s one thing. However, one in ten, one in 15, they lose all control. So it's not really an addictive drug, but some people can become reliant on it with a sort of psychological dependence and you do start to become more tolerant of Ketamine meaning you need a higher dose each time to get that same dissociative effect and as you take more Ketamine, you increase your risk of overdose.

Anecdotes

Dominic Milton Trott, the author of The Drug Users Bible, self-administered over 150 drugs over a 10 year period to document how to use them more safely. He led a relatively normal life, working in IT and as a father in the UK. Later on in life, he became interested in researching psychedelics and recording his experiences. He also frequented online drug forums, where he noticed that some users would suddenly drop off the radar, having died during their experimentation. He thought that if he could share his knowledge of what to expect along with the relevant safety information - the proper dosage, duration, precautions, etc - he could help to save lives.

Regarding his experiment, the dealer described his supply as 83% Pure S-Ketamine, and was predictably positive regarding its quality, claiming that it was "about twice as potent as racemic ketamine" (racemic being the other type of ketamine). With respect to the thresholds suggested across the Internet and given his experience with other dissociatives, 50mg seemed to be a reasonable first time dose. He measured this in preparation.

He has used ketamine on a handful of occasions since this first experiment, and it is a drug that he has increasingly come to terms with regarding expectation. The earlier tried and tested ephenidine experiences created a mindset of

longevity to his dissociative endeavours, which ketamine could not meet. However, after the first couple of experiments the two hour duration became less of a disappointment and more a feature. It became increasingly acceptable and positive. He has never chased ketamine (via redosing), but instead, he identified a niche use for it, in which it was capable of providing both insight and pleasure. Having stated this, his ranking of ephenidine as his favourite dissociative had not changed. Whilst enjoying this chemical, he says there is a 'but'. This, according to him, is that there are definite side effects to prolonged or frequent use as we mentioned earlier, like how regular ketamine use is reported to cause kidney and/or bladder damage. These are extremely serious issues, and they are what prevented him from pushing this chemical too far, or dipping into it too often.

Conclusion

Recent research has shown that ketamine has additional uses besides acting as an anaesthetic and reducing pain, including the modulation of specific receptors, anti-inflammatory effects, and the induction of synaptic formation, all of which suggest that ketamine may be used to treat a variety of clinical conditions. This implies that ketamine has excellent potential, but this is constrained by its abuse potential and dissociative characteristics. Preclinical research has therefore concentrated on understanding the electrophysiological, behavioral, and molecular mechanisms underlying ketamine's antidepressant effects. The fields of optical imaging and in vitro modelling both advanced gradually. Future research would benefit from using cutting-edge platforms and tools, such as humanised three-dimensional models, organoids with autonomous developmental systems, and blood-brain barrier microvessels on a chip. In addition to offering crucial insights into the neurobiology of major depression, an understanding of the mechanisms underlying ketamine's antidepressant effects would also help identify and raise awareness of new and creative therapeutic targets for creating the next generation of fast-acting antidepressants, which might have fewer side effects and exert their effects more quickly. Even at low and subanesthetic doses, the inhibition of NMDAR has serious side effects that make prolonged use of the medication necessary. As a result, the receptors are completely blocked, making it impossible to use the medication to treat depression.