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Ketamine - A Promising Anti-Depressant? Brief Review

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Abstract: ***Depression is a common but serious disorder. It is very hard to diagnose and some people may suffer from treatment-resistant depression. Depression exploits the person mentally and it leads to serious actions if not treated properly. To evade this along with anti-depressant therapy patients were given augmentation treatments. Lately, ketamine is found to be a promising treatment for Treatment-resistant depression but there are possible risks. Studies have been conducted to determine the ketamine effects and it can be concluded from all the studies that ketamine is effective in treating treatment-resistant depression. But the drug has a risk of being abused and there are some serious side effects. So it can be said that ketamine is a double-edged sword that needs thorough and precise research. This is a review article where some of the studies are briefly discussed.***

Keywords: Depression, Ketamine, Major Depressive Disorder, Treatment-Resistant Depression

1. Introduction

Ketamine, named as C1581 is a phencyclidine derivative which was intended to be used for anesthesia, analgesic, immobility, loss of consciousness and amnesia. But the use of the compound has been declined due to many side effects. Recently, an isomer of ketamine S-(þ)ketamine is found to be having greater potency and fewer side effects and it has been regarded for clinical use [1].

2. Mechanism of Action

Ketamine acts on the Central nervous system and has local anesthetic properties. The primary mechanism of action is a non-competitive antagonism of the N-methyl-D-Aspartate (NMDA) receptor where it reduces the presynaptic release of glutamate and behaves as an anaesthetic and analgesic. It is assumed that the anesthetic properties of ketamine are due to the inhibition of neuronal sodium channels. Ketamine is also known to have interaction with opioid receptors with a preference for mu (μ) and kappa (κ) receptors. But it is considered to be 10 times more affined to NMDA receptors than to the opioid receptors. There is also evidence supporting the antagonistic interaction of ketamine with the monoaminergic, muscarinic, and nicotinic receptors. It produces anticholinergic symptoms such as tachycardia and bronchodilation [1].

There is growing evidence indicating the additional mechanisms involving ketamine metabolites in exhibiting antidepressant actions [3]. Some studies have been conducted where ketamine is used as an off-label medication for treating treatment-resistant depression. This is a review article that includes some of the ketamine trials where it is used for treating depression.

3. Methods

A literature review was performed using search engines like PubMed, Google with the keywords “ketamine”, “ketamine and depression”. No limitations were used while selecting the articles. Duplicate records when found in selected articles are extracted and removed.

Methods: Secondary Research is conducted by reviewing PubMed, Google.

Design: Narrative review, Meta-Analysis, Case report, Randomised double-blind, and placebocontrolled safety and efficacy studies.

Etiology: Treatment-resistant Major Depressive disorder.
Outcomes (Primary and secondary): Montgomery-Asberg Depression Rating Scale score, Hamilton Depression Rating Scale, Beck Depression Inventory, Adverse events, Substance Use, psychotomimetic effects, Quick Inventory of Depressive Symptomatology Score-SelfReport, Clinical Global Impression (CGI) severity and improvement measures, Young Mania Rating Scale (YMRS).

4. Results

4.1 Intravenous ketamine therapy in a patient with a treatment-resistant major depression [4]

This is a Case report of a 55-year-old male subject who was diagnosed with treatment-resistant major depression accompanied by alcohol and benzodiazepine dependence. He was given an intravenous infusion of 0.5 mg/kg Ketamine over a period of 50 minutes. The subject first reported improvement of his symptom score within 25 mins of infusion. There was a significant improvement of his symptoms (HDRS from 36-16; BDI from 26-9) which peaked on his second day (post-infusion). The positive effects lasted for a period of 7 days as reported by the subject. It was concluded in the study that ketamine showed “strong antidepressant effects” and these actions were not affected by alcohol or benzodiazepine dependence.

4.2 Safety and Efficacy of Repeated-Dose Intravenous Ketamine for Treatment-Resistant Depression [5]

In 10 symptomatic TRD medication-free patients, ketamine was given in repeated oral doses (0.5mg/kg) 40 minutes IV infusion. If there is an improvement in symptoms on the second day they were given an additional 5 doses on an outpatient basis. Out of 10, 9 patients who met response criteria were included for repeated doses of ketamine. 8 patients relapsed after the sixth infusion (on average) and

one patient remained anti-depressant free with minimal depressive symptoms for >3 months. There were minimal positive psychotic symptoms and three patients experienced "significant but transient dissociative symptoms". Mild side effects were noted.

4.3 Antidepressant Efficacy of Ketamine in Treatment-Resistant Major Depression: A TwoSite Randomized Controlled Trial [6]

In a placebo-controlled, double-blinded, randomized trial 72 patients were given either Ketamine 0.5 mg/kg or midazolam (placebo) 0.045 mg/kg infused over 40 minutes. There was a significant improvement in the Ketamine group at 24 hours when compared to the midazolam group. The durability of the drug effect was measured on 1, 2, 3, and 7 days after infusion as a function of treatment, time, and interaction of treatment and time, after adjustment for the site. The MADRS scores on day 7 did not differ as a function of the site. There were no serious side effects with the short term and sub-anesthetic use of ketamine in nonpsychotic depressed patients. These data support the hypothesis that NMDA receptors modulation accelerate clinical improvement.

Note: In this study, midazolam is used as an active placebo based on the criteria that both the drugs have similar PK characteristics.

4.4 Rapid and Longer-Term Antidepressant Effects of Repeated Ketamine Infusions in Treatment-Resistant Major Depression [7]

In an open-label, single-arm, two-phase study; 24 patients were given Ketamine infusion and as per response-criteria 21 entered into the Phase-2 study. On the whole, the study was concluded with major findings such as the evident anti-depressant effect of ketamine in the course of treatment with a broad-spectrum effect on individual symptoms of depression. And the rapid response to the first infusion surmises the sustained response to subsequent infusions. Mild and well-tolerated side effects were noted.

4.5 Riluzole for relapse prevention following intravenous ketamine in treatment-resistant depression: a pilot randomized, placebo-controlled continuation trial [8]

This is a two-phase study where enrolled patients were given lamotrigine prior to ketamine. After 4 hours, ketamine was infused over 40 minutes. Following 72 hours post ketamine, patients who met response criteria were randomized into Riluzole (100–200 mg/d) or placebo. It was concluded that 65% of TRD patients who received ketamine met 24-hr response criteria. Riluzole could not abate the relapse in the first month which resulted in early trial termination. Ketamine given with or without lamotrigine was well tolerated. Mild or moderate dissociative symptoms were noted.

4.6 Rapid antidepressant effects of repeated doses of ketamine compared with electroconvulsive therapy in hospitalized patients with major depressive disorder [9]

In a blinded study, 18 patients were randomized to either ketamine hydrochloride (0.5 mg/kg over 45 min) or Electroconvulsive Therapy on 3 test days (every 48 h). There was a significant improvement in HDRS scores within 24 hours in the ketamine group and was consistent throughout the study. And it was concluded that Ketamine is effective as ECT in improving depressive symptoms in MDD patients and has rapid anti-depressant effects when compared with ECT.

Table: The Intervention, sample size, primary outcomes of the trials discussed above

Title of the Study	Intervention	Sample Size	Primary Outcomes
Intravenous ketamine therapy in a patient with a treatmentresistant major depression	IV ketamine	Case report	Hamilton Depression Rating Scale (HDRS), and Beck Depression Inventory (BDI)
Safety and Efficacy of Repeated-Dose Intravenous Ketamine for Treatment-Resistant Depression	Ketamine	10	Montgomery-Åsberg Depression Rating Scale score
Antidepressant Efficacy of Ketamine in TreatmentResistant Major Depression: A Two-Site Randomized Controlled Trial	Ketamine (n=47) Midazolam (n=25)	73	Montgomery-Åsberg Depression Rating Scale (MADRS)
Rapid and Longer-Term Antidepressant Effects of Repeated Ketamine Infusions in Treatment-Resistant Major Depression	Ketamine 3 times weekly	24	Montgomery–Asberg Depression Rating Scale score
Riluzole for relapse prevention following intravenous ketamine in treatment-resistant depression: a pilot randomized, placebocontrolled continuation trial	Lamotrigine pretreatment (n=13) placebo pretreatment (n=13); Ketamine (n=26) Phase-2 Riluzole (n=6), placebo (n=8)	26	Montgomery–Asberg Depression Rating Scale, Safety assessments
Rapid antidepressant effects of repeated doses of ketamine compared with electroconvulsive therapy in hospitalized patients with major depressive disorder	Ketamine - IV infusion Electroconvulsive therapy	18	Beck Depression Inventory (BDI) and Hamilton Depression Rating Scale (HDRS),

5. Discussion

Ketamine is an old drug that is now studied for new indications. It has the potential to become a first-line anti-depressive medication, especially for refractory major depression, as well as suicidal ideation in unipolar and bipolar disorders [12].

There is a potential role for NMDA receptor-modulating drugs in the treatment of depression [2]. Short-course ketamine medication is established treatment both for unipolar depression and depressive episodes of the bipolar affective disorder [13]. From the articles discussed above, and as per systematic reviews and meta-analysis ketamine shows a significant and rapid antidepressive action. Ketamine can rapidly reduce suicidality and also relieves other serious symptoms of depression and it is also effective for treating depression combined with anxiety [13]. It is administered as infusion intravenously 1 to 3 times per week, where it exhibited quick action and is also effective [10]. It stands out from other treatments because while other treatments take weeks or even months to show effects ketamine shows its effect rapidly and even in patients who had failed transcranial magnetic stimulation, ECT (which is the most effective treatment for patients who failed to respond to other therapies) [13]. A single intravenous dose of the glutamatergic modulator ketamine produces a robust and rapid antidepressant effect in persons with TRD; this effect continues to remain significant for 1 week [17]. It seems from the above studies that ketamine is the most effective, novel, and fastacting drug with mild side effects. But, the safety of prolonged treatment with ketamine is not known to a sufficient degree. However, even long periods (up to 1.5 years) of ketamine treatment have not been associated with adverse effects. It would be appropriate to use shortcourse ketamine treatment more often than is currently done [13]. The side effects from all the studies were reported as mild, tolerated and patients also experienced significant but transient dissociative symptoms [5].

It must be noted that Ketamine is also not an FDA approved drug for the use of depression [19]. It lacks a clear dosage regime and there is no evidence that it can be prescribed and it is still under consideration [11]. Middle- and long-term efficacy and safety have yet to be explored [16].

Research into the non-medical use of ketamine suggests that the long-term effects can include flashbacks, social withdrawal, and memory loss [14]. Reports suggest that ketamine produces a variety of symptoms including, but not limited to anxiety, dysphoria, disorientation, insomnia, flashbacks, hallucinations, and psychotic episodes [19]. New administration routes might serve as an alternative to intravenous regimes for potential usage in outpatient settings [15] but it needs to be studied in a large population.

6. Conclusions

From the above studies, ketamine appears to be a suitable drug for TRD, but there are many setbacks which cannot be neglected. Ketamine is known as “Club drug” in 1990 and because of its mind-altering effect, it is prone to abuse [14] and is a class B, schedule 4(1) drug [18]. This is a major problem because it leads to substance abuse which might augment the depression symptoms.

Though it seems facile to conduct a trial; there are many limitations, such as for selecting the patients a thorough history is mandatory to overcome substance abuse in the future, but we cannot be certain that it is enough. In clinical trials, the drug is given by the investigator onsite and the subject is not in direct contact with the drug so there might not be any issue of over dosage. But once the drug is prescribed on an out-patient basis, proper usage of the drug is not assured even though strict procedures are followed while dispensing. And the long term side effects of the drug are still up in the air. So careful consideration is necessary and it should not be limited to the conventional parameters like indication, efficacy, and side effects of the drug instead unsought use must be addressed precisely.

Abbreviations

BDI: Beck Depression Inventory
CGI: Clinical Global Impression
ECT: Electroconvulsive therapy
FDA: Food and Drug Administration
HDRS: Hamilton Depression Rating Scale
MADRS: Montgomery-Asberg Depression Rating Scale score
MDD: Major depressive disorder
NMDA: N-methyl-D-Aspartate
PK: Pharmacokinetics
TRD: Treatment-resistant depression
YMRS: Young Mania Rating Scale

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