

Concerns on the Use of Ketamine in the Treatment of Depression

To the Editor,

Major depressive disorder is the third leading cause of global disability and is often associated with incomplete recovery, numerous relapses, and functional impairment. Up to 20% of the patients remain unresponsive to standard antidepressants, progressing to treatment-resistant depression (TRD).^{1,2}

Emerging evidence suggests that ketamine, an N-methyl-D-Aspartate antagonist with proven efficacy and safety as an anaesthetic agent, is associated with robust and rapid antidepressant effects. The rate, dose, and route of ketamine administration has varied widely across studies, with 0.5 mg/kg given intravenously over 40 min being the most widely recommended. However, the short-term nature of the antidepressant effect has led to the need for repeat therapy.^{2,3}

Ketamine is categorized as a Schedule III controlled substance under the Narcotic Drugs and Psychotropic Substances (NDPS) Act, 1985 in India. Esketamine, the S-enantiomer of ketamine, was approved by the USFDA for use in depression, intranasally, in 2019. Common side effects of ketamine in anaesthetic dosages include hemodynamic instability, emergence reactions, and respiratory depression. These are seldom seen in the subanaesthetic dosages typically used to treat depression.^{3,4}

However, an increase in systolic (up to 19 mmHg) and diastolic (up to 13 mmHg) blood pressure within 40 min of infusion, along with severe cardiac arrhythmias like atrial fibrillation and ventricular extrasystoles, have been reported post-ketamine infusion in TRD patients.^{4,5} These adverse effects are seen in a dose-dependent manner, necessitating dose adjustment. In obese patients (Body Mass Index >30 kg/m²), calculating the dose as per the ideal body weight may be prudent.⁶

Dissociation symptoms and psychotomimetic effects like visual hallucinations, unusual thought content, dysphoria, and mania have been reported and observed

to peak following an infusion of ketamine and resolve rapidly within 2 h of the infusion.³⁻⁵ Non-dissociative effects include agitation, mild sedation, vomiting, nausea, blurred vision, dizziness, and vertigo. Moreover, the long-term use of ketamine has a potential risk of abuse and addiction. Bladder dysfunction and liver injury have also been demonstrated with repeated ketamine infusion therapy.²⁻⁴

An increase in the unlicensed use of ketamine in depression has led to the formulation of comprehensive guidelines for the safe delivery of ketamine in affective disorders. Ketamine is recommended as a third-line agent for TRD, with limited evidence regarding the efficacy of a longer course of 6-8 repeated infusions.⁷

However, recent studies advocate the administration of ketamine on an outpatient basis for depression, which necessitates utmost caution regarding patient selection, evaluation of systemic comorbidities like hypertension, and safe delivery over the recommended infusion period of 40 min. Ketamine is relatively contraindicated in patients with a history of cardiovascular disease, poorly controlled hypertension, active liver disease, or elevated intraocular pressure. Moreover, concurrent use of psychiatric agents like fluoxetine and sertraline, which inhibit the cytochrome p-450 system, leads to a decrease in the metabolism and clearance of ketamine.³

The immunologic potential of ketamine has also not been extensively studied. There are various case reports of allergic reactions to intravenous ketamine confirmed by intradermal testing, manifesting with severe symptoms like erythema and laryngospasm, necessitating the use of epinephrine.⁸ Accidental ketamine overdosage or undiagnosed infusion pump malfunction can also compromise airway patency, which is disastrous when unrecognized or without equipment to secure the airway. The occurrence of such complications is reduced with oral ketamine. The administration of oral ketamine is prevalent in India as it's inexpensive and easy to administer in facilities with limited access to healthcare resources.

We strongly recommend forming a centralized database and registry of ketamine use to facilitate the collection of high-quality data, safety reports, and side effects. This can be used to formulate centralized guidelines regarding the route, dose, and frequency regimes. It is also essential that, for its safe delivery, ketamine be administered by specialist physicians with thorough knowledge of its safety and efficacy profile. Moreover, they should be affiliated with centers with sufficient resources for monitoring vitals (heart rate, blood pressure, and oxygen saturation), provision of resuscitation, and basic life support care in case of an untoward reaction or overdosage. A thorough review of any allergies and concurrent medications like benzodiazepines and opiates, which might potentiate the effect of ketamine, should be performed. Informed risk consent should be obtained after educating the patients about the benefits and risks. A thorough evaluation of systemic comorbidities, accurate dose calculation and safe drug delivery, adequate observation post-infusion, and assessment of fitness for discharge should be done. It should be ensured that the patients have returned to a normal state of function, enabling them to return to their usual living environment. The long-term use of ketamine is associated with a potential for addiction, and periodic reevaluation of the severity of TRD and urine toxicology screening, if necessary, should be done. The dose and frequency of ketamine should be limited to the minimum necessary to obtain an appropriate clinical response. Further, multicenter studies are recommended to establish the safety profile of ketamine.


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Towards a Comprehensive Classificatory System for Problematic Internet Use: A Path Forward

To the Editor,

The Internet has become an integral part of everyday life. Globally, the number of people using the Internet has grown from 37 million in the pre-COVID era in 2019 to over 51 million as of April 2023.¹ A plausible explanation for the rise can be attributed to its role in coping with the high levels of psychological distress caused by the pandemic.² Problematic Internet Use is not limited to “Internet gaming disorder” (IGD), in fact, several other Internet-based activities, that is, social networking, pornography use, shopping, and gambling, have been identified as potentially “addictive” and eventually high-risk.

The Diagnostic and Statistical Manual, 5th ed. (DSM-5) gave initial attention to IGD with the inclusion of a preliminary description, clinical symptoms, and a potential threshold for diagnosis, that is, at least five of the nine symptoms from preoccupation, tolerance, withdrawal, loss of control, loss of interest in other activities, psychosocial problems, deception, escape and work or social neglect.³ Later, the International Classification of Diseases, 11th ed. (ICD-11) included a formal Gaming Disorder (GD) diagnosis with three core symptoms: loss of control of gaming habits, heightened priority to gaming, and continued or increased gaming despite negative consequences.⁴ There is a minor variation between the two models, with DSM-5 being more specific regarding the nine IGD criteria while ICD-11 adopting a more general description of the condition, omitting some specific criteria like preoccu-

tion, deception, escape, and tolerance.⁵ However, the manuals mutually agree on the experience of significant impairment or distress for a clinical diagnosis of the disorder, irrespective of the medium of gaming, for about a year.^{3–5}

Here, it is worth mentioning that the initial proposal for including internet-related disorders in the DSM-5 consisted of various subtypes, including instant messaging, social networking, pornography use, shopping, and so on. However, the manual did not incorporate subtypes except gaming due to limited research support for other high-risk behaviors.⁶

Problematic Internet use has been studied using various self-report tools, most based on the diagnostic standards for pathological gambling, substance abuse, or, more recently, IGD.^{7–9} Post-2013, several researchers have highlighted the usefulness of DSM-5 in assessing various high-risk Internet use behaviors for both clinical and