Ketamine: New Use for an Old Hat

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Abstract

Objective: This article aims at examining the available knowledge about ketamine as a novel treatment option for management of treatment-resistant major depression.

Method: This is a non-systematic review utilizing search words ‘ketamine’ and ‘depression’. Approximately 70 papers were reviewed of 1,800 papers that were identified in PubMed and Google Scholar.

Results: Multiple double blind randomized control trials demonstrated the efficacy of ketamine intravenous infusion in acute management of depression and treatment-resistant depression. Ketamine shows benefits in depressed mood within hours of its infusion and the effect is maintained for several days. Ketamine may also be associated with cardiovascular, neurological, psychotomimetic, and dissociative side effects.

Conclusions: Current data points to a rapid and robust action of ketamine as an antidepressant, even in treatment-resistant patients. Long-term efficacy and safety remain unclear. Available data are insufficient to recommend its routine use in clinical practice in psychiatry or its inclusion in guidelines for management of depression, but support ongoing examination of this anesthetic as an antidepressant treatment.

Keywords
Ketamine, Depression, Antidepressant, N-Methyl-D-Aspartate (NMDA) receptor

Introduction

Depression is one of the leading causes of disability not only in the US but worldwide as well. It is ranked third for global disease burden by the WHO [1] and estimated to affect 350 million people worldwide [1]. The economic burden of depression is estimated to have increased by 21.5% from 2005 to 2010 (from $173.2 billion to $210.5 billion) [2]. During an episode of depression, one may experience symptoms that are present most of the day, nearly every day. These include feelings of sadness, emptiness, or unhappiness; loss of interest in normal activities; sleep disturbances; tiredness and lack of energy; changes in appetite; and frequent thoughts of death and suicidal thoughts. Symptoms should be severe enough to affect functions of daily life [3].

Despite the clinical significance of depression, the pathophysiology underlying depression is still poorly understood. The monoamine hypothesis of depression enjoyed considerable support for more than 40 years; focusing on central deficiency of serotonin, norepinephrine and (to a lesser extent) dopamine. But it is clear that there are significant gaps in our understanding of this complex disorder [4]. Most clinically available antidepressants act in different ways leading to increase the monoamine synaptic signal. Unfortunately, there is a lag of therapeutic effects and disappointing remission rates of the current available antidepressant treatments, leaving a significant unmet need.

For a couple of decades preclinical data has been accumulating in regard to the role of the glutamate system in the pathophysiology of depression [5]. It has been observed that patients with depression have higher plasma and CSF glutamate compared to controls [6,7]. Of the glutamate antagonists available clinically, ketamine seems to be the most promising. In the year 2000, Ber man, et al. published an article about seven patients with
treatment-resistant depression who were administered a ketamine intravenous infusion that resulted in significant improvement of their symptoms [8].

Methods

Keywords of ‘ketamine’ and ‘depression’ were used in Pubmed and Google Scholar. The resulting 1,643 references in Pubmed, and the first 150 of the 93,000 references in Google Scholar were reviewed. Of these, papers describing controlled trials in the treatment of severe depression were examined. Since the purpose of this review was to provide a useful review for anesthesiology professionals, we did not perform a systematic review, but utilized important studies that edify regarding the use and consequences of ketamine in depressed patients. When available the Standardized Mean Difference (SMD) was included to allow for relative comparison the observed therapeutic effect between various studies [9].

Ketamine

Ketamine (2-[2-chlorophenyl]-2-[methylamino]cyclohexanone) is an arylcycloalkylamine compound. It is structurally similar to Phencyclidine (PCP) and cyclohexylamine. The free-base form of ketamine is highly lipid soluble. It is commercially available as an aqueous preparation of the hydrochloride salt [10]. Ketamine can be administered via multiple routes, including oral, intravenous, intramuscular, subcutaneous, intranasal, epidural, transdermal, intra-articular, and sublingual [11].

Ketamine is a noncompetitive antagonist of the voltage gated N-Methyl-D-Aspartate (NMDA) receptor, inhibiting the influx of sodium and in the presence of the co-agonist glycine [12]. The interaction with multiple peripheral receptors is responsible for ketamine’s transient cardiovascular, respiratory, and sympathomimetic side effects [13].

Ketamine in depression

Berman, et al. [8] described the first study showing that ketamine is effective as an antidepressant when administered at subanesthetic doses. Subsequently, several studies confirmed this finding. One of the reasons ketamine is gaining a lot of attention is that it is the only treatment modality with ultrarapid response, as early as 2 hours [14]. Multiple meta-analyses have been performed showing a robust, yet transient, antidepressant effect of a subanesthetic dose of ketamine in patients with treatment-resistant depression [15-18]. The studies reviewed in this paper utilized the intravenous route of administration. While ketamine can be administered orally, it has much lower bioavailability (about 20%) [19]. This fact, coupled with the potential for abuse of prescribed ketamine, preclude routine oral use.

A meta-analysis performed by Lee, et al. in 2015 [20] (done using the data provided by the authors of the original manuscripts of 5 randomized placebo-controlled trials) showed a large and statistically significant antidepressant effect at 24 h post-infusion, with overall Standardized Mean Difference (SMD) of 1.01. The SMD allows for a relative comparison between studies that are statistically significant [9]. The effect size dropped from large to moderate at 7 days post-infusion. Fond, et al. [17] meta-analysis in 2014 included 9 randomized placebo-controlled trials, showed similar statistically significant results with overall SMD of 0.99. A Cochrane network systemic review in 2015 [16] was done using 25 double- or single-blind RCTs comparing ketamine, mexiteline, or other glutamate receptor modulators with placebo or other active psychotropic drugs, or Electroconvulsive Therapy (ECT) in adults with unipolar major depression; 1,242 subjects were included. Results showed that among all the glutamate modulators investigated only intravenous ketamine was more effective than placebo with odd’s ratio of 10.77 at 24 hours (95% Confidence Interval [CI] 2.00 to 58.00), 12.59 at 72 hours (95% CI, 2.38 to 66.73) and 2.58 at one week (95% CI, 1.08 to 6.16) [16].

Since Ketamine can be used as an anesthetic, its use as part of the anesthesia administered for induction of seizure in ECT has been investigated. Li, et al. [20] performed a meta-analysis of 16 studies that investigated the efficacy of ECT plus ketamine plus other anti-esthetic agents, or ECT with other anti-esthetic agents in the absence of ketamine. There were 346 patients receiving add-on ketamine anesthesia in ECT and 329 controls. The addition of ketamine increased the antidepressant response significantly (p < 0.001). This effect was seen if patients received either unilateral or bilateral ECT.

Most of the studies done with ketamine as a treatment for depression used subanesthetic doses at (0.5 mg/kg) infused usually over 40 minutes as the original work done by Berman, et al. [8]. More hemodynamic instability was noticed in patients with body mass index more than 30 kg/m² [21] requiring caution in this population or using lower dose.

Side effect profile

As an anesthetic, a loading dose of 1.5 to 2.0 mg/kg IV in children or 1.0 mg/kg IV in adults over 30-60 seconds is usually given. An additional incremental dose of ketamine (0.5 to 1.0 mg/kg) may be used if initial sedation is inadequate [22]. Possible side effects include transient laryngospasm, transient apnea or respiratory depression, hypersalivation, emesis (usually in recovery), muscular hypertonicity, clonus, hiccupping, and recovery agitation [22]. Although ketamine has a direct vasodilata-
Drug-Drug Interactions

Psychotomimetic and dissociative effects

Abuse potential

Ketamine is a known substance of abuse. Possibly due to its psychedelic like properties, and/or its agonist activity at mu opioid receptors, as well as increase dopamine release [28-30]. Early studies in depressed patients that specifically exclude patients with a history of substance misuse, have not demonstrated problems with abuse [21], but long term studies are still lacking. High doses of ketamine in rats (intraperitoneal 25-80 mg/kg) revealed evidence of neuronal degeneration and apoptosis [31]. Ketamine has been used widely in emergency room setting for pediatric age (usually between 4-6 years) for the past 4 decades with no human studies showing any evidence for apoptosis or neuronal degeneration [32]. No long-term neurodevelopmental follow up studies has been done to the author’s knowledge which would be helpful as more conclusive evidence.

Psychotomimetic and dissociative effects

The psychedelic like properties of ketamine has been known for a long time. Studies examining these properties showed psychotomimetic effects (conceptual disorganization, hallucinations, suspiciousness, and unusual thought content) and dissociative effects (objects seem unreal or moving in slow motion, alternation of visual or auditory perception or out of body experience) [21,33]. Dissociative and psychotomimetic (less common and severe) side effects were evident in studies using ketamine for depression in subanesthetic dosage [21,27]. These effects are usually transient and resolve with 4 hours of the infusion [21,27].

Drug-Drug Interactions

Ketamine is metabolized through the hepatic cytochrome P450 enzymes (mainly 3A4) [34]. CYP3A4 inducers like rifampin and St. John’s wort can increase the metabolism and clearance of ketamine. Enzyme-inhibiting substances such as clarithromycin and grapefruit juice can prolong the half-life of the parent compound.

Possible Mechanism of Action

Although the antidepressant effects of ketamine are obvious from clinical trials, the underlying mechanism is still not clear. Ketamine is known to have variable clinical effects at different doses. For example, at higher doses it acts as a hypnotic anesthetic, lower doses may be hallucinogenic, and lower doses still appear to be antidepressant. This pattern is suggestive of variable affinities of different receptors or processes. For anesthesia, the presumed mechanism is its effects as a NMDA receptor antagonist [35]. However, this effect is unlikely to mediate the antidepressant effect since the drug has already been eliminated from the body at the height of clinical response. Dendritic spine density in multiple brain areas such as the prefrontal cortex, limbic system, and hippocampus is lower in animals susceptible to depression [36,37] and animals exposed to chronic stressor-a model for depression [38]. Similarly, the volume of the prefrontal cortex and hippocampus is reduced in patients with major depression [39,40]. Ketamine has been shown to rapidly (within 24 hours) increase the number of synapses in the prefrontal cortex [41,42]. These observations take into account pathophysiological changes seen in depression and the time course of those changes [43]. Furthermore, in animal models of depression, the R enantiomer of ketamine had a more potent antidepressant effect compared to S enantiomer [44,45]. That is despite that fact that S-ketamine 3-4 times more potent at inhibiting NMDA receptor compared to R-ketamine [46].

Conclusion

Much is known about the pharmacological properties of ketamine owing to its long history of use as an anesthetic medication. Accumulating evidence suggests that it may also be a safe and effective antidepressant. Research looking at this and other glutamate system modulators is growing. However, while the antidepressant effect is rapid, it is relatively short-lived. Some studies have looked at repeated ketamine administration to obtain a longer lasting response [47] but there is a dearth of information on long-term effects of ketamine. Despite the promising initial results for the use of ketamine in treatment resistant depression, it is important to remember that it is still not approved by the FDA for that indication and still considered an experimental treatment. The American Psychiatric Association (APA) in 2017 released a consensus statement regarding the use of ketamine in depression [48]. In that document, the APA recommends caution as due to the huge gaps in knowledge that still exist. Clin-
ical researchers need to continue to examine the use of ketamine in treatment-resistant depression, with specific emphasis placed on the consequences of repeated dosing and long-term effects of both brief and extended exposure to ketamine.

References

1. Mathers C, Boerma T, Fat DM (2008) The Global Burden of Disease: 2004 Update. World Health Organisation.

2. Greenberg PE, Fournier AA, Sisitsky T, et al. (2015) The economic burden of adults with major depressive disorder in the United States (2005 and 2010). J Clin Psychiatry 76: 155-162.

3. Association AP (2013) Diagnostic and statistical manual of mental disorders (DSM-5). American Psychiatric Pub.

4. Hirschfeld RM (2000) History and evolution of the monoamine hypothesis of depression. J Clin Psychiatry 61: 4-6.

5. Paul IA, Skolnick P (2003) Glutamate and depression: Clinical and preclinical studies. Ann NY Acad Sci 1003: 250-272.

6. Levine J, Panchalingam K, Rapoport A, et al. (2000) Increased cerebrospinal fluid glutamine levels in depressed patients. Biol Psychiatry 47: 586-593.

7. Paul IA, Skolnick P (2003) Glutamate and depression: Clinical and preclinical studies. Ann NY Acad Sci 1003: 250-272.

8. Berman RM, Cappiello A, Anand A, et al. (2000) Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 47: 351-354.

9. Faraone SV (2008) Interpreting estimates of treatment efficacy. J Clin Psychiatry 69: 8-15.

10. Mathai DS, Mathew SI (2017) Ketamine. In: Schatzberg AF, Nemeroff CB, American Psychiatric Association Publishing Textbook of Psychopharmacology. (5th edn), American Psychiatric Association Publishing, 549-562.

11. Kotilräs-Klemesjärvi A, Luczak J (2004) Subanesthetic ketamine: An essential adjuvant for intractable cancer pain. JPSM 28: 100-102.

12. Niciu MJ, Henter ID, Luckenbaugh DA, et al. (2014) Glutamate receptor antagonists as fast-acting therapeutic alternatives for the treatment of depression: Ketamine and other compounds. Annu Rev Pharmacol Toxicol 54: 119-139.

13. Domino EF (2010) Taming the ketamine tiger. The Journal of the American Society of Anesthesiologists 113: 678-684.

14. Zarate CA, Singh JB, Carlson PJ, et al. (2006) A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry 63: 856-864.

15. Green SM, Roback MG, Kennedy RM, et al. (2011) Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update. Ann Emerg Med 57: 449-461.

16. Eikermann M, Grosse-Sundrup M, Zaremba S, et al. (2012) Ketamine activates breathing and abolishes the coupling between loss of consciousness and upper airway dilator muscle dysfunction. Anesthesiology 116: 35-46.

17. Murrough JW, Iosifescu DV, Chang LC, et al. (2013) Antidepressant efficacy of ketamine in treatment-resistant major depression: A two-site randomized controlled trial. Am J Psychiatry 170: 1134-1142.

18. Lindefors N, Barati S, O’Connor WT (1997) Differential effects of single and repeated ketamine administration on dopamine, serotonin and GABA transmission in rat medial prefrontal cortex. Brain Res 759: 205-212.

19. White PF, Way WL, Trevor AJ (1982) Ketamine—the pharmacology and therapeutic uses. Anesthesiology 56: 119-136.

20. Liu JX, Zerbo S, Ross S (2015) Intensive ketamine use for multiple years: A case report. Am J Addict 24: 7-9.

21. Hayashi H, Dikkes P, Soriano SG (2002) Repeated administration of ketamine may lead to neuronal degeneration in the developing rat brain. Paediatr Anaesth 12: 770-774.

22. Green SM, Cote CJ (2009) Ketamine and neurotoxicity: Clinical perspectives and implications for emergency medicine. Ann Emerg Med 54: 181-190.

23. Krystal JH, Karper LP, Seibyl JP, et al. (1994) Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry 51: 199-214.

24. Mion G, Villevieille T (2013) Ketamine pharmacology: An update (pharmacodynamics and molecular aspects, recent findings). CNS Neurosci Ther 19: 370-380.

25. MacDonald JF, Miljkovic Z, Pennefather P (1987) Use-dependent block of excitatory amino acid currents in cultured neurons by ketamine. J Neurophysiol 58: 251-266.

26. Traber DL, Wilson RD, Priano LL (1970) Blockade of the hypotensive response to ketamine. Anesth Analg 49: 420-426.

27. Corssen G, Domino EF (1966) Dissociative anesthesia: Further pharmacologic studies and first clinical experience with the phencyclidine derivative CI-581. Anesth Analg 45: 29-40.

28. Zaremba S, Niciu MJ, Henter ID, et al. (2014) Glutamate receptor antagonists as fast-acting therapeutic alternatives for the treatment of depression: Ketamine and other compounds. Annu Rev Pharmacol Toxicol 54: 119-139.

29. White PF, Way WL, Trevor AJ (1982) Ketamine—the pharmacology and therapeutic uses. Anesthesiology 56: 119-136.

30. Liu JX, Zerbo S, Ross S (2015) Intensive ketamine use for multiple years: A case report. Am J Addict 24: 7-9.

31. Hayashi H, Dikkes P, Soriano SG (2002) Repeated administration of ketamine may lead to neuronal degeneration in the developing rat brain. Paediatr Anaesth 12: 770-774.

32. Green SM, Cote CJ (2009) Ketamine and neurotoxicity: Clinical perspectives and implications for emergency medicine. Ann Emerg Med 54: 181-190.

33. Krystal JH, Karper LP, Seibyl JP, et al. (1994) Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry 51: 199-214.

34. Mion G, Villevieille T (2013) Ketamine pharmacology: An update (pharmacodynamics and molecular aspects, recent findings). CNS Neurosci Ther 19: 370-380.

35. MacDonald JF, Miljkovic Z, Pennefather P (1987) Use-dependent block of excitatory amino acid currents in cultured neurons by ketamine. J Neurophysiol 58: 251-266.
36. Qu Y, Yang C, Ren Q, et al. (2017) Regional differences in dendritic spine density confer resilience to chronic social defeat stress. Acta Neuropsychiatr 1: 1-6.

37. Iniguez SD, Aubry A, Riggs LM, et al. (2016) Social defeat stress induces depression-like behavior and alters spine morphology in the hippocampus of adolescent male C57BL/6 mice. Neurobiol Stress 5: 54-64.

38. McEwen BS (2008) Central effects of stress hormones in health and disease: Understanding the protective and damaging effects of stress and stress mediators. Eur J Pharmacol 583: 174-185.

39. MacQueen GM, Yucel K, Taylor VH, et al. (2008) Posterior hippocampal volumes are associated with remission rates in patients with major depressive disorder. Biol Psychiatry 64: 880-883.

40. Drevets WC, Furey ML (2010) Replication of scopolamine’s antidepressant efficacy in major depressive disorder: A randomized, placebo-controlled clinical trial. Biol Psychiatry 67: 432-438.

41. Li N, Lee B, Liu RJ, et al. (2010) mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science 329: 959-964.

42. Duman RS, Li N, Liu RJ, et al. (2012) Signaling pathways underlying the rapid antidepressant actions of ketamine. Neuropharmacology 62: 35-41.

43. Sleigh J, Harvey M, Voss L, et al. (2014) Ketamine—More mechanisms of action than just NMDA blockade. Trends in Anaesthesia and Critical Care 4: 76-81.

44. Zanos P, Moaddel R, Morris PJ, et al. (2016) NMDAR inhibition-independent antidepressant actions of ketamine metabolites. Nature 533: 481-486.

45. Yang C, Shirayama Y, Zhang JC, et al. (2015) R-ketamine: A rapid-onset and sustained antidepressant without psychotomimetic side effects. Transl Psychiatry 5: e632.

46. Moaddel R, Abdakhmanova G, Kozak J, et al. (2013) Sub-anesthetic concentrations of (R,S)-ketamine metabolites inhibit acetylcholine-evoked currents in α7 nicotinic acetylcholine receptors. Eur J Pharmacol 698: 228-234.

47. Singh JB, Fedgchin M, Daly EJ, et al. (2016) A double-blind, randomized, placebo-controlled, dose-frequency study of intravenous ketamine in patients with treatment-resistant depression. Am J Psychiatry 173: 816-826.

48. Sanacora G, Frye MA, McDonald W, et al. (2017) A consensus statement on the use of ketamine in the treatment of mood disorders. JAMA Psychiatry 74: 399-405.