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Review Article

# Ketamine for Treatment-Resistant Depression

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## Abstract

Major depressive disorder (MDD) is of influence on about 350 million individuals worldwide, which is causing disability consecution and damaging consequences to the affected community and individuals. Treatments as antidepressant are affecting the system of monoamine where symptoms of depressive were relived in about 50% of cases. Such ratio turns into obviously low in depressed persons who failed already to cure following 2 or additional antidepressant drugs at sufficient duration and doses regarding it a treatment-resistant depression (TRD). There is an obvious requisite for quick action and influenced treatments. Ketamine (KMN) is considered an anesthetic old drug that has a promising quick action as an antidepressant in TRD patients with MDD, concentrating on clinical issues, i.e. administration route, dose, and action duration. Other indication proposes that KMN might be influenced in stress disorder as posttraumatic and ideation as acute suicidal.

**Keywords:** Ketamine, Esketamine, Resistant Depression

## Introduction

Ketamine (KMN), as an anesthetic agent introduced in the 1960s, has assembled striking interest for the past 20 years as an arising management for major depressive disorder (MDD). With its high efficacy evidence in treatment-resistant depression (TRD) and its potential action as antisuicidal, investigations have been structured on brain clarify influences of KMN. The KMN strength to put out quick antidepressant influences as early as a small number of hours following administration. Such is in striking difference to the delayed influences recognized with customary antidepressants, frequently need several therapy weeks for response clinically. In addition, KMN seems to have an exclusive action mechanism involvement glutamate modification through receptors actions of N-methyl-D-aspartate (NMDA) and amino 3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, as well as besides subsequent activation of brain-derived neurotrophic factor (BDNF) and mechanistic target of rapamycin synaptic plasticity.[1] KMN is an antagonist non-competitive (NMDA) receptor and was untypically utilized as anesthetic being dissociative. It was 1st recorded to have antidepressant characteristics in 2000, when it was determined that subanesthetic KMN dose intravenous (IV) administration in MDD symptoms abatement immediately and lasting to 72 h following treatment.[2] Foregoing as randomized controlled trials (RCTs) imprint such spotting, determining a 60%–70% level of KMN response in population of TRD.[3] KMN following administration is of a quick influence clinically within 2–4 h. Despite antidepressant of KMN characteristics are as well short lived, enduring 1 week average after infusion being single (10–14) and (18–19) days after subsequent infusions.[4,5] In addition, KMN has also been well known of actions as antianhedonic and antisuicidal.[6] Esketamine has a quickly clinical influence through numerous hours and sustain capability in cases where patients not responding to other different antidepressants, it emerge of having a peculiar action mechanism which is different from traditional drugs as antidepressant. Reports at this time on other KMN administration types are inadequate. Whereas one RCT on intranasal (IN) KMN,[7] imply that administration as IN might be alternative as possible, another report was canceled early because of poor endurance to the formulation as IN.[8] Other studies[9,10] have described that despite it rests experimental naturally, preservation of IN KMN is clinically helpful in cases where patients are of noncompliance other treatments

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options. Researches on sublingual and normal oral KMN were the susceptible of a current systematic assessment.[11] One pilot preceding investigation is also recommended that subcutaneous or intramuscular paths might be choices being possible.[12] Esketamine as IN was permitted via FDA in USA in March 2019 for MDD which not responding to 2 or further antidepressants. Such recommendation was according to 2 maintenance-phase and 3 acute-phase studies. Trial of phase III over two hundred cases utilizing esketamine concomitant to an antidepressant sustained serious recovery in depression at 4 weeks in comparison to those utilizing a placebo nasal spray. Retrospective data as actual-world clinically reveal a 44% response rate following 6 IV KMN treatments in a complex patient's society with multiple co morbidities and depression of ultra-resistant.[13,14]

## Methodology

It is review of the available knowledge and papers on the subject of using ketamine in depression, we use search engines:- (Google scholar, Research gate, Google books) and the key words to search were:- ketamine therapy, desketamine, depression, after this search we include relevant article that were puplished during (2000-2020).

## Adverse Influences of Ketamine

KMN side influence associated with use of KMN include emergence reactions, increased cardiac output, double vision, vivid dreams, increased intra ocular pressure and injection site pain, mostly of which happen throughout the period of infusion and thereafter shortly. Such doses as subanesthetic can also be related with neuropsychiatric influences as short-lasting. Such transient and acute influences including an upsurge in blood pressure (typically asymptomatic), vomiting and nausea, dizziness, drowsiness, and dissociation, less common side influence include muscle twitching and spasm, increased salivation.[14] Blood pressure must be check up previous and following KMN administration till it proceeds to values being normal.[15]

## Biomarkers Predicting Response to Ketamine

### Sleep

KMN has strong influences on rising sleep as total and of slow-wave sleep, slow-wave activity (SWS, SWA).[16] and its antidepressant influence were related to such influence.[17] SWA and SWS improvement, peculiarly at initial night, is regarded a demanding aspect in mechanism of KMN as quick action of antidepressant in MDD, and same issue were observed with as repetitive transcranial magnetic stimulation.[18] Such SWA increment strongly correspond with rising in pre-clinically plasma BDNF and synaptic plasticity.[19] Also in KMN responsive MDD patients.[16-17] BDNF is a recognized possible antidepressant response marker.[20] The increased degree was observed to anticipate acute response mood to KMN.[21] Excitingly, such improvement in SWA, SWS might be particular to unipolar depression patients.[22] Total sleep improvement, peculiarly minimization in holy electroencephalogram, early night awakening, can be apparatus where KMN apply its antisuicidal influences.[23] Such must be an attractive future study area as mechanisms of nonantidepressant requisite to be enlightened to fully elucidate the KMN anti-suicidal influences.[24] KMN also shows of having serious consequence on systems of circadian rhythm, and its influences on glutamate possible inhibit portion of such symultaneity of light/dark and The internal clock is moderatly mediated via glutamate in the retinothalamic tract.[25]

### Cognition

Treatment of KMN in a definite MDD treatment agreement also display encouraging outcome in cognition and cognitive symptoms. Three patients groups with resistant treatment as bipolar and unipolar depression; TRD anxious and nonanxious depression were received 6 KMN infusions for 12 days along with alike cognitive examining in a period of 2 weeks of follow-up. Of the studies, in cognitive function, no any deterioration was observed. Verbal learning and processing speed were improved, but such was correlated significantly with depressive symptoms' improvement.[26-28] In TRD patients, 0.5 mg/kg single infusion also was observed as beneficial slightly in response control and attention as well.[29] This was a concern in which chronic KMN utilize might cause deficits as cognitive ones. KMN chronic and heavy utilizers were noticed of having a diversity of deficits of cognitive function through numerous domains. They include memory verbal/visual memory and word reading, executive function and motor speed, besides verbal fluency, verbal learning specific to medial temporal and frontal cognition, and speed of processing. Chronic KMN small group utilizers have also revealed spatial disturbances of memory and altered activity as hippocampal.[30-32]

### Metabolism and Inflammation

Metabolic syndrome, with a variety of manifestation counting: Hypercholesterolemia, hypertension, hyperglycemia and widening WC is prevalent in mood disorders patients. A new research shows a metabolic syndrome of 38% prevalence in TRD patients, and it was predicted that relatively $^{1}/_{3}$ of patients that depressed have increased markers of inflammation.[33] A serious earlier complicated accord found between syndrome as metabolic and disorders of mood and such association show to prove inflammation. Metabolic syndrome in TRD patient is 3 times extra prevalent in patients of high (C-reactive protein [CRP]), marker of inflammation.[34] Organized report studying at predeators of feedback in TRD advocate that markers of inflammation of interleukin-6, CRP and antidepressant drug response of anti-inflammatory characteristics, as well as KMN.[35] Communications mechanisms among KMN, depression, inflammation and metabolism still ambiguous, but are possible arbiterate via various factors. Increased (body mass index) has been formed as response to KMN prediction.[36,37]

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## Neuroimaging

A widely spreading literature is there on neuro-anatomical of response to KMN biomarkers medication. MDD was approved to influence, among other areas, the pre frontal cortex, anterior cingulate, the hippocampus and there is proof that mode of action of KMN on these areas specifically.[38,39]

## Route of Administration

KMN is administrated via several rout include: IV infusion, IN, sublingual, intramuscular, oral, rectally (suppository). In many studies, depressive symptoms considerably corrected following KMN IV administration in comparison to placebo. Whereas other research correlated the antidepressants influence duration with IN KMN and IV,[40,41] and achieve no difference was there between IV and IN administration from day 1 over the correlation is according to a single research with IN KMN.[7] Also, it is essential to analyze the KMN treatment interaction with current antidepressant and/or therapy of enhancement (antipsychotics, anxiolytics, and mood stabilizers). Clinical trials are mostly of need a complementary medication washout, whereas just few have examined efficacy of KMN as a continuing antidepressant treatment associate or therapy as electroconvulsive. Both designs of trials have demonstrated that KMN is efficient in depression correction.[3] Hence, in practice as clinical, it is not mandatory for specialist to washout patient's current antidepressant medication.[40] KMN is mostly administered frequently in 0.5 mg/kg dose, but a seldom dose of 0.1 mg/kg being low is adequate, while others might need 0.75 mg/kg. The KMN dose is properly applied through forty min, though efficacy and safety have been confirmed in a period between 2 and 100 min. Administration of Bolus is influenceive and safe if the drug is administered in IM and SC rout, whereas the IV route is the most frequently employed. KMN infusion therapy involves[6] low-dose IV KMN infusions over the course of 2 weeks.[41]

## Single Intravenous Infusion Efficacy Against Intravenous Infusions Being Repeated

KMN administration is as single doses of IN and IV have always revealed antidepressant influence for concurently 7 days. Less reports have displayed the influences of recurrent KMN administrations. In an exploratory examining the[6] IV KMN infusions influence over 2 weeks, revealed that 24 participant of 70.8% with depression as unipolar and contemporary medications free responded with an ordinary response continuing duration of 18 days, response following 6 IV KMN infusions was expected strongly for responding at 4 h following the 1st infusion. The responding duration after the[6] infusion continued between (25–168) days; studies achieve that responding to a repeated KMN applications sequence can be expected following the 1st one or 2 infusions. This is significant as in clinical practice longer KMN administrations successions would just be confirmed in patients undergoing early responding to the 1st 2 treatments.[41]

## Influence of Ketamine on Anhedonia and Suicidal Ideation

Suicidal ideation in the midst of the highest clinically regarding of depression, and still a dominant cause of death. Studies always reveal a serious decline in SL following administration of KMN. In a report appraise implement of KMN on suicidality in TRD patients, single KMN doses declined both SL and depression, with provide recovery for 2 weeks after infusions being repeated.[42,43] In a 14 patients study with MDD expressing suicide enter to the Department of Emergency, a KMN single dose (0.20 mg/kg) carry out for 1–2 min diminish Sl obviously when seeing 40 min postinfusion.[43,44] A suicidal patients study with a different anxiety and mood disorders enter to unit of inpatient psychiatric revealed fast Sl improvement following IV KMN in comparison to midazolam.[4] Last research recommend that defenit anti suicidal KMN influences might be associated to recovery in executive functioning and cognitive emotional, (planning, memory, behavioral inhibition, cognitive flexibility); the networks as neural including the prefrontal support of cortex both recovery in cognition and depression.[45] Also, Lally *et al*. described that following a single IV KMN dose, patients of 87% display recovery in anhedonia at 4 h post infusion advancement in anhedonia was correspond with improvement in total depression;[46] therefore, it is confused if in anhedonia the improvement is pseudo-specific (because of antidepressant influence). Given that deterioration in the reward brain system is affiliated with suicidality, depression, and anhedonia, where such might be possible where targets of KMN such circuit as neural that consists of the dorsal areas being anterior cingulate orbitofrontal cortex, basal ganglia, cortex, and hippocampus.[45-47]

## Contraindications

KMN is contraindicated in those with elevated blood pressure would face complications risk like uncontrolled hypertension, aortic dissection, aneurysms, or myocardial infarction. It is restricted in those with prior history of hypersensitivity to the drug. It is not needed for utilize throughout pregnancy, obstetrics, or for breastfeeding women as it is unknown if such drug enter into breast milk. Utilize in patient severely alcohol-intoxicated might cause death. Also, its restricted in patients with schizophrenia because of the possible exacerbating of the underlying condition and in patients with elevations of cerebrospinal fluid (CSF). Few studies attribute that the CSF elevation worry with KMN has been overmentioned.[48]

## How to Prepare for Ketamine Treatment

In general, fasting before each KMN infusion is recommended. This could mean avoiding food and drink the night before and the morning of treatment, depending on when infusion is scheduled. Also shouldn't have caffeine, including soda and coffee, before treatment. Certain medications may also need to be discontinued temporarily before undergo KMN treatment.

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It is best not to be overtired or stressed, so that relax during treatment and get a good night sleep.

The treatment takes about 90 min from start to finish, KMN can have a sedating influence, since sit for some time in a relaxed state, shouldn't wear any binding or uncomfortable clothing.

Following the treatment, should not drive for the rest of the day, so a family member needed to accompany the patient for driving to home.[49]

## Conclusion

There has been raising concern about KMN in the last decades, largely due to its quick and promising antisuicidal and antidepressant actions in TRD patients. The preclinical and clinical researches have caused eventual consideration of it's utilize in psychiatry, and such will carry on to be an influenceive more investigations area. Individual differences among patients include differences in sex and suitable regimens determination for therapy of maintenance need to be studied. Also, a requisite is there for investigating extra dependable biomarkers to predict KMN response. KMN rests an auspicious choice for such TRD suffering, and it is led to follow the theory which realizing neurochemical mechanism of KMN.

Administration of KMN was correlated with quick clinical recovery (within 24 h) in patients of TRD, depression as bipolar, PTSD, and such with acute SI. The single KMN influence dose emerges to stay up to 7 days in TRD as unipolar and 3–4 days in bipolar depression. Severe depression with anxiety or cognitive dysfunction might be an excellent target for KMN treatment. Repeated KMN doses are stated to be harmless and offer prolong responding clinically. Responding to a frequent KMN administrations series might be expected following the 1st one or 2 infusions. IN KMN has positive influences in comparison with IV KMN and is developed nowadays for patients of self-administrated. The 0.5 mg/kg dose as IV KMN typically was used. We can be use KMN in besides ongoing treatment as antidepressant. Further monitoring must be necessary for patients with previous cardiovascular disease history. Previous psychosis history might be regarded contraindication as relative.

## Limitation and Criticism

Review of previous articles on KMN use in depression shows that long-term efficacy of KMN has not been investigated also regarding side effect of longer period of use and multiple infusion. They are only tested injected type of drug, so we cannot know whether nasal application might change the way that side effect appear. Therefore, following of patient more than 3 month is needed to measure craving and dependence or abuse. Interest in KMN use will continue because of work of KMN to relief depression is so swiftly when comparing it with other failed antidepressant drug. However, many questions in regard to extended use is must put in mind.

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### Conflicts of interest

There are no conflicts of interest.

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