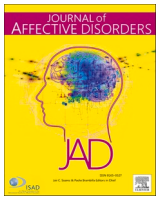
Journal of Affective Disorders 411 (2026) 121970

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad



Research paper

Interdisciplinary, Delphi-driven consensus guidelines on the use of intravenous ketamine infusions for depressive disorders from the American Society of Ketamine Physicians, Psychotherapists, and Practitioners (ASKP3)

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ARTICLE INFO

Keywords:
IV ketamine
Racemic ketamine
Depression
Psychiatry
Delphi
Guidelines

ABSTRACT

Background: Off-label use of intravenous ketamine (IVK) for depression is a widespread practice with limited regulation in the United States. There is an urgent need for current, evidence-informed treatment guidelines to facilitate patient safety, clinical decision-making, and care quality in real-world contexts.
Methods: The American Society of Ketamine Physicians, Psychotherapists and Practitioners (ASKP3) convened an interdisciplinary working committee tasked with creating guidelines for use of IVK for depression in outpatient settings. Guideline development followed a two-stage process: 1) a hybrid systematic and targeted evidence review and preliminary drafting by the committee, and 2) consensus refinement through a modified Delphi method using a panel composed of the committee and ASKP3 expert faculty. Panelists rated their agreement with proposed guideline items using a 9-point Likert scale, and consensus was predefined as a median rating ≥ 7 with

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https://doi.org/10.1016/j.jad.2026.121970
Received 11 March 2026; Received in revised form 11 May 2026; Accepted 14 May 2026
Available online 16 May 2026

an interquartile range ≤ 2 after Round 2. Consensus strength was evaluated using percentage agreement thresholds.
Results: Of 39 invited experts, 28 completed at least one round of the survey. Consensus was achieved on 73 of 75 of proposed guideline items (97%), with most items reaching very strong consensus (i.e., ≥90% of panelists rating a statement within the 7–9 range). Guideline items were organized across seven key practice areas.
Conclusions: By combining a hybrid literature review and Delphi process, we developed expert consensus recommendations for the safe and effective use of IVK for depression. These guidelines can support decision-making, standardize clinical practice, improve patient outcomes, and promote equitable access to this emerging treatment, while informing ongoing research and policy development.

1. Background

Depression is among the top contributors of global disease burden, but its pharmacological treatment has long been challenged by the limited efficacy, poor tolerability, and delayed onset of conventional antidepressant therapies for some patients (Baig-Ward et al., 2023). Ketamine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, was approved for medical use by the United States Food and Drug Administration (FDA) in 1970 as an anesthetic and became available as a generic medication in the 1990s. In 2000, the first randomized controlled trial using a subanesthetic dose of intravenous (IV) ketamine for depression indicated positive outcomes (Berman et al., 2000). Since then, numerous studies have demonstrated a favorable short-term safety and efficacy profile for ketamine as a rapid-acting antidepressant (McIntyre et al., 2021; Namiot et al., 2024). Despite some limitations of this literature – including a modest number of randomized controlled trials, predominantly short-term follow-up, and heterogeneous study designs – ketamine has been adopted into routine clinical practice as an "off-label" treatment for depression (Mathai and Mathew, 2024).

In 2019, the FDA approved intranasal esketamine (the (*S*)-enantiomer of racemic ketamine) for use as an adjunctive therapy in adults with treatment-resistant depression (TRD). Importantly, this decision marked a shift from the monoaminergic approach that had until then dominated psychiatric drug development and signified the first NMDA receptor antagonist to receive FDA approval for a depressive indication, following decades of preclinical and clinical research on this drug class (Wilkinson et al., 2024). FDA approval of esketamine expanded to include adults with major depression and suicidal ideation and behavior in 2020 and, as of January 2025, includes its use as a monotherapy in adults with TRD. Major criticisms of esketamine have centered on the uncertainty surrounding the short-term efficacy data that was submitted to the FDA and the limited durability of treatment effects (Fountoulakis et al., 2025). Other questions, such as the safety and effectiveness of repeated administration, have been partially addressed by emerging post-marketing real-world evidence (Sanacora et al., 2025). Reflecting its growing role in psychiatric treatment, esketamine generated over $1 billion in revenue in 2024 (Bayer, 2025).

Racemic ketamine is widely available as an inexpensive, generic medication in the US, but its lack of patent protection and challenges with current approval pathways have limited progress toward expanded regulatory approval of ketamine for psychiatric indications (Mathai et al., 2022a; Sahragardjoonegani et al., 2021). As a result, ketamine remains an off-label treatment for depression, which may influence factors such as insurance coverage, institutional adoption, clinical standardization, and public perception. This remains the case despite an accumulating body of research suggesting that ketamine demonstrates comparable or superior benefit, safety, and tolerability relative to esketamine (Bahji et al., 2021; Correia-Melo et al., 2020; Elmosalamy et al., 2025; Feng et al., 2025; Meisner et al., 2025; Nikolin et al., 2023; Saelens et al., 2025; Singh et al., 2023; Terao et al., 2024). Arketamine, the (*R*)-enantiomer of racemic ketamine, may contribute to these advantages, as preclinical studies suggest that it prolongs antidepressant effects and clinical data indicate that it produces fewer dissociative and psychotomimetic effects compared with esketamine (Kawczak et al., 2024; Leal et al., 2025). It should be noted, however, that long-term efficacy and safety data are considerably more extensive for intranasal esketamine than for IV racemic ketamine (Sanacora et al., 2025), and the uncertainty surrounding long-term outcomes with IV ketamine remains a meaningful limitation of the current evidence base.

Key differences in administration and regulatory oversight for ketamine and esketamine should also be highlighted. Due to potential risks for sedation, dissociation, and misuse, esketamine is highly regulated through a Risk Evaluation and Mitigation Strategy (REMS) drug safety program that was mandated by the FDA as a condition for drug approval (Janssen Pharmaceuticals, 2020). The REMS program restricts use of esketamine to its approved dosages, indications, and administration settings. This ensures that clinical practice replicates the conditions studied in research trials submitted to the FDA. Esketamine must be dispensed and administered in certified healthcare settings under professional supervision and with monitoring of patients for at least two hours after dosing (Janssen Pharmaceuticals, 2020). Healthcare professionals must also complete REMS training and become certified to correctly administer the drug, monitor patients, and report adverse events. No analogous program currently exists for racemic ketamine. As such, there is greater flexibility in how ketamine can be used by clinicians but also increased risk for misuse and harm. To the authors' knowledge, this represents the only instance of such marked regulatory differences between single enantiomers of the same molecule.

Currently, esketamine may be favored over racemic ketamine given its FDA approval, standardized protocols, and lower out-of-pocket costs through insurance coverage and manufacturer assistance programs (Elmosalamy et al., 2025). It may also better align with patient preferences and clinic workflow in some contexts, as it avoids IV cannulation and provides a less invasive administration route (Elmosalamy et al., 2025; Mathai et al., 2021). However, other factors discussed previously—such as drug cost, effectiveness, safety, and flexibility—underscore the value of racemic ketamine as a therapeutic option distinct from esketamine, particularly if care were standardized. In practice, off-label use of ketamine is already widespread, highlighting the urgent need for guidelines to ensure safe and effective clinical practice (Pacilio et al., 2025; Wilkinson et al., 2024).

Several key efforts have been made to steer best practices involving the use of ketamine for depressive disorders. Given that most published research to date has focused on IV ketamine (IVK), prior consensus efforts have primarily addressed this route of administration. A consensus statement on the use of IVK to treat mood disorders was published by the American Psychiatric Association in 2017 (Sanacora et al., 2017). This resource was not intended to serve as a definitive guideline, as the authors cited insufficient knowledge about the effectiveness and safety of treatment in real-world settings to support such an effort then. Another international expert opinion published in 2021 synthesized ongoing evidence for ketamine and esketamine in TRD (McIntyre et al., 2021). However, this effort was classified primarily as a literature review, lacked an interdisciplinary process, and reported conflicts of interest in over half of the authors with the drug sponsor of esketamine. Notable guidelines have been written by academic groups in Canada (Swainson et al., 2021), New Zealand, Australia (Bayes et al., 2021; Beaglehole et al., 2023; Hussain et al., 2025), the United Kingdom (Jelen et al.,

2024; Singh et al., 2017), France (Lengvenyte et al., 2022), Norway (Berthold-Losleben et al., 2025), and even within the US Department of Veteran Affairs (VHA Office of Integrated Veteran Care, 2025). Various practitioners in the US have also proposed recommendations for safe and ethical use of ketamine for psychiatric indications (Harding, 2023; Mathai et al., 2022a; Ryan and Bennett, 2020; Wolfson et al., 2026; Wolfson and Braunstein, 2025), though none of these are reflective of large-scale, real-world expert consensus.

There have been several developments that now make a consensus treatment guideline for IVK in the broader US health care system not only possible but essential. Substantial research has emerged in recent years, including real-world evidence from thousands of patients supporting the use of IVK for mood and anxiety disorders (Alnefeesi et al., 2022; Fancy et al., 2023; Gutierrez et al., 2024; Hietamies et al., 2023; McInnes et al., 2022; Oliver et al., 2022). FDA approval of esketamine has expanded to additional indications, with mounting data confirming the safety and clinical utility of these new approaches (Oraee et al., 2024). Reasons for concern have also become more apparent. Home use of oral ketamine has been increasing in popularity and injectable subcutaneous ketamine is now being offered by mail without clear standards to guide these practices (Wilkinson et al., 2024). Ketamine misuse is on the rise, compounding pharmacies making ketamine are being scrutinized, and reports of ketamine-related deaths have added to heightened vigilance and demands for oversight (Wilkinson et al., 2024). Across care settings, the medical and psychiatric competencies required for treatment remain poorly defined.

The American Society of Ketamine Physicians, Psychotherapists and Practitioners (ASKP3) was founded in 2016 and currently includes more than 400 multidisciplinary professionals. ASKP3 has been at the forefront of identifying and disseminating best practices for ketamine treatment through forums such as annual conferences, sponsored training sessions, public workshops with the FDA, meetings with state regulatory agencies, and patient-centered educational resources. The guidelines presented here extend previous efforts by ASKP3 (Sullivan et al., 2020) and reflect the latest developments in knowledge related to the use of IVK for depressive disorders. We have centered our work on treatment of depression with IV ketamine, as this indication and route have the most robust evidence base for efficacy, safety, and clinical procedures. Although emerging research suggests potential benefits of ketamine for other conditions (Kwan et al., 2024; McInnes et al., 2025; Whittaker et al., 2021) and alternative routes of administration (Duong et al., 2026; Mathai et al., 2024, 2021; McIntyre et al., 2020a; Saelens et al., 2025; Silberbauer et al., 2026), the predominantly observational nature of these data and lack of high-quality evidence preclude guideline development in these areas at this time.

There is substantially more evidence to support clinical guidelines for IVK for depression; however, important gaps remain, particularly with respect to real-world implementation and practice. This Delphi consensus project aimed to bridge these gaps by developing evidence-informed, expert-driven recommendations that integrate existing literature with collective clinical expertise. These recommendations are intended for individual practitioners, healthcare organizations, regulatory bodies, and third-party payers seeking to implement or oversee safe and effective IVK treatment for depression.

2. Methods

2.1. Working committee formation, delphi planning, and panel selection

In 2024, ASKP3 convened a working committee of 5 board members and 14 faculty, drawn from the organization's larger expert faculty group, to develop guidelines for the use of IVK in depressive disorders. The Delphi method was selected to reduce bias related to a typical working group process, allow for systematic refinement of guideline items, and promote quantifiable consensus. A modified process was used to incorporate both literature appraisal and expert opinion, in which a preliminary list of guideline items – generated by the working committee and informed by a literature review – was provided to an expert panel for iterative revision.

The Delphi panel was composed of members of the working committee and the remaining ASKP3 expert faculty. The expert faculty group included 36 interdisciplinary healthcare professionals who had been previously chosen by ASKP3 to help with organizational tasks. Faculty selection occurred through a process that considered clinical expertise with ketamine-based treatments, academic and research contributions to the field, professional diversity across disciplines (including psychiatry, emergency medicine, anesthesiology, nursing, and psychology), geographic representation across the US and internationally, and willingness to participate in ongoing ASKP3 educational activities. Working committee membership was further refined based on relevant domain expertise and availability for the project timeline.

One faculty member on the working committee (DSM) oversaw survey methodology and was excluded from Delphi participation. The 35 remaining expert faculty were invited to participate, along with 4 of 5 board members serving on the working committee. One non-clinician board member (KAB) served in an administrative role and was therefore excluded as a panelist.

2.2. Identification of key questions, hybrid literature review, and guideline drafting

The working committee identified seven essential question domains related to the use of IVK for depression to form the basis of the guidelines These domains were selected to address areas in which the current literature is limited, inconsistent, or ambiguous and requires further interpretation to guide clinical practice. Specifically, these included: 1) the published evidence for IVK in depressive disorders; 2) clinician qualifications and treatment settings; 3) key components of the psychiatric evaluation prior to treatment; 4) key components of the medical evaluation prior to treatment; 5) best practices for safe initiation and maintenance; 6) elements of written informed consent; and 7) essential documentation. By focusing on these areas, the Delphi method could generate expert consensus to fill critical gaps and support safe, effective, and standardized clinical practice.

Subgroups of committee members were assigned to draft preliminary answers to each question domain, informed by existing literature. One committee member (DSM) supported the literature review methodology and evidence synthesis. A hybrid literature review was conducted using both a systematic and targeted approach. This decision was made to ensure comprehensive review for one guideline domain that focused primarily on evidence appraisal, while allowing flexibility for other domains where experimental data were lacking. The systematic search was primarily designed to support Delphi consensus development rather than to serve as an independent systematic review.

To review the evidence for IVK for depressive disorders (Guideline Question 1), we conducted a systematic search of PubMed/MEDLINE, Embase, and the Cochrane Database of Systematic Reviews) for studies published between January 2020 to July 2025, in accordance with PRISMA 2020 guidelines. This search was guided by ***PICOS*** criteria: ***P****opulation* = adults with unipolar or bipolar depression; ***I****ntervention* = IV ketamine treatment; ***C****omparator* = with or without a comparator; ***O****utcome* = standard clinical outcomes related to depression and suicidality (e.g., severity, response, and remission); ***S****tudy design* = meta-analysis. The review was not prospectively registered (e.g., PROSPERO). The search was restricted to meta-analyses to prioritize high-level evidence; primary studies and other designs were incorporated through a complementary targeted review (see below). The date range was selected to capture recent evidence syntheses in a rapidly evolving literature and to extend, rather than duplicate, prior review and consensus efforts. Search terms and exclusion criteria are provided in the Supplementary Materials. Title, abstract screening, and study selection were performed by two reviewers (DSM and LAM), with discrepancies

resolved through discussion. Two reviewers (DSM and AMA) independently conducted data extraction using a standardized template that included potential sources of conflict; these reviewers also independently conducted quality and bias assessments for the included studies using the JBI critical appraisal tool (Hilton, 2024). Discrepancies were resolved through consensus.

In parallel, a targeted literature review was conducted using the same databases to inform all guideline domains. Guideline questions 2–7 were informed exclusively by this targeted review rather than a formal systematic review of the literature. No date restrictions were applied. Data from meta-analyses, systematic reviews, and randomized controlled trials (RCTs) were prioritized as the highest quality of evidence for recommendations, though large retrospective studies, small open-label trials, case series, and other existing guidelines were also considered. Findings from both reviews were synthesized narratively and used to form a preliminary draft of guideline items. The strength of research evidence for each item was indicated by the Oxford Centre for Evidence-Based Medicine (OCEBM) level (Durieux et al., 2013).

2.3. Delphi procedure and consensus determination

A preliminary narrative literature synthesis and draft guideline document – organized by the seven guideline domains and summarizing the evidence relevant to each – was prepared by the working committee and distributed to all expert panelists prior to Round 1. For purposes of this project, expertise was operationalized as recognized clinical experience with ketamine-based treatments, contributions to the academic or clinical literature, and active engagement with ASKP3's educational mission. Consensus-building and identification of areas of disagreement were achieved through a survey procedure in which panelists remained anonymous to one another.

A team of academic collaborators (DSM, MC, JOR, and ALM) from Baylor College of Medicine (BCM) with expertise in Delphi methods provided technical and analytic support for all Delphi-related procedures. Surveys were administered using BCM REDCap, a secure, web-based platform hosted at BCM. Invitations with study information and survey links to participate were first emailed to the 17 eligible members of the working committee for pilot testing. The survey instrument was revised based on feedback and then distributed to the final panel of 39 experts (i.e., 35 expert faculty and 4 board members), with the goal of achieving an end panel size of approximately 15–20 participants completing two rounds of rating. All experts were invited to complete both rounds of the Delphi and received one email invitation and up to two reminders for each round. They were encouraged to participate in both rounds for a better consensus-building process and were also offered voluntary acknowledgement in any resulting publication for their contributions.

In Round 1, panelists were asked to consider both the summarized evidence and their clinical experience, then rate their level of agreement with proposed guideline items using a 9-point Likert scale (1 = strongly disagree; 5 = uncertain; 9 = strongly agree). They were encouraged to provide free-text comments to clarify their positions, express concerns, or note any missing considerations. Responses were analyzed for measures of central tendency (i.e., median, interquartile range), percentage agreement (i.e., % of panelists rating a statement within the 7–9 range), and open-ended feedback that was aggregated across all experts. Comments were reviewed to identify opportunities for item clarification. Minor revisions to the guideline items at this stage were driven primarily by consistent feedback patterns; however, the study team also adopted high-value individual recommendations when they were deemed likely to enhance interpretability and support consensus while preserving item constructs.

In Round 2, panelists evaluated the revised list of items using the same rating protocol and were provided with their prior responses, quantitative summaries of group ratings, and aggregate feedback from Round 1 to inform subsequent ratings. Consensus was defined a priori as a median rating ≥ 7 with an interquartile range ≤ 2 on the Likert scale after Round 2. As a sensitivity check, items with $\geq$75% agreement were also noted. To aid in the interpretation of panelist agreement, consensus strength was defined using percentage agreement thresholds: moderate ($\geq$75%), strong ($\geq$80%), and very strong ($\geq$90%). Statistical summaries and response rates for both rounds were reported. Statements that failed to reach consensus after two rounds were discarded and reported as areas lacking agreement. Following survey completion, minor editorial revisions were made by the working committee only when necessary to ensure accuracy and clarity, while preserving the meaning of consensus statements.

Several measures were implemented to mitigate the risk of conformity effects, anchoring bias, and undue influence. These included: anonymous individual voting using a secure REDCap platform (panelists were not aware of one another's specific responses); provision of aggregate quantitative feedback and de-identified qualitative comments from panelists between rounds; independent methodological oversight by academic collaborators with Delphi expertise; and pre-specified consensus thresholds.

2.4. Ethical considerations

Participants were provided with a study information sheet describing the purpose, procedures, risks and voluntary nature of participation, with completion of the survey indicating implied consent. Demographic information was not collected within the survey to preserve confidentiality. Because the expert panel was small and its members were familiar with one another, collecting or reporting identifying characteristics for respondents could have increased the risks of identification, response bias, and potential professional consequences related to non-participation. To maintain transparency regarding panel composition, professional characteristics and specialty information for all invited experts were summarized using publicly available sources rather than respondent-level survey data. These procedures were reviewed and approved by the BCM Institutional Review Board.

3. Results

3.1. Literature review and guideline drafting

The PRISMA flow diagram for the systematic review of the evidence base for IVK for depression is provided in Fig. 1; a total of 24 meta-analyses were included in this review. The narrative synthesis of findings from both the systematic literature review and the complementary targeted review is presented in the Appendix. These findings were used to draft 75 guideline items that were evaluated by the Delphi expert panel. Characteristics of the meta-analyses included in the systematic review, the results of the Joanna Briggs Institute (JBI) critical appraisal assessments of these studies (Hilton, 2024), and the original guideline items derived from the literature review and committee drafting process can be found in the Supplementary Materials.

3.2. Delphi recruitment, study flow, and panel characteristics

For pilot testing, 6 of 17 invited experts (35%) consented to participate and completed the initial survey. In Round 1, 21 of 39 invited experts (54%) consented to participate and completed the survey. Nineteen of these went on to complete Round 2 along with 7 panelists who completed Round 2 only, leading to 26 of 39 experts (67%) participating in Round 2 and 28 of 39 experts (72%) participating in either Round 1, Round 2, or both. Surveys were administered from October to December 2025. A study flow diagram including professional characteristics and primary specialty area for all 39 invited experts is shown in Fig. 2.

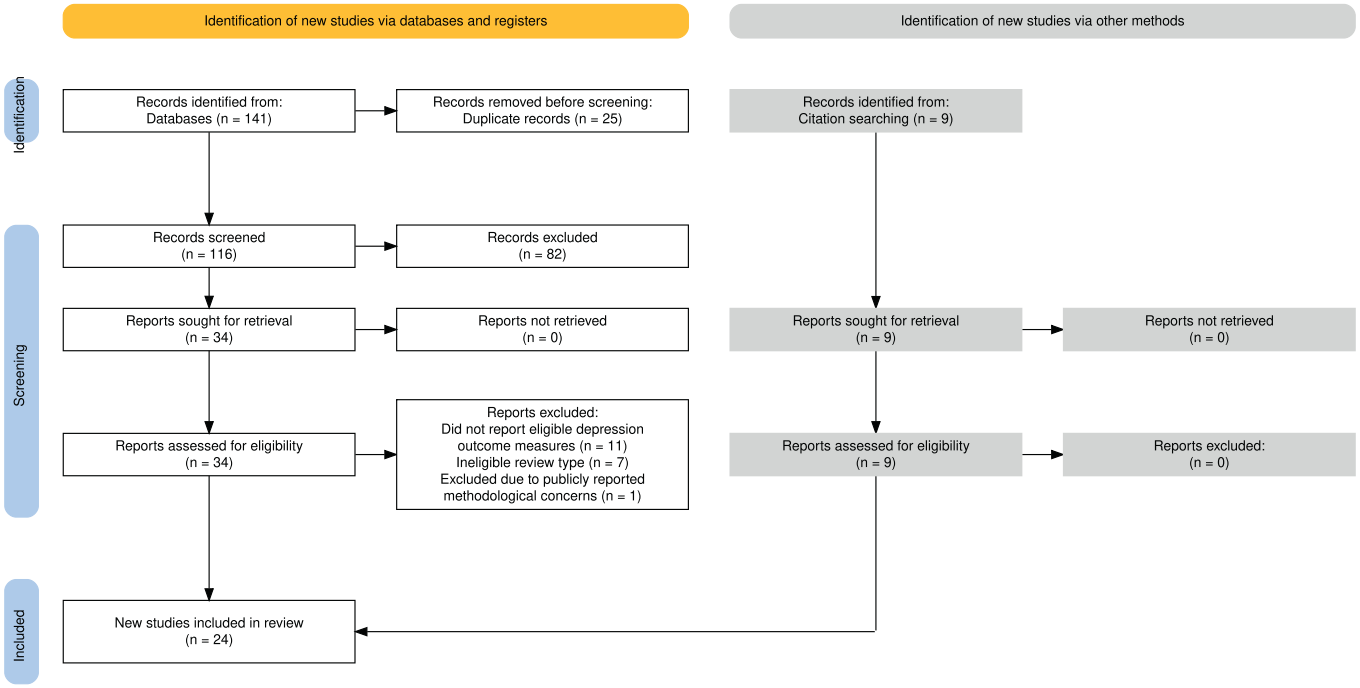

Fig. 1. PRISMA flow diagram for systematic review of meta-analyses.

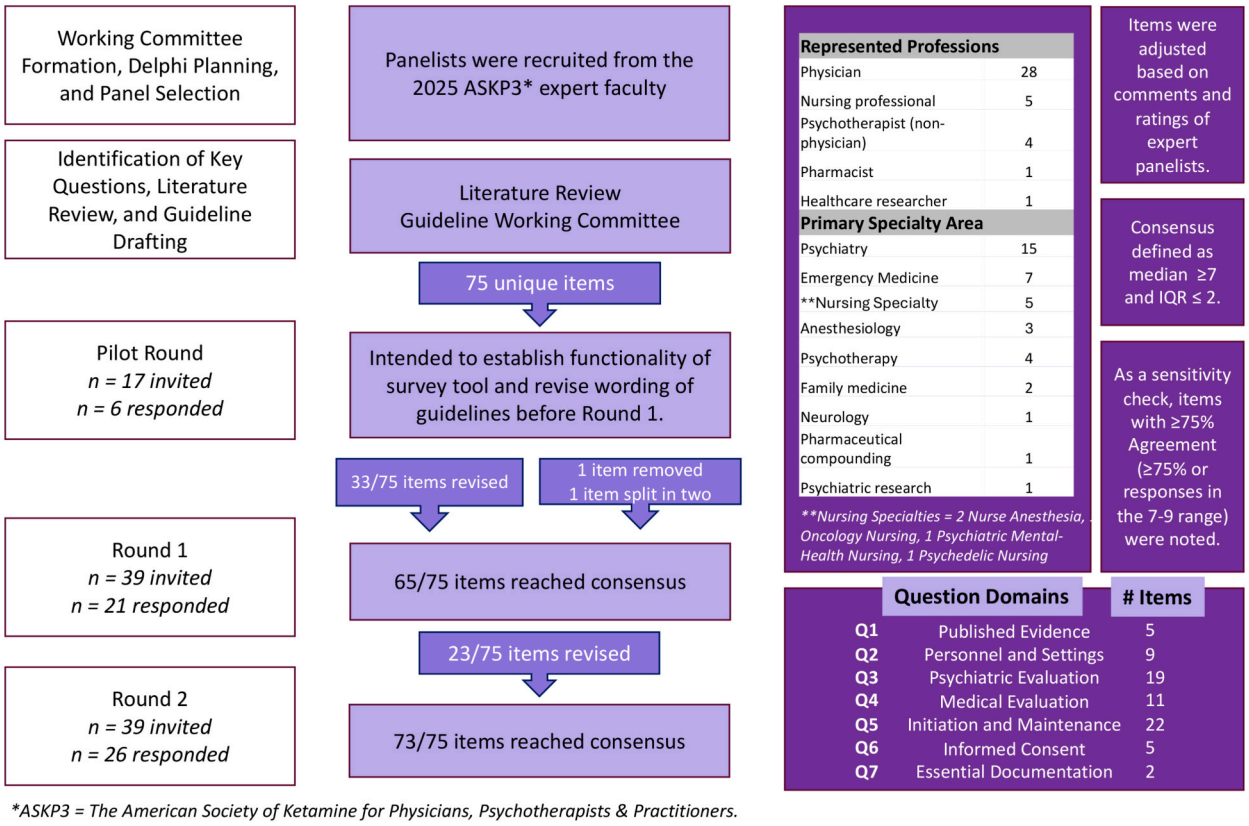

Fig. 2. Delphi study flow diagram and characteristics of the invited expert panel (n = 39).

3.3. Delphi rounds

Consensus was achieved on 73 of 75 proposed guideline items (97%) by survey completion. These items are shown in Table 1, along with the degree of consensus and evidence grade for each item. Of the 73 items that achieved consensus, 53 (73%) reached very strong consensus, 16 (22%) reached strong consensus, and 4 (5%) reached moderate consensus. Changes in panelist agreement over Rounds 1 and 2 of the survey are shown in Fig. 3. A detailed record of item evolution across rounds, including quantitative ratings and aggregated feedback, is

Table 1
Delphi consensus guidelines on the use of intravenous ketamine infusions for depressive disorders in outpatient settings.

Guideline Item		Expert Consensus[a]	Evidence Grade[b]
Section 1: *What is the published evidence for IV ketamine (IVK) for depressive disorders?*			
1.1	The acute antidepressant effect of IVK in patients with depressive disorders is well-established.	Very Strong	Level 1
1.2	Existing data support an acute/induction phase of treatment with ketamine that includes approximately 4–6 infusions over 2–4 weeks.	Very Strong	Level 1
1.3	There is insufficient published evidence to support additional clinical benefit from administering ketamine three or more times weekly compared with twice-weekly dosing during induction treatment.	Strong	Level 1
1.4	While some degree of titration above 0.5 mg/kg of ketamine may be warranted based on clinical response and patient-specific factors, there remains limited published evidence regarding the safety and efficacy of doses greater than 1.0 mg/kg.	Strong	Level 1
1.5	While there is evidence that subjective qualities of the ketamine experience may predict antidepressant efficacy for some patients, this research literature remains inconclusive. Caution is therefore recommended around ongoing dose escalation that is aimed primarily at reproducing a particular intensity of subjective experience for patients rather than achieving demonstrable clinical benefit.	Moderate	Level 1
Section 2: *Who can provide IVK for depression and in what settings?*			
2.1	Ketamine should be administered and overseen by licensed medical professionals with expertise in the assessment, diagnosis, and management of individuals with depressive disorders.	Very Strong	Level 5
2.2	We do not recommend restricting ketamine-based treatment for depression solely to medical professionals with formal anesthesia or critical care specialty training. However, to ensure adequate medical competence, treatment personnel should at minimum have training in IVK for depression, be able to conduct a medical assessment to determine or confirm treatment appropriateness, be able to identify and respond to medical risks associated with IVK (e.g., sedation, airway compromise, hemodynamic instability, and vomiting), and work collaboratively with the patient's broader medical care team.	Very Strong	Level 5
2.3	In situations where ketamine treatment professionals lack sufficient psychiatric or medical expertise, we recommend a team-based model of care ensuring that appropriately qualified professionals are integrated into the patient's evaluation and treatment process.	Very Strong	Level 5
2.4	IVK for depression should be administered in healthcare settings that are capable of cardiorespiratory surveillance and by medical professionals who are qualified to monitor heart rate, blood pressure, and oxygen saturation.	Very Strong	Level 5
2.5	BLS certification and training in conscious sedation should be considered the minimum competency standard for healthcare professionals administering IVK for depression. Clinicians should also be equipped to recognize and manage cases in which patients inadvertently transition to a deeper level of sedation than intended.	Moderate	Level 5
2.6	Treatment personnel should provide IVK for depression in a private, comfortable and adaptable medical setting with attention to how the patient environment may influence treatment.	Very Strong	Level 3
2.7	Treatment personnel should be familiar with the range of subjective experiences (e.g., emotional, cognitive, perceptual) that may arise during ketamine treatment, and recognize that some may be challenging for patients to tolerate.	Very Strong	Level 5
2.8	In settings where multiple patients are receiving treatment simultaneously, there should be sufficient qualified healthcare personnel on-site to ensure medical and psychiatric safety for all patients at all times during treatment.	Very Strong	Level 5
2.9	The treatment facility and personnel should have a standardized approach to escalating the level of care during an adverse event as necessary.	Very Strong	Level 5
Section 3: *What are the necessary elements of a psychiatric evaluation prior to IVK for depression?*			
3.1	The psychiatric evaluation for ketamine treatment should include a detailed psychiatric history, mental status exam, formulation and diagnosis, assessment of risk, and shared discussion regarding the treatment plan.	Very Strong	Level 5
3.2	When IVK is used for depression, the patient's psychiatric history and current symptoms should be sufficiently reviewed to support the diagnosis of a major depressive episode related to major depressive disorder or bipolar disorder, consistent with DSM-5 criteria.	Strong	Level 5
3.3	We recommend use of standardized scales to quantify depression severity.	Very Strong	Level 5
3.4	Patients should be assessed for the appropriateness of concurrent therapy with a mood-stabilizing medication and closely monitored for mood switching if ketamine is being used for the treatment of bipolar depression.	Very Strong	Level 1
3.5	Prior trials of medications and non-pharmacological interventions should be reviewed and evaluated as decisions are made about the appropriateness of ketamine treatment.	Very Strong	Level 5
3.6	Some degree of basic psychological assessment (e.g., exploring personality structure, coping styles, and psychological functioning) is encouraged as part of the psychiatric evaluation.	Strong	Level 5
3.7	Patients with comorbid personality disorders may benefit from ketamine on a case-by-case basis but may require additional mental health support and safety planning.	Very Strong	Level 2
3.8	Ketamine should not be used in adults with psychotic features who are at risk for worsening impairment, unless the anticipated benefits of treatment are deemed to outweigh the risks involved, and the treatment team is experienced in managing these conditions.	Very Strong	Level 5
3.9	Ketamine should not be used in adults with severe dissociative conditions who are at risk for worsening impairment (e.g., dissociative identity disorder), unless the anticipated benefits of treatment are deemed to outweigh the risks involved, and the treatment team is experienced in managing these conditions.	Strong	Level 5
3.10	Ketamine should not be used in adults with mixed manic or hypomanic symptoms who are at risk for worsening impairment, unless	Strong	Level 5

(*continued on next page*)

Table 1 (*continued*)

Guideline Item		Expert Consensus[a]	Evidence Grade[b]
	the anticipated benefits of treatment are deemed to outweigh the risks involved, and the treatment team is experienced in managing these conditions.		
3.11	Ketamine should not be used in adults with neurocognitive disorders who are at risk for worsening impairment (e.g., dementia types prone to delirium, psychosis, or behavioral dysregulation), unless the anticipated benefits of treatment are deemed to outweigh the risks involved, and the treatment team is experienced in managing these conditions.	Strong	Level 5
3.12	Ketamine should not be used in adults with active substance use disorders who are at risk for worsening impairment (e.g., individuals with poor adherence to care or not engaged in a comprehensive substance use treatment program), unless the anticipated benefits of treatment are deemed to outweigh the risks involved, and the treatment team is experienced in managing these conditions.	Strong	Level 5
3.13	High-risk, primary mental health conditions other than depression (e.g., psychosis, mania, severe substance use disorders) should be stabilized first, prior to considering treatment with ketamine over other approaches.	Very Strong	Level 5
3.14	If ketamine is initiated in high-risk psychiatric populations, we recommend psychoeducation about potential risks, thorough documentation of informed consent, a well-documented risk-benefit assessment, clearly defined and time-limited treatment protocols, close psychiatric and subspecialty monitoring for adverse reactions, established criteria for stopping treatment, and use of strategies for risk mitigation.	Very Strong	Level 5
3.15	Patients at immediate and high risk of suicide should be managed by clinicians experienced in handling this risk in community settings or may require treatment in more controlled and secure environments for ketamine administration (e.g., inpatient/residential).	Very Strong	Level 5
3.16	Decisions about treatment selection should be informed by the psychiatric evaluation, clinical data, and a review of the potential benefit of alternative treatment options that may be available to the patient (e.g., adjustments in medication, switching antidepressants, augmenting with other psychotropic medications, or other FDA-approved interventions).	Very Strong	Level 5
3.17	Decisions about treatment selection should occur collaboratively, involve the patient and their relevant clinicians, and incorporate the patient's personal and sociocultural preferences.	Very Strong	Level 5
3.18	Realistic expectations regarding the goals of treatment should be set for the patient, patient's support system, and treatment professionals.	Very Strong	Level 5
3.19	If adjunctive psychotherapy is expected to provide benefit, the details of this option should be clearly communicated to patients, including who might provide the therapy, the therapist's qualifications, and the proposed setting and timing of sessions relative to ketamine administration.	Very Strong	Level 5
Section 4: *What constitutes an appropriate medical evaluation for IVK for depression?*			
4.1	A comprehensive medical evaluation should include information about the patient's medical history, including past and present medical conditions, surgeries, allergies, medications, family history of medical illness, a medical review of symptoms, and the relevant components of a systems-focused physical exam.	Very Strong	Level 5
4.2	Ketamine is contraindicated in individuals who have shown hypersensitivity to the drug.	Very Strong	Level 5
4.3	Ketamine is contraindicated in individuals for whom a significant elevation of blood pressure or intracranial pressure would constitute a serious hazard.	Strong	Level 5
4.4	Ketamine is not currently recommended in patients who are pregnant, given insufficient data to draw conclusions about any drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.	Moderate	Level 5
4.5	Caution should be exercised in patients with cardiovascular conditions who are at risk for hemodynamic complications, and consultation with medical specialists is encouraged prior to moving forward with treatment in these populations.	Very Strong	Level 5
4.6	Caution should be exercised in patients who are at risk for potential airway or respiratory compromise, and consultation with medical specialists is encouraged prior to moving forward with treatment in these populations.	Very Strong	Level 5
4.7	Factors that could affect the metabolism of ketamine should be considered, including age, advanced liver or renal disease, and drug-drug interactions.	Very Strong	Level 5
4.8	For medical screening, blood pressure, heart rate, respiratory rate, and oxygen saturation should be collected during the initial assessment and before each dosing session.	Strong	Level 5
4.9	If there are persistent, significant abnormalities in vital signs (e.g., systolic blood pressure $>$ 150 mmHg, diastolic blood pressure $>$ 100 mmHg, heart rate $>$ 100 bpm, or oxygen saturation $<$ 95%) and there is uncertainty regarding patient safety prior to drug administration, treatment should be deferred until further assessment is conducted and medical stability is confirmed.	Strong	Level 5
4.10	Laboratory studies or diagnostic tests may be appropriate to collect on a case-by-case basis for the workup of medical causes of depression (e.g., untreated endocrine disorders, neurological conditions, infections, chronic inflammatory and autoimmune diseases, nutritional deficiencies, etc.).	Very Strong	Level 5
4.11	Laboratory studies or diagnostic tests may be obtained on a case-by-case basis to determine medical appropriateness for treatment (e.g., comprehensive metabolic panel, complete blood count, pregnancy test, and EKG) with the potential for expanded testing based on individual risk factors.	Very Strong	Level 5
Section 5: *What are the best practices for safe initiation and maintenance of IVK for depression?*			
5.1	In addition to ensuring appropriate personnel, setting, and assessment before IVK, clinicians should conduct a thorough informed consent process with patients and offer adequate preparation for drug administration.	Very Strong	Level 5
5.2	Preparation for IVK with patients should include an exploration of beliefs about the illness, personal motives for treatment, expectations, and concerns.	Very Strong	Level 5
5.3	Preparation for IVK with patients should include psychoeducation involving ketamine, its mechanisms of action, its common effects, its potential risks, reasonable appraisals of	Very Strong	Level 5

(*continued on next page*)

Table 1 (*continued*)

Guideline Item		Expert Consensus[a]	Evidence Grade[b]
	benefit, and strategies for responding to a variety of challenging medical or psychiatric experiences that may occur.		
5.4	Preparation for IVK should include discussion of any necessary precautions (e.g., to not eat or drink for a period of time prior to treatment, to not drive or engage in potentially hazardous activities following dosing until after a night of restful sleep, to make any necessary arrangements for transportation ahead of time, etc.).	Very Strong	Level 5
5.5	The clinical team should aim to develop rapport and trust with the patient prior to drug administration.	Very Strong	Level 5
5.6	Ketamine for IV infusions should be sourced from an FDA-approved drug manufacturer (i.e., a commercially available product) whenever possible.	Very Strong	Level 5
5.7	If a commercially manufactured product is unavailable and compounded ketamine is used for treatment, clinicians should prioritize sourcing from an FDA-registered 503B compounding pharmacy, and patients should be informed of FDA warnings related to use of compounded ketamine products.	Very Strong	Level 5
5.8	Ketamine for IV infusions should be administered with a pump that ensures regulated dose delivery.	Very Strong	Level 5
5.9	Use of additive or proprietary formulations of ketamine as a treatment for depression is not currently recommended.	Very Strong	Level 5
5.10	For ketamine-naïve patients with depression, we suggest initiating IVK at 0.5 mg/kg over ~40 min with an induction series of 4–6 infusions over 2–4 weeks, with adjustments guided by patient response and preference.	Moderate	Level 1
5.11	It may be reasonable to carefully titrate dose above 0.5 mg/kg in patients who do not initially respond to treatment, while also considering the limited data on the safety and efficacy of doses exceeding 1.0 mg/kg and providing clinical justification for any doses above this threshold.	Strong	Level 1
5.12	Doses lower than 0.5 mg/kg may be appropriate to initiate for some patients, particularly those who are anxious about side effects, have demonstrated difficulty tolerating higher ketamine doses, are known to be sensitive to medications, or have impaired drug metabolism.	Very Strong	Level 1
5.13	IVK should be administered by a qualified medical professional, and patients should be monitored for a period of time (e.g., 30–60 min) after the completion of the infusion until they have returned to baseline, can ambulate independently with steady gait, and are assessed as medically and psychologically stable to safely leave the healthcare setting with arranged transportation.	Very Strong	Level 5
5.14	Vital signs should be checked before drug administration and after treatment completion, with the potential for additional vital sign monitoring during the infusion as determined by the overseeing clinician to be appropriate.	Strong	Level 5
5.15	Patients should be observed for any signs of distress or adverse reactions during treatment, and the clinical team should be prepared to provide basic medical, psychiatric, and emotional support as needed with defined protocols for safety and care escalation.	Very Strong	Level 5
5.16	Following dosing sessions, we recommend some form of psychological aftercare (e.g., structured check-ins, psychoeducation, supportive psychotherapy, integration-focused therapy) that supports patients as they process experiences with ketamine, work through emotionally and psychologically difficult content, manage potential disappointments about treatment, navigate safety, and strive for durable benefit.	Strong	Level 5
5.17	Clinics administering IVK should have protocols and communication with patients for managing patient safety concerns (e.g., worsening suicidality) outside of scheduled treatment sessions or business hours.	Very Strong	Level 5
5.18	Maintenance treatment may be appropriate to consider on a case-by-case basis for relapse prevention in individuals who have failed other treatments for depression, demonstrate a clear positive outcome from ketamine induction (e.g., ≥50% improvement), and are at risk of relapse without continued treatment.	Strong	Level 1
5.19	Maintenance treatment may occur on fixed, time-based intervals or flexible, symptom-based schedules, but in either case, the priority is to lengthen the infusion interval as tolerated while sustaining clinical benefit.	Very Strong	Level 5
5.20	Maintenance treatment should occur within a larger mental health treatment plan (e.g., including lifestyle modifications, behavioral activation, skills development, increased social support, and/or psychotherapy).	Very Strong	Level 5
5.21	Ketamine discontinuation should be considered if patients fail to respond to ongoing treatment or lack functional improvement despite optimization of drug and non-drug factors related to treatment.	Very Strong	Level 5
5.22	To evaluate the relative benefits and risks of ongoing treatment versus stopping or changing therapies, we recommend continuous assessment and documentation of the rationale for maintenance treatment, use of validated scales for tracking clinical response, and detailed record of side effects and adverse events with treatment.	Very Strong	Level 5
Section 6: *What are the elements of written informed consent for IVK for depression?*			
6.1	We recommend the use of a written consent procedure for IVK that includes the following key elements: patient information, medication details (including disclosure of off-label use and rationale for treatment), potential benefits and requirements of treatment (e.g., quality of evidence to guide maintenance treatment, potential time/financial commitment, and patient responsibilities while engaging in treatment), health risks/adverse effects (including risks unique to psychoactive drug administration), options for alternative treatment, voluntary nature of treatment, outline of general procedures (e.g., for evaluation, monitoring, follow-up, and emergency/safety), and a consent statement with signature of the patient/legal guardian, the treatment professional, and date.	Very Strong	Level 5
6.2	The consent document should be readable, with language that is appropriate for the patient and their level of education.	Very Strong	Level 5
6.3	It should be determined that the patient is capable of making an informed, independent, and voluntary decision.	Very Strong	Level 5
6.4	Before signing, patients should have the opportunity to discuss consent with their clinician and have all questions answered to their satisfaction.	Very Strong	Level 5

(*continued on next page*)

Table 1 (*continued*)

Guideline Item	Expert Consensus[a]	Evidence Grade[b]
6.5 After signing, patients should be offered a copy of the signed consent form for their records.	Very Strong	Level 5
Section 7: *What are the essential elements of documentation for IVK for depression?*		
7.1 We recommend documentation of the initial medical and psychiatric evaluation, including the clinical assessment, rationale for treatment, preliminary treatment plan, assessment of concomitant medications, risk considerations, and informed consent procedure.	Very Strong	Level 5
7.2 For subsequent treatment visits, we recommend documentation of any relevant interval history or clinical assessments, the overall course of treatment, details of individual dosing sessions, ongoing clinical monitoring (including management of adverse events), post-treatment observations, and aftercare instructions.	Very Strong	Level 5

[a] Degree of consensus: Moderate ≥75% agreement (i.e., ≥ 75% of panelists rating item in 7–9 range); Strong ≥80% agreement; Very Strong ≥90% agreement.

[b] Evidence level indicates strength of research evidence based on Oxford Centre for Evidence-Based Medicine (OCEBM) levels: Level 1 = Supported by data from meta-analyses and systematic reviews of RCTs; Level 2 = Supported by data from RCTs; Level 3 = Supported by data from non-randomized controlled cohorts; Level 4 = Supported by data from case series or case-control studies; Level 5 = Supported by mechanism-based reasoning, expert opinion and/or existing guidelines.

provided in the Supplementary Materials.

Two items failed to reach consensus and were removed from the guidelines after Round 2. One of these items proposed that ketamine-based treatment for depression should not be restricted to medical professionals with post-graduate training in psychiatry. Panelist feedback indicated that some experts viewed post-graduate psychiatric training as the appropriate standard of care for those offering IVK for depression based on the required competencies. Similarly, another panelist suggested that ketamine clinicians who can offer multiple mental health treatment options may be better positioned to maintain a balanced view of available therapeutic alternatives. The other item that failed to reach consensus proposed that adjusted or ideal body weight, rather than actual body weight, be used to calculate the starting dose in ketamine-naïve individuals with obesity. Feedback indicated one panelist who advocated for dosing based on actual body weight, while another proposed setting a maximum dose to help guard against excessive drug exposure. Despite not meeting formal consensus criteria, both removed items were agreed on by 73% of experts.

4. Discussion

By combining a systematic and targeted review of existing literature with expert consensus methodology, we aimed to create an evidence-based standard for the use of IV ketamine in treating depression in outpatient settings in the United States. Unlike previous efforts toward consensus guidelines (McIntyre et al., 2021; Sanacora et al., 2017), we used an interdisciplinary framework to account for diverse clinical perspectives, evaluated substantial data that has been published in recent years from both clinical trial and real-world settings, and focused on developing a highly practical resource that could be implemented across stakeholders.

The final 73-item guideline presented here reflects strong expert consensus across several key domains. The high degree of consensus observed here likely reflects several factors. First, the guideline items were grounded in a literature review and draft framework, which may have reduced conceptual variability in early phases of the Delphi process. Second, item revision across rounds focused on clarifying language and incorporating feedback to consolidate areas of shared agreement. Finally, the panel consisted of experts working within an emerging but increasingly converging evidence base, which may indicate genuine alignment around standards of care rather than artificial consensus. Qualitative data revealed meaningful differences in clinical reasoning, further reinforcing the idea that agreement was achieved through use of pragmatic, evidence-informed items and careful iterative refinement, rather than through conformity among panelists.

Our findings lend additional support for the effectiveness, safety, and feasibility of IVK for depression. It should be noted that due to the published evidence base, these guidelines primarily focus on the induction series of ketamine treatment (i.e., the initial 4–6 infusions). While research in repeated maintenance ketamine treatment is limited and still underway (Smith-Apeldoorn et al., 2022), experts strongly

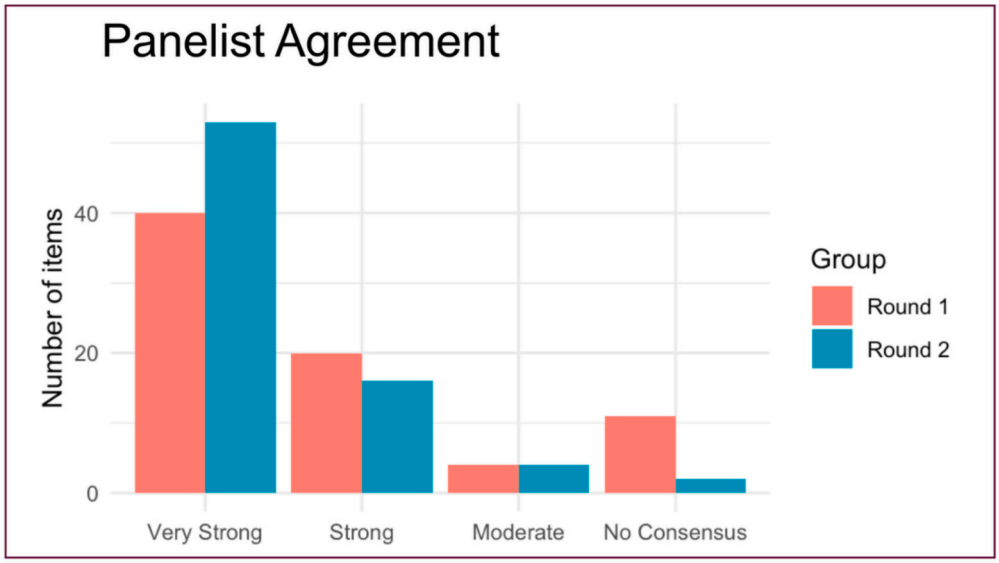

Fig. 3. Evolution of panel agreement for guideline items across Delphi rounds.

agreed that maintenance dosing is a reasonable strategy for relapse prevention in select patients when used within the context of a larger mental health treatment plan and with the goal of reducing the frequency of treatment over time. The practices outlined around patient selection, informed consent, care infrastructure, and clinical monitoring can help mitigate both short- and long-term risks of IVK for patients.

Based on the ratings and feedback gathered, one critical area for ongoing standardization is to establish the degree of psychiatric training and mental health proficiency required to provide IVK for depression. Differing views on this issue are clear from other guidelines (Bayes et al., 2021; Hussain et al., 2025; McIntyre et al., 2021; Ryan and Bennett, 2020; Sanacora et al., 2017; Swainson et al., 2021; Wolfson and Braunstein, 2025) and may stem from specialty-based perspectives on what constitutes best practice. Expert feedback also indicated a need for guidance around dosing limits for IVK, as prospective research evaluating doses above 1.0 mg/kg actual body weight remains limited despite being a high-priority area (Li et al., 2025a). In addition to exploring these issues, future guideline efforts could address best practices related to non-IV routes of ketamine administration, applications beyond depression, at-home use without direct clinical supervision, and the use of adjunctive psychotherapies with ketamine.

Several limitations should be noted: the relatively small size and professional familiarity of the Delphi panel may have limited the independence of responses and generalizability of the findings to the broader population. Furthermore, the absence of systematic disclosures for all Delphi panelists—due to the anonymized design—represents a source of bias, as undisclosed financial relationships may have influenced responses. However, the existence and diversity of this expert group also represent a strength, and measures were taken to protect confidentiality and minimize risks of undue influence. Because participant demographic information was intentionally not collected in a way that might be linked to individual responses, respondent-level and subgroup analyses were also not possible. Such analyses could have provided insight into how characteristics such as profession and specialty may influence ratings. Finally, consensus for some items reflected expert judgment rather than well-established scientific literature. Although expert consensus offers meaningful guidance in areas where evidence is limited, it should not be interpreted as a substitute for continued research and empirical validation.

Ultimately, ketamine has evolved from its initial use as an anesthetic agent into a versatile therapeutic tool capable of relieving suffering in individuals with depression. As the use of IVK for depression continues to expand across clinical settings without consistent oversight, it is essential that data-driven, practical, and ethically grounded recommendations are used to support high-quality, patient-centered care. We intend for these standards to provide a foundation for safe and effective clinical practice, facilitate informed decision-making, and promote greater consistency and access in care delivery. Continued research, real-world evidence, and interdisciplinary collaboration will be crucial to refining and strengthening these guidelines over time, ensuring that clinical practice matures alongside scientific discovery.

CRediT authorship contribution statement

David S. Mathai: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Formal analysis, Conceptualization. **Madeleine Cluck:** Writing – review & editing, Writing – original draft, Software, Formal analysis. **Amna M. Aslam:** Writing – review & editing, Writing – original draft, Validation, Software, Methodology, Formal analysis. **Erin Amato:** Writing – review & editing, Project administration, Conceptualization. **Arsalan Azam:** Writing – review & editing, Writing – original draft. **Michael Banov:** Writing – review & editing, Writing – original draft. **Kathleen A. Barrett:** Writing – review & editing, Project administration, Conceptualization. **Carl J. Bonnett:** Writing – review & editing. **David Feifel:** Writing – review & editing, Writing – original draft. **Nicolas Grundmann:** Writing – review & editing, Writing – original draft, Conceptualization. **H. Samuel Ko:** Writing – review & editing, Project administration, Conceptualization. **Rupert McShane:** Writing – review & editing, Writing – original draft. **Sandhya Prashad:** Writing – review & editing, Project administration, Conceptualization. **Tatiana Santini:** Writing – review & editing, Writing – original draft. **Lowan H. Stewart:** Writing – review & editing, Writing – original draft. **Patrick Sullivan:** Writing – review & editing, Project administration, Conceptualization. **Stefany D. Wolfsohn:** Writing – review & editing. **Jill O. Robinson:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Conceptualization. **Amy L. McGuire:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Formal analysis, Conceptualization. **L. Alison McInnes:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Formal analysis, Conceptualization.

Disclosures

DSM is owner of Sattva Medicine and has received consulting fees from ASKP3 and Beckley Clinical. AMA is an employee at Radial. EA is owner of Montana Psychiatry and Brain Health Center, serves as a speaker for Johnson & Johnson, and is a stockholder in Turnwell Mental Health, Inc. AA is owner of Daydream MD. MB is owner of Psych Atlanta/Hightop Health. KAB is a paid consultant with ASKP3. CJB is owner of Klarisana. DF is owner of Kadima Neuropsychiatric Institute and serves as a consultant for AtaiBeckley, Helus, and Otsuka. NG is owner of Ember Health. HSK is owner of Reset Ketamine. RMcS runs a ketamine clinic on behalf of his employer Oxford Health NHS Foundation Trust. SP is owner of Houston Center for Advanced Psychiatric Treatment. TS is an employee at BrainStim Health. LHS is an owner of Axon Clinic. PS is owner of Initia Nova Medical Solutions. SDW is owner of Ventura Center for Advanced Therapeutics. LAM is an employee at Mindful Health Solutions and serves on the Scientific Advisory Board for Osmind. DSM, AMA, EA, AA, MB, CB, DF, NG, HSK, RMcS, SP, TS, LHS, PS, SDW, and LAM all serve as volunteer faculty with ASKP3. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: DSM is owner of Sattva Medicine and has received consulting fees from ASKP3 for work related to this study and Beckley Clinical. AMA is an employee at Radial. EA is owner of Montana Psychiatry and Brain Health Center, serves as a speaker for Johnson & Johnson, and is a stockholder in Turnwell Mental Health, Inc. AA is owner of Daydream MD. MB is owner of Psych Atlanta/Hightop Health. KAB is a paid consultant with ASKP3. CJB is owner of Klarisana. DF is owner of Kadima Neuropsychiatric Institute and serves as a consultant for AtaiBeckley, Helus, and Otsuka. NG is owner of Ember Health. HSK is owner of Reset Ketamine. RMcS runs a ketamine clinic on behalf of his employer Oxford Health NHS Foundation Trust. SP is owner of Houston Center for Advanced Psychiatric Treatment. TS is an employee at BrainStim Health. LHS is an owner of Axon Clinic. PS is owner of Initia Nova Medical Solutions. SDW is owner of Ventura Center for Advanced Therapeutics. LAM is an employee at Mindful Health Solutions and serves on the Scientific Advisory Board for Osmind. DSM, AMA, EA, AA, MB, CB, DF, NG, HSK, RMcS, SP, TS, LHS, PS, SDW, and LAM all serve as volunteer faculty with ASKP3. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgements

The authors thank our patients who have been our teachers, along with the clinicians and staff at various institutions that made this work possible. We thank Jeffrey Becker and Michael Mantz for their contributions to the ASKP3 working committee and to early stages of guideline development. We would also like to thank John Dougherty, Tiago Gil, Lucinda Grande, Brandon Kitay, Kim Le, Brittany O'Brien, Megan Oxley, Nykol Bailey Rice, Scott Shannon, Laura Wiginton, Jeffrey Zabinski, and the other ASKP3 expert faculty who contributed to the Delphi panel. Rupert McShane acknowledges support from the National Institute for Health Research Oxford Health Biomedical Research Centre. Article open access processing fees were paid for by the American Society of Ketamine Physicians, Psychotherapists, and Practitioners.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2026.121970.

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