Ketamine: A possible solution to depression?

Ketamine is a dissociative psychedelic which was first synthesized in 1956 and only officially became an official option for depression treatment within the last few years with its FDA approval in 2019 in both the US and Europe[1,2]. Its anti-depressant effects only started getting seriously researched in the 2000s[2]. Despite its very effective and extensive use in medicine since the 1970s, it has only recently started being used as a very efficient depression treatment[3]. It was first used as an anesthetic (and still is) for many different procedures and pain disorders due to the dissociative anesthesia it produces upon injection. Patients injected with ketamine were able to keep perfect respiratory drive and reflexes while benefiting from the analgesic effects in a safe manner. The research on its underlying mechanisms is also providing new insights on how anesthesia and consciousness might be related[4]. Overall, ketamine's diverse potential is seen as unique and promising within the medical field.

Ketamine treatments are often seen negatively by the general public as it is mostly known as a horse tranquilizer and recreational drug. After its initial use in clinical settings as an anesthetic and sedation for both humans and animals – especially horses – it also became a popular recreational drug due to its dissociative, euphoric, and drunk-like state when taken at smaller doses. Chronic recreational use was found to be correlated with memory impairments, persistent depressive, delusional, and dissociative thinking, as well as hepatic dysfunction and many other health concerns[5,6]. Ketamine's many benefits are therefore poorly known to the public, and the stigma surrounding it make it somewhat of a disregarded treatment and might explain why its research on other potential uses for treatment only started recently.

Soldiers during the Vietnam war used ketamine to treat injuries and suicidal thoughts, emergency responders to suicide attempts also use ketamine to calm down patients, and many stories regarding suicidal thought relief followed ketamine administration in these different cases[7]. This is how the research into its use for depression treatment started. Antidepressants' poor effectiveness despite the prevalence of depression is another factor for the necessity of more research on new and more effective treatments. Many patients do not respond to monoamine signaling treatments – called treatment-resistant depression (TRD) – and for those who do, relapse is very common. This is due to the limitations of the monoamine hypothesis of depression which explain why monoamine treatments are not an effective solution as depression is not necessarily caused by monoamine imbalances. Certain patients with comorbid disorders such as bipolar disorder also do not respond to antidepressant and need different solutions[8]. Since ketamine was accepted by the FDA as a depression treatment, it has only been allowed for patients suffering from severe TRD, keeping classic antidepressants as the primary treatment for depression. Ketamine treatment is not recommended for patients suffering from dementia or psychosis like

schizophrenia, for teenagers as the long-term effects on still-developing brains may be problematic, and for patients with a history of substance use disorder[1].

Following ketamine's rise in popularity for depression treatment, research on other psychedelics' potentials for the same treatment has also greatly increased, specifically for serotonergic psychedelics. Researchers have found that psylocibin and DMT also have great potential in treating depression, as they promote neural plasticity structurally and functionally in the prefrontal cortex (PFC) which has been correlated with significant improvements in depression symptoms[9,10]. This mechanism is thought to be the same as ketamine's[9]. Overall, ketamine's research for depression treatment has led the way for different approaches and innovative ideas for new depression treatments that can help patients with TRD and act rapidly.

Ketamine works by acting on the cortico-limbic system. It binds to NMDA receptors on GABAergic interneurons as a non-competitive antagonist by inhibiting current in both sodium and potassium voltage-gated channels. This prevents the reuptake of dopamine and serotonin. This is called the disinhibition hypothesis, however there are still contradicting results on how it really works. This is the main mechanism thought to explain the antidepressant effects of ketamine, however there are many more which are still not well understood such as the mechanism on opioid receptors. Additionally, acute administrations potentiate synaptic connectivity and plasticity[3]. Ketamine can be safely administered in many ways; IV, oral, nasal, IM, rectal, and subcutaneous or epidural[4]. Ketamine has an S- isomer and an R- isomer and is usually used as an equal mix of both; R,S-ketamine, however, the one used in treatment for depression is S-ketamine administered through a nasal spray[2]. S-ketamine has higher affinity to the NMDAR binding sites and produces much more powerful anesthesia than R-ketamine, and is associated with better analgesia, faster recovery, less cardiac stimulation and spontaneous motor activity, as well as less emergence delirium and psychotomimetic side effects[4]. However, R-ketamine in animal models has shown to be more potent and have longer lasting antidepressant effects than S-ketamine and produce less side effects than both S-ketamine and R,S-ketamine[2,4]. R-ketamine is therefore now being researched regarding its use for humans[2].

There are many benefits to ketamine treatment. Aside from its ability to treat TRD and rapidly ease suicidal thoughts as previously mentioned, its efficacy can be seen after a single IV dose where patients have high response and remission rates after 4 to 72 hours. Such results often make ketamine seem like the 'golden' antidepressant treatment, though it is important to remember that not all patients respond to it and that early relapse is quite common as the effects are often short-lived[11]. In a study on repeated ketamine IV infusions for 10 patients with TRD, they observed mild side effects during and after infusions and minimal positive psychotic symptoms with high response rates from 9 patients. Though one

patient remained medication-free with almost no depression symptoms after the treatment, almost all patients relapsed within a month after the last infusion[12]. However, another study on major depression patients – not TRD patients – with a single IV dose of ketamine showed significant symptom improvements within 72 hours[13]. This may indicate that ketamine treatment is more effective for less severely depressed or treatment non-resistant patients. Ketamine also has better cognitive side effects than electro convulsive therapy (ECT) as well as faster antidepressant effects[14]. Lastly, this treatment is very versatile and may also help treat co-morbid disorders like alcohol use disorder, PTSD, OCD etc…[1].

Just like any other treatment, ketamine also has negative side effects. As previously stated, early relapse is common and there is a lack of response from certain patients. Other side effects may include high blood pressure – which can be dangerous for some fragile patients – headaches and dizziness, nausea, dissociation, anxiety, intoxication etc. Its repeated dosage may also become less effective over time, hence requiring larger doses which is not sustainable[1]. Studies comparing ketamine to placebos may be inaccurate due to its acute psychoactive effects which make it hard to mask the placebo. A study that successfully masked the ketamine treatment from the placebo with surgical anesthesia demonstrated no greater effect of a single IV ketamine dose in acutely reducing depressive symptoms compared to the placebo[15]. We should also keep in mind that different ketamine isomers have different effects which we should further study in order to find a better way to administer it with minimal side effects.

In conclusion, research on ketamine regarding depression treatment is very promising and gives hope to patients who have never been able to treat themselves, however, research is incomplete as we are still unsure of its mechanism and there are disagreements and contradicting results. Additionally, IV infusions of R,S-ketamine and S-ketamine are more effective than the S-ketamine nasal spray currently used, but lack research on safety and efficacy of repeated infusions necessary for treatment[14]. Meanwhile, other studies showed that nasal ketamine had longer-lasting effects when taken with regular antidepressant[1]. The sample size of studies also remains very small; in Singapore, only 2 patients have received this treatment. Despite how powerful the treatment can be, antidepressants are still to be taken during the treatment period, and therapy is often necessary to try to maintain the effects of the treatment. Ketamine is therefore not the entire solution. This treatment is also very costly, averaging $600 per infusion, and is not covered by insurance[1]. Lastly, it is important to remember that casual use of ketamine does not treat depression.

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