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The Ketamine Side Effect Tool (KSET): A comprehensive measurement-based safety tool for ketamine treatment in psychiatry

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ABSTRACT

Objectives: On a background of the rapidly expanding clinical use of ketamine and esketamine for treatment of depression and other conditions, we examined safety monitoring, seeking to identify knowledge gaps relevant to clinical practice.

Methods: An international group of psychiatrists discussed the issue of safety of ketamine and esketamine and came to a consensus on key safety gaps.

Results: There is no standard safety monitoring for off-label generic ketamine. For intranasal esketamine, each jurisdiction providing regulatory approval may specify monitoring. Treatment is often provided beyond the period for which safety has been demonstrated, with no agreed framework for monitoring of longer term side effects for either generic ketamine or intranasal esketamine.

Limitations: The KSET has established face and content validity, however it has not been validated against other measures of safety.

Conclusions: We recommend the Ketamine Side Effect Tool (KSET) as a comprehensive safety monitoring tool for acute and longer term side effects.

1. Ketamine use in depression

Ketamine, a long-used dissociative anaesthetic and analgesic, has over the past two decades emerged as a 'novel' antidepressant with a

unique efficacy, safety and mechanistic profile compared to conventional antidepressant medications – acting as a high-affinity *N*-methyl-D-aspartate (NMDA) receptor antagonist that modulates glutamatergic transmission. The rapidly expanding use of ketamine for treatment-

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resistant depression (TRD) and potentially other psychiatric disorders is occurring in the context of a lack of a standardized safety monitoring system, with structured assessment of longer term and cumulative effects of repeated treatments given over months-years. Implementation of appropriate systems for safety monitoring is urgently needed and the Ketamine Side Effect Tool (KSET) provides such a system, comprising modules for Screening, Baseline, Acute Treatment and Follow-up assessments, using a measurement-based system to monitor the safety of both acute and longer-term treatment (Short et al., 2020). An international group of psychiatrists involved in ketamine research and clinical implementation discussed the issue of safety and concurred on the importance of standardizing safety and side effect monitoring with ketamine, resulting in a collaboration to author this commentary.

Generic or ‘racemic’ ketamine, (*R,S*)-ketamine, consists of two stereoisomers, (*R*)-ketamine (arketamine) and (*S*)-ketamine (esketamine), with the latter newly available as an intranasal formulation. Robust data have been published on the high efficacy of racemic ketamine and esketamine in individuals with TRD (Bahji et al., 2020; Popova et al., 2019). Additionally, racemic ketamine rapidly decreases suicidal ideation, with robust effects as early as 24 h after treatment (Xu et al., 2016), with intranasal esketamine similarly showing rapid improvement in those with depression at imminent risk of suicide (Canuso et al., 2018). Fewer human studies have been conducted using arketamine, though animal studies suggest it may have a greater antidepressant effect and fewer psychotomimetic effects compared to ketamine and esketamine (Leal et al., 2021).

Based on the body of evidence, ketamine and esketamine therapy are currently being increasingly used in clinical practice worldwide. Generic racemic ketamine, which is off-patent, is licensed for use in anesthesia and sedation in many countries e.g. USA, UK, Australia, Canada, India, Brazil, Spain, and is thus used “off-label” in the treatment of depression. Esketamine (e.g. per oral) is prescribed off-label in many European countries (Veraart et al., 2021). In contrast to the above, intranasal esketamine has been licensed for TRD in over 40 jurisdictions worldwide with approval by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). Additionally, the FDA and EMA have also approved intranasal esketamine for use in patients with MDD and depressive symptoms with suicidal ideation or behavior.

2. Current limitations in the safety monitoring of ketamine in depression

The acute safety of ketamine treatment (i.e. in the hours immediately after each treatment) has been demonstrated during the investigational period of research trials, including after a single racemic ketamine treatment in early trials (McGirr et al., 2015), an acute course of up to four weeks of repeated treatments with racemic ketamine (Phillips et al., 2019; Kryst et al., 2020) or intranasal esketamine (Popova et al., 2019; Daly et al., 2019) and also maintenance treatment up to 48 weeks with intranasal esketamine (Wajs et al., 2020). Post-marketing intranasal esketamine data has led to some discussion of whether further clarification of safety is required in the domains of dissociation, sedation and suicidal ideation (Gastaldon et al., 2021; Doherty et al., 2021). Furthermore, to date, there is only limited data on cumulative and longer term effects of repeated treatment, assessed by active enquiry using structured assessments.

Currently, there are several concerns with the safety monitoring accompanying ketamine and esketamine treatment in clinical settings:

- i. For generic ketamine which is provided off-label, no standard for safety monitoring exists, leaving it to the judgement of individual clinicians to adequately monitor for acute and longer-term effects. For intranasal esketamine, each jurisdiction providing regulatory approval may specify safety monitoring. The Risk Evaluation and Mitigations Strategy (REMS) is mandated in the US and provides evaluation of acute effects of dissociation, sedation and blood

pressure at each treatment session, but not longer term or cumulative adverse effects.

- ii. Treatment is often provided beyond the period for which safety has been demonstrated. This particularly applies to treatment beyond four weeks for generic ketamine preparations (e.g. Sakurai et al. (2020) described up to 11 months of maintenance IV therapy), and treatment beyond 48 weeks for intranasal esketamine, though longer term data on safety are forthcoming for the latter (ClinicalTrials.gov NCT02782104).

There is no agreed framework for monitoring of longer term side effects (e.g. years) for either generic ketamine or intranasal esketamine.

Additional complexities include the different methods by which ketamine is administered in terms of drug formulation (racemic, (*S*)- or (*R*)-ketamine; compounds used in drug preparation), treatment route (intravenous, intramuscular, subcutaneous, intranasal, per oral, sublingual, etc.), dosing approach (single doses repeated every few days; sustained infusions lasting hours to days; fixed dose versus dosing titrated to response), use in combination with other medications, and use in patients with comorbid somatic and psychiatric conditions. The relative safety of these treatment approaches has not been systematically or adequately studied.

A systematic review of side effects of ketamine used in depression identified reporting of acute side effects (i.e., psychiatric, psychotomimetic, cardiovascular, neurological), but very limited information on the safety of long-term ketamine therapy (Short et al., 2018). Yet it is known that chronic unsupervised repeated use may lead to serious medical complications. This risk is to-date reported in chronic recreational high-dose users in whom urological toxicity, hepatotoxicity, cognitive deficits and dependency were noted (Short et al., 2018). Cases of treatment-emergent side effects (e.g., withdrawal or hypomania) in patients with high doses and frequency of administration have been reported (Hu et al., 2021).

3. The KSET as a tool to monitor ketamine safety

Given the above concerns regarding safety monitoring for racemic ketamine and esketamine it behoves the clinician to apply appropriate safety standards. While it is acknowledged that structured safety monitoring adds clinical burden to the patient and practitioner, this must be balanced against potential harm to patients if such monitoring is not undertaken.

Seeking to bridge these knowledge and safety gaps, the Ketamine Side Effect Tool (KSET) was developed for use with all formulations of ketamine and its enantiomers. It arose from our experience in ketamine clinical trials (Loo et al., 2016), and a systematic review of safety which identified several limitations in the field (Short et al., 2018). Firstly, most studies utilized passive reporting versus active surveillance of side effects. Passive reporting tends to underestimate, and active surveillance usually overestimates such side effects; however given the relative nascence of the field it would be prudent to overestimate potential side effects until further safety data accumulate. A further identified limitation was the use of differing standardized scales (e.g., Brief Psychiatric Rating Scale, BPRS; Clinician-Administered Dissociative States Scale, CADSS) which were not designed specifically for ketamine and may be underestimating key side effects. Based on the above, relevant physical, psychiatric, psychotomimetic and cognitive side effect domains were included in the KSET, which were further refined via a Delphi consensus of experts to establish face and content validity.

The four KSET modules include:

- i. Screening – assesses medical issues to be considered before prescribing ketamine, highlighting contraindications or any need for caution;
- ii. Baseline – examines symptoms prior to commencing treatment to allow for comparison at follow-up;

- iii. Acute Treatment – completed immediately after dosing, this allows for assessment of acute side effects and includes a record of vital signs. A second section (completed prior to treatment) captures any delayed or cumulative side effects experienced since the last dose, and a third section (completed following treatment) contains a discharge check-list;
- iv. Follow-up – allows assessment of medium- and long-term side effects (Short et al., 2020).

The KSET is accompanied by detailed instructions for its use which provide guidance on the purpose and use of each of the forms as well as when associated investigations should be performed (Short et al., 2020). Overall, the KSET uses a severity rating scale to capture acute side effects during a single treatment (e.g., hypertension, dissociation, sedation), potential cumulative side effects across a course of treatment (e.g. urinary symptoms) and longer-term effects (e.g. dependence) assessed at follow-up intervals. The checklist provides a structured clinical approach to assess fitness for discharge after each acute treatment. The modules are designed for completion by a clinician though some items can be pre-filled by self-report to reduce clinician burden.

With the rapid emergence of ketamine and its enantiomers in clinical settings, there is an ethical responsibility to ensure appropriate consideration is given to safety and potential long-term side effects. The ‘opioid crisis’ provides a cautionary lesson where initial lack of consideration was given to longer-term adverse effects such as addiction potential. Failure to responsibly implement adequate safety monitoring with the clinical use of ketamine may result in harm to patients and negatively impact the adoption of this most promising treatment.

It is an imperative that the clinical implementation of ketamine therapy is accompanied by a robust and detailed framework for evaluating acute and longer-term safety. The KSET is a comprehensive measurement-based instrument which meets such a need and has been designed specifically for this purpose. Input from international experts has established face and content validity. It is currently freely available for wide dissemination. Clinical and research centers are encouraged to use the KSET as a part of their ketamine clinical services or research studies. They are also invited to participate in a collaborative effort to collate and evaluate data to further clarify safety outcomes. Future use of the KSET has potential to facilitate a global data registry on ketamine side effects occurring across the various treatment parameters and across time.

Author statement

AB was lead author with other authors each contributing equally.

Conflict of interest

All of the authors (except for SP, LP, PCP, PG, Andre Brunoni) were involved in the development of the KSET. Adam Bayes, BS, VG, PR-P, JF and CL declare no conflicts of interest. CAZ is listed as a co-inventor on a patent for the use of ketamine in major depression and suicidal ideation. CAZ is listed as co-inventor on a patent for the use of (2R,6R)-hydroxynorketamine, (S)-dehydronorketamine, and other stereo-isomeric dehydro and hydroxylated metabolites of (R,S)-ketamine metabolites in the treatment of depression and neuropathic pain; and as co-inventor on a patent application for the use of (2R,6R)-hydroxynorketamine and (2S,6S)-hydroxynorketamine in the treatment of depression, anxiety, anhedonia, suicidal ideation, and posttraumatic stress disorders. He has assigned his patent rights to the US government but will share a percentage of any royalties that may be received by the government. Declan McLoughlin has received speaker’s honoraria from MECTA, Otsuka and Janssen and an honorarium from Janssen for participating in an esketamine advisory board meeting. RS received research funding for 2 randomized clinical trials with generic oral esketamine from the

Netherlands Organisation for Health Research & Development and the National Health Care Institute, a speakers fee from Janssen Pharmaceuticals, and consultancy fee from Clexio biosciences, both outside the submitted work. JV received a speakers fee from Janssen Pharmaceuticals, outside the submitted work. PG has within the last three years had a research contract with Douglas Pharmaceuticals for developing a ketamine tablet, and is named on a patent; he has attended a Janssen Pharmaceuticals advisory board. RM’s department has received funds from Janssen for Scientific Advisory Board meetings. Donel Martin undertook consultancy work for Douglas Pharmaceuticals for a ketamine study. TPC has received honorarium from J&J to be a local advisory board for ESK. Andre Brunoni receives grants from São Paulo Research State Foundation FAPESP (2019/06009-6) and Academy of Medical Sciences (NAFR 12/1010). He also receives in-kind support from Soterix Medical, Flow Neuroscience, and Magventure.

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