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Mapping consent practices for outpatient psychiatric use of ketamine

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ABSTRACT

Background: Given increasing community-based and off-label use of ketamine for psychiatric indications, we examined current informed consent processes from a convenience sample of outpatient ketamine clinics to identify areas of congruence with current evidence and opportunities for growth.

Methods: Using a rubric developed from existing practice guidelines, we conducted an exploratory analysis of informed consent documents (IC-Docs) from 23 American clinics offering ketamine as a psychiatric treatment. Domains assessed included clinical content, procedures, and syntax.

Results: Participating clinics (23/288) varied widely in their constitution, training, and services provided. We found that IC-Docs addressed a majority of consent elements, though did so variably on an item-level. Areas for improvement included communication around long-term adverse effects, treatment alternatives, medical/psychiatric evaluation prior to treatment, medical/psychological support during treatment, adjunctive psychological interventions, and subjective/dissociative-type effects. All forms were limited by poor readability.

Limitations.

Our study was limited by convenience sampling along with possible underestimation of verbal consent processes.

Conclusions: As ketamine continues to emerge as a psychiatric intervention, both patients and providers will benefit from a deliberate consent process informed by scientific, ethical, and pragmatic factors toward the goal of shared decision-making regarding treatment.

1. Introduction

Psychiatric applications of ketamine have existed for approximately 50 years (Khorramzadeh and Lotfy, 1973), though constrained for decades by a lack of regulatory approval and concerns surrounding nonmedical drug use (Ahmed and Petchkovsky, 1980). This shifted with the first randomized controlled trial (RCT) of ketamine for depression (Berman et al., 2000), a larger replication study (Zarate et al., 2006) and subsequent trials of ketamine and its derivatives with positive findings, making way for the U.S. Food and Drug Administration (FDA) approval of esketamine – one isomeric form of ketamine – as an antidepressant and antisuicidal agent. Notwithstanding indices of considerable progress, ketamine might still be thought of as a repurposed anesthetic and analgesic drug, only now achieving wider acceptance for its psychotropic effects (Schatzberg, 2019). To this effect, many psychiatric uses of ketamine are currently "off-label," or involving an unapproved indication, dosage, or form of administration (Wilkinson et al., 2017).

Off-label prescribing of medications can be seen as a double-edged sword. On the one hand, such prescribing may be a lawful and beneficial practice that allows prescribers to use their best judgment and offer solutions to patients despites gaps in regulatory processes (Gupta and Nayak, 2014). But often lacking the extent of evidence required for FDA-approval, off-label drug use can also represent a premature application of prescriptive authority that may shift risk-benefit ratios toward adverse drug events (Eguale et al., 2016; Zhang et al., 2016). This freedom is accompanied, then, by the expectation that prescribers strive to base their decisions on "firm scientific rationale and on sound medical evidence" (U.S. Food and Drug Administration, 1998).

What might be considered adequate supporting data for the off-label use of a medication? There is no simple answer. One argument against the putative expertise of the prescriber is the finding that 73 % of prescriptions for off-label indications lack strong scientific support, defined

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as data on effectiveness collected from controlled trials or documented in clinical settings (Radley et al., 2006). Observational data, case reports (Radley et al., 2006), and other scientific literature supporting a plausible physiological mechanism for drug application represent lower standards of evidence (Syed et al., 2021). However, the final question of rationale is left open to the interpretation of each individual drug prescriber (Smith, 2006), and medical liability is judged on a case-by-case basis (Syed et al., 2021). In the context of increasing numbers of community-based practitioners offering ketamine as an indiscriminate psychiatric treatment (Wilkinson et al., 2017), several groups have proposed best practice guidelines derived from existing evidence (McIntyre et al., 2021; Sanacora et al., 2017; Singh et al., 2017; Sullivan et al., 2020; Wesley and Bennett, 2020). However, even clinical standards can vary widely and are constantly evolving, particularly for novel or repurposed medications, such as ketamine (Syed et al., 2021).

Clinicians providing ketamine for psychiatric use must ultimately reconcile the benefits of this innovative and consequential treatment with the heightened liability of operating, for now, on regulatory margins. In addition to understanding the legal premise and standards for negligence, prescribers can mitigate risk through a rigorous consent process for treatment (Paterick et al., 2008; Riley and Basilius, 2007). Informed consent comprises the ethical, legal, and administrative process (Hall et al., 2012) by which a healthcare provider educates a patient on the risks, benefits, and alternatives of a medical intervention toward the goal of shared decision-making regarding treatment (Shah et al., 2021).

While neither necessary nor sufficient for valid medical consent (Paterick et al., 2008), written informed consent documents (IC-Docs) can provide structure for such conversations (Fedson et al., 2018). Written consent is also an endeavor in mutualism—aspiring to provide patients with a clear reference for what treatment entails and prescribers with documented protection from negligent practice claims, and especially so, for pioneering drug applications (Syed et al., 2021). IC-Docs are uniquely suited for the analysis of emerging clinical practices given the information they contain regarding the proposed nature of treatment, the extent to which practice reflects existing guidelines, and opportunities for improved patient education (Fedson et al., 2018). Consequently, the purpose of this study was twofold: 1) to conduct an exploratory analysis of IC-Docs for the outpatient psychiatric use of ketamine, and 2) to create a preliminary standard for these consent forms toward the goal of establishing best practices for patients and providers alike.

2. Methods

2.1. Participants

Our sample consisted of 23 clinics offering ketamine as a psychiatric treatment recruited from the online directory of the American Society of Ketamine Physicians, Psychotherapists, and Practitioners (ASKP[3]): https://askp.org/directory/. ASKP[3] is a non-profit professional organization representing healthcare providers who utilize ketamine for mental health disorders and pain conditions. Providers of clinics registered in this directory were ASKP[3] members in good standing with the organization at the time of the study and with no history of severe licensing action. Clinics in the directory were excluded from this analysis if they were not based in the U.S. and/or did not offer English-language IC-Docs. We populated information present in IC-Docs, clinic websites, and the public domain to further characterize clinics offering ketamine for psychiatric indications (i.e., location of practice, offered routes of administration, stated indications, provider background/training and relevant certifications).

2.2. Procedures

A total of 288 registered ketamine providers were identified using the ASKP[3] directory at the time of the initial search and were contacted from August to December 2020. We sent a formal email request to these clinics informing them of the purpose of the study, assuring their anonymity and requesting a copy of their consent documents, if interested in study participation. The providers either a) replied with IC-Docs (n = 25) b) declined to participate in the study (n = 6) or c) did not respond (n = 257). We excluded two international forms, given the possibility of significant differences regarding informed consent and regulatory process outside the U.S., leading to a final sample of 23 forms. This protocol was developed with oversight from the Baylor College of Medicine Institutional Review Board (IRB) and determined not to constitute human subjects research.

2.3. Grading instrument

We developed an analytical framework for critically evaluating eligible IC-Docs using best practice guidelines from three existing sources: the ASKP[3] Standards of Practice in the Therapeutic Use of Subanesthetic Ketamine (Sullivan et al., 2020), the KRIYA Research Institute Ethical Guidelines for Ketamine Clinicians (Wesley and Bennett, 2020), and a recent international expert opinion on available evidence for ketamine and esketamine in treatment-resistant depression (McIntyre et al., 2021). We combined specific elements represented in these guidelines with general principles of informed consent (Fedson et al., 2018) to create a final grading rubric with 24 distinct elements (see Supplement for detailed grading instrument).

These elements were organized into three primary domains: 1) clinical content, 2), procedures, and 3) syntax. Grading of clinical content was based on the inclusion of the risks (i.e., short-term adverse reactions, long-term adverse reactions, safety/contingency protocols), benefits (i.e., proposed goal/effect of treatment, context for expected benefit and success factors related to treatment), alternatives to (i.e., proposed alternatives and risk/benefit considerations of each), and voluntary nature (i.e., options to decline/withdraw and risk/benefit considerations) of treatment. Grading of procedures was based on the inclusion of the role of medical evaluation prior to treatment, on-site availability of medical support (i.e., vital signs monitoring and availability of medical professional), the role of psychiatric evaluation prior to treatment, on-site availability of psychological support, administration protocols (i.e., approximate number of treatments, dosage, and rationale for decisions around drug administration), and potential adjunctive role of psychotherapy with treatment. Grading of syntax was based on the inclusion of the name of the treating clinic, indication for ketamine/esketamine, distinction between ketamine and esketamine, information regarding possible off-label use, patient name/signature, date of consent, witness signature, signature of the individual explaining the IC-Doc, and readability.

Items were graded as missing (score = 0), incomplete (score = 1), or complete (score = 2) for more complex elements, or as missing (score = 0) or complete (score = 1) for simpler elements. Clinical content and procedures were generally treated as complex elements, with the exception of “noted benefits,” “noted alternatives,” and “noted voluntary nature of treatment” for clinical content and “noted on-site availability of psychological support” and “noted psychotherapy as adjunct to treatment” for procedures, which were treated as simple elements. All syntax elements were graded as simple elements. Analysis of IC-Doc readability, a syntax element, was conducted through a publicly available website (readable.com) using three readability formulas: 1. Flesch-Kincaid (Kincaid et al., 1975), 2. Gunning Fog (Gunning, 1971), and 3. Simple Measures of Gobbledygook, or SMOG (McLaughlin, 1969). These formulas account for semantic (length of word) and syntactic (length of sentence) parameters considered to be the best predictors of textual difficulty (DuBay, 2004), and generate scores corresponding to the grade level of education required to read the text (e.g., 6–6.9 = 6th grade). IC-Docs were required to read at or below an 8th grade level, corresponding with the U.S. adult average reading level, across all three

formulas to receive a rubric score of 1 and were otherwise scored as 0.

The rationale for all possible rubric scores was defined and standardized per individual item (see Supplement).

2.4. Additional measures

Though not explicitly stipulated in existing guidelines and thus not included in our formal grading rubric, we examined several additional items of interest in IC-Docs. These included psychiatric considerations (e.g., whether forms addressed the possibility of worsening suicidality with treatment), whether the forms uniquely considered special psychiatric populations (e.g., individuals with psychotic or substance-use disorders), and whether they presented dissociative properties of ketamine in a framework other than as an adverse treatment event.

2.5. Analytic plan

Two authors with advanced medical training and familiarity with ketamine as a psychiatric treatment (S.L. & V.M.) recorded clinic characteristics, independently graded each IC-Doc using the constructed rubric, and gathered additional items of interest from forms. Graded items were organized around the domains of clinical content, procedures, and syntax (Table 1); score discrepancies were resolved with case-by-case discussion, with a third author (D.M.) serving as tiebreaker if a consensus was not reached. Clinic characteristics, IC-Doc scores, and items of interest were presented as descriptive statistics of individual items for clarity (e.g., x/23 or y % of forms noted z). All 23 clinics were considered for each possible analysis, except for that of geographic region, in which case one clinic was excluded due to its presence in multiple regional locations, and for provider specialty and certifications, in which case three clinics were excluded due to the absence of discrete provider information that was publicly available. Summary measures were used to calculate IC-Doc scores as a percentage of the highest score possible for each individual domain and then combined across domains, to generate an overall IC-Doc score.

Table 1
Informed consent document (IC-Doc) item-level analysis for all ketamine clinics.

	Missing	Incomplete	Complete
1. Content			
Risks			
Short-term adverse effects	0 (0 %)	3 (13.0 %)	20 (87.0 %)
Long-term adverse effects	3 (13.0)%	4 (17.4 %)	16 (69.6 %)
Safety/contingency protocols	1 (4.3 %)	3 (13.0 %)	19 (82.6 %)
Benefits			
Noted	1 (8.7 %)	–	22 (95.7 %)
Success factors	0 (0 %)	2 (8.7 %)	21 (91.3 %)
Alternatives			
Noted	12 (52.2 %)	–	11 (47.8 %)
Associated risks and benefits	20 (87.0 %)	3 (13.0 %)	0 (0 %)
Voluntary nature of treatment			
Noted	2 (8.7 %)	–	21 (91.3 %)
Associated risks and benefits	21 (91.3 %)	2 (8.7 %)	0 (0 %)
2. Procedures			
Role of medical evaluation prior to ketamine treatment	7 (30.4 %)	11 (47.8 %)	5 (21.7 %)
Requirement for on-site medical support during treatment	8 (34.8 %)	10 (43.5 %)	5 (21.7 %)
Role of psychiatric evaluation prior to ketamine treatment	14 (60.9 %)	2 (8.7 %)	7 (30.4 %)
Requirement for on-site psychological support during treatment	19 (82.6 %)	–	4 (17.4 %)
Administration protocols	2 (8.7 %)	2 (8.7 %)	19 (82.6 %)
Psychotherapy as possible adjunct to treatment	10 (43.5 %)	–	13 (56.5 %)

	Missing	Complete
3. Syntax		
Name of clinic	2 (8.7 %)	21 (91.3 %)
Indication for ketamine	1 (8.7 %)	22 (95.7 %)
Acknowledges difference between esketamine and ketamine	20 (87.0 %)	3 (13.0 %)
Mentions that use of drug and/or route may be off label	2 (8.7 %)	21 (91.3 %)
Date of consent	4 (17.4 %)	19 (82.6 %)
Patient name/signature	4 (17.4 %)	19 (82.6 %)
Witness signature	17 (73.9 %)	6 (26.1 %)
Person explaining IC-Doc signature	13 (56.5 %)	10 (43.5 %)
Readability scores at or below 8th grade reading level	23 (100 %)	0 (0 %)

3. Results

3.1. Clinic characteristics

3.1.1. Regions

Our final sample of 23 clinic IC-Docs was representative of a broad geographical distribution. One form was obtained from a clinic with multiple regional locations. The remaining clinics represented the following U.S. census regions: Northeast (1/22, 4.5 %), Midwest (3/22, 13.6 %), South (8/22, 36.4 %) and West (10/22, 45.5 %).

3.1.2. Route of administration

The most common routes of administration (ROA) were intravenous (IV: 15/23, 65.2 %) followed by intramuscular (IM: 8/23, 34.8 %), intranasal (IN: 5/23, 21.7 %) and oral (PO: 5/23, 21.7 %) (Fig. 1). Most clinics offered a single route of administration (14/23, 60.9 %). The remaining clinics, which offered multiple ROAs (9/23, 39.1 %), included the following combinations: IM/PO (4/23, 17.4 %), IN/IV (2/23, 8.7 %), IM/IV (1/23, 4.3 %), IN/IM (1/23, 4.3 %) and IM/PO/IV (1/23, 4.3 %).

3.1.3. Stated indications

The stated psychiatric indications for treatment, listed in descending order of prevalence, were as follows: major depressive disorder (MDD) (23/23, 100 %), post-traumatic stress disorder (PTSD) (21/23, 91.3 %), generalized anxiety disorder (14/23, 60.9 %), obsessive-compulsive disorder (OCD) (13/23, 56.5 %), bipolar disorder (10/23, 43.5 %), and substance use disorders (6/23, 26.1 %) (Fig. 2). Some forms further specified antidepressant uses of ketamine for post-partum depression (4/23, 17.4 %) and persistent suicidality (1/23, 4.3 %). Three forms (13.0 %) indicated that antidepressant uses of ketamine were for treatment-resistant depression. Clinics also indicated the utility of ketamine for pain, including: unspecified chronic pain (12/23, 52.2 %), fibromyalgia (8/23, 34.8 %), migraines (7/23, 30.4 %), neuropathic pain (3/23, 13.0 %), complex regional pain syndrome (2/23, 8.7 %), amputation/phantom limb pain (2/23, 8.7 %), lower back pain (1/23, 4.3 %), surgical pain (1/23, 4.3 %), rheumatoid arthritis (1/23, 4.3 %), and central desensitization syndrome (1/23, 4.3 %).

3.1.4. Provider background/training

Of 20 clinics with discrete information available on provider backgrounds and training, there was considerable diversity in professional representation. These clinics represented a total of 90 healthcare providers (median = 2.5 healthcare providers per clinic, range = 1–20). All clinics (100 %) included at least one medical provider with prescriptive

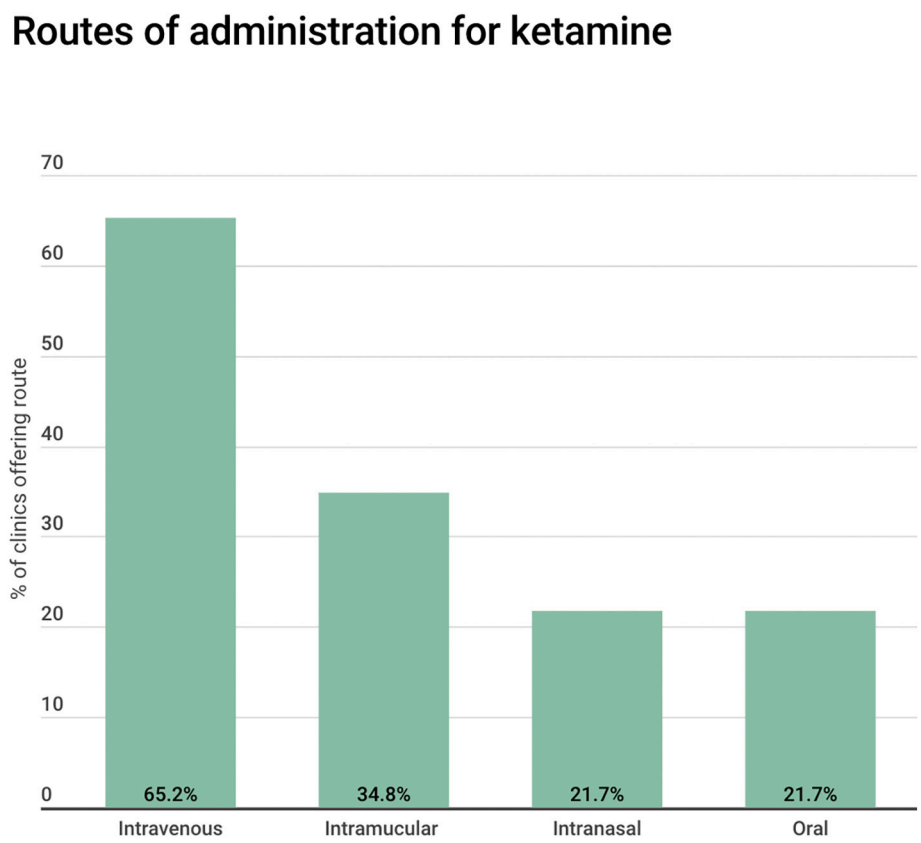

Fig. 1. Common routes of administration (ROA) for ketamine among participating clinics. Most clinics (14/23, 60.9 %) offered a single ROA, although nine clinics (39.1 %) offered multiple routes.

authority. Eight clinics (40 %) included a psychiatric prescriber, consisting of a psychiatrist in all cases except for one clinic consisting of a psychiatric mental health nurse practitioner. An additional five clinics (25 %) employed any mental health clinician, while the remaining seven did not (Fig. 3). Treatment teams otherwise consisted variably of medical (i.e., physicians, physician associates, advanced practice registered nurses, registered paramedics) and non-medical providers (i.e., psychologists, social workers, licensed marriage and family therapists, licensed mental health counselors, licensed professional counselors, licensed psychological associates, and certified trauma professionals). Medical specialties represented included psychiatry, anesthesiology, internal medicine, family medicine, emergency medicine, and physical medicine and rehabilitation (PM&R).

3.1.5. Certifications

Five of 20 clinics (20.7 %) listed additional certifications for working with ketamine or psychedelic treatments. Four reported that their clinicians completed a Ketamine Assisted Psychotherapy (KAP) training from one or more programs, including The Ketamine Training Center, Polaris Insight Center, KRIYA Institute, or the Psychedelic Research and Training Institute (PRATI). One of these clinics also indicated that employees had been trained with the Multidisciplinary Association for Psychedelic Studies Public Benefit Corporation (MAPS-PBC). Another clinic reported their staff had completed an online ketamine infusion therapy course via the Ketamine Academy.

3.2. IC-Docs: clinical content

3.2.1. Risks

Twenty of 23 clinics (87.0 %) completely noted short-term adverse effects (i.e., from three or more distinct organ systems), while the remaining (3/23, 13.0 %) noted short-term adverse effects for one to two organ systems. Sixteen clinics (70.7 %) completely noted long-term adverse effects (i.e., at least two out of three: potential for abuse/addiction, renal/urinary toxicity, and neurotoxicity), four clinics (17.4 %) only noted one long-term adverse effect, and three clinics (13.0 %) did not list any long-term adverse effects of ketamine. Nineteen clinics (82.6 %) completely addressed safety/contingency protocols (i.e., no driving or operating machinery following drug administration; anticipation and management of short-term medical or psychiatric adverse reactions), three (13.0 %) noted one safety-related protocol, and the remaining one clinic (4.3 %) did not address safety protocols.

3.2.2. Benefits

Twenty-two of the 23 forms (95.7 %) proposed the beneficial effects and goals of treatment, while one (4.3 %) failed to note benefits of treatment. Twenty-one of the 23 forms (91.3 %) provided further context for what benefits patients might reasonably expect (e.g., "condition may be temporarily, permanently or not improved," "results not guaranteed," etc.) and discussed success factors involved in the maintenance and/or optimization of outcome. Two forms (8.7 %) contextualized expectations of benefit but did not discuss maintenance and/or optimization factors.

3.2.3. Alternatives

While risk and benefits were well represented in most consent documents, fewer than half of the forms (11/23, 47.8 %) noted the possibility of alternative treatment. Of those 11, three clinics (13.0 %) noted the potential benefits of pursuing alternative treatment, but not any associated risks of doing so.

3.2.4. Voluntariness of treatment

Twenty-one of the 23 clinics (91.3 %) described the voluntary nature of treatment and/or acknowledged that the patient could freely

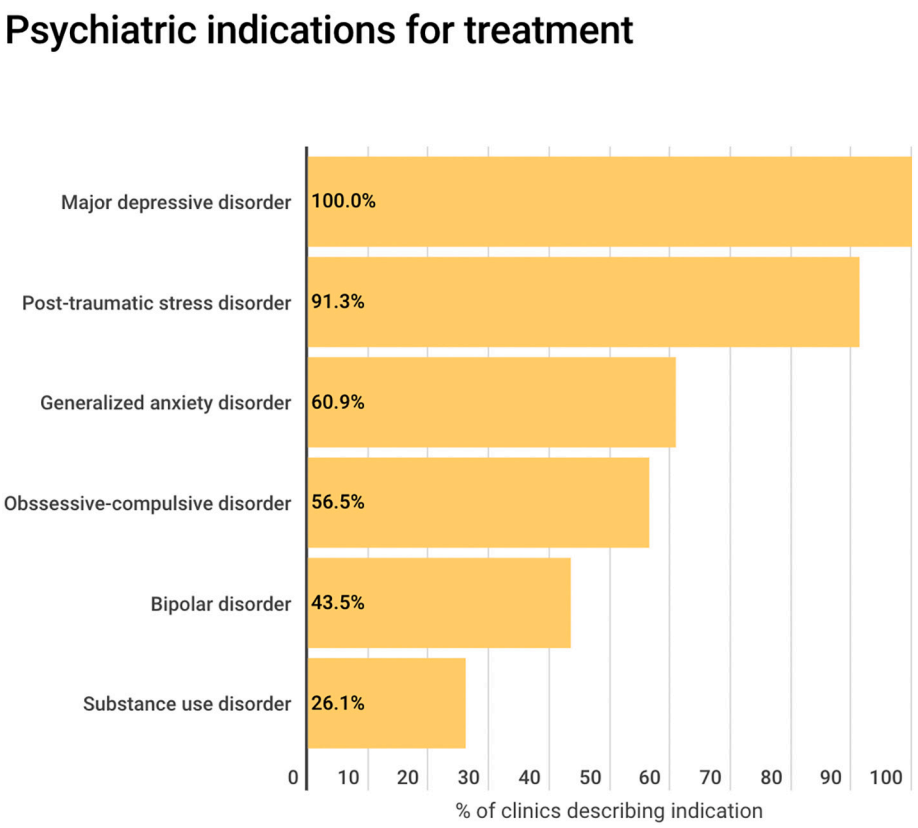

Fig. 2. Psychiatric indications for treatment among participating clinics. Some consent forms further specified antidepressant uses of ketamine for post-partum depression, persistent suicidality, or treatment-resistant depression.

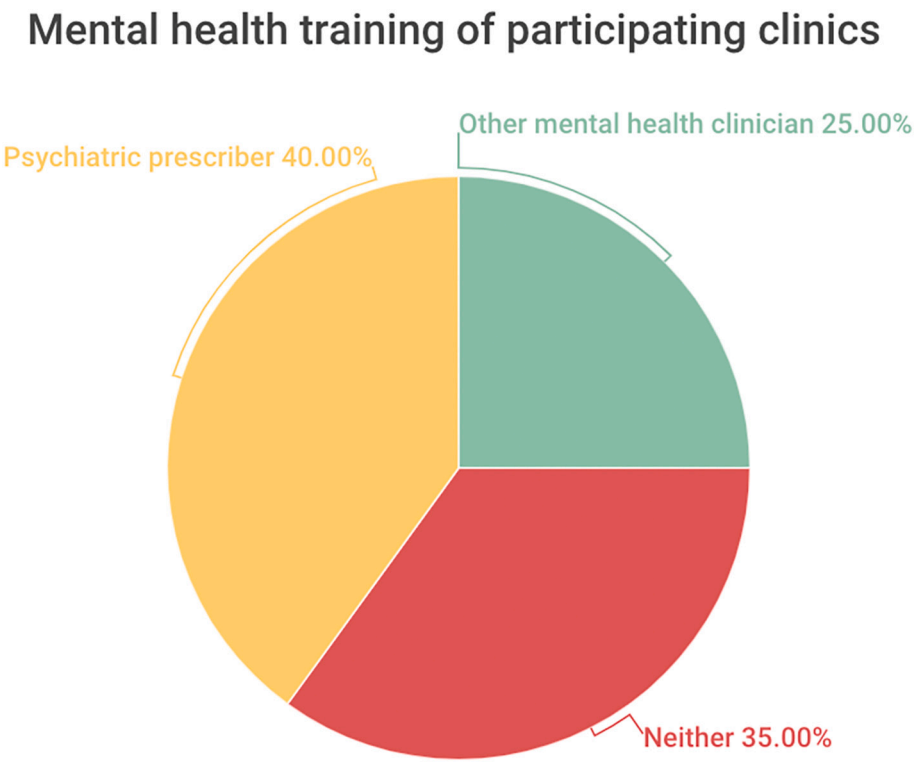

Fig. 3. Formal mental health training varied among clinics offering ketamine as a psychiatric treatment. All clinics consisted of at least one medical provider with prescriptive authority.

withdraw from treatment, while the remaining two clinics (8.7 %) did not include this language. As with alternatives to treatment, a large majority (21/23, 91.3 %) of forms failed to note both the associated risks and benefits of pursuing no treatment, with the remaining two clinics (8.7 %) noting benefits but not risks.

3.3. IC-Docs: procedures

3.3.1. Role of medical evaluation

A complete description of a medical evaluation emphasized the importance of both historical (e.g., comprehensive medical history) and objective (e.g., vital signs, physical exam, laboratory studies) data prior to treatment. Of the 23 IC-Docs analyzed, only five (21.7 %) included both elements, while eleven (47.8 %) noted the importance of a single element and seven (30.4 %) engaged neither.

3.3.2. On-site availability of medical support

Five clinics (21.7 %) reported availability of both an on-site medical professional and vital signs monitoring, and eight (34.8 %) noted neither. Of the ten (43.5 %) that included just one of these two elements, eight noted vital signs monitoring, and two noted the availability of a medical professional on-site.

3.3.3. Role of psychiatric evaluation

For this measure, forms were scored as complete if they discussed the need for a comprehensive psychiatric assessment prior to the initiation of ketamine. Seven clinics (30.4 %) had complete descriptions, two (8.7 %) had vague or incomplete descriptions, and fourteen (60.9 %) did not note the role of preceding psychiatric evaluation.

3.3.4. On-site availability of psychological support

Four of 23 clinics (17.4 %) mentioned the on-site availability of a mental health professional while the remaining nineteen (82.6 %) did not.

3.3.5. Administration protocols

Nineteen of the 23 forms (82.6 %) were graded as complete, for noting at least two out of three of the following elements: approximate number of treatments, dosage, and rationale for adjustments in dose or number of treatments. Two clinics (8.7 %) only noted one of the three, and the remaining two (8.7 %) mentioned none of these elements. Clinics generally utilized a protocol of four to six drug administrations in close succession (2–4-week period) with the possibility of ongoing maintenance or "booster" sessions as discussed with the treatment team. A minority of clinics (8/23, 34.8 %) described specific dosages: among these, IV doses were consistently listed as 0.5 mg/kg over 40–60 min of infusion, IM doses ranged from 50 to 100 mg (with the possibility of doses up to 150 mg, though this was not recommended), and PO doses ranged from 50 to 400 mg.

3.3.6. Psychotherapy as an adjunct to treatment

Thirteen of the 23 forms (56.5 %) mentioned the adjunctive value of psychotherapy before, during, or after treatment, with the remaining ten (43.5 %) not addressing adjunctive therapy.

3.4. IC-Docs: syntax

Most forms included common IC-Doc elements such as the clinic name (21/23, 91.3 %), indication for treatment (22/23, 95.7 %), date of consent (19/23, 82.6 %), and patient name/signature (19/23, 82.6 %). Areas for witness (6/23, 26.1 %) and provider (13/23, 43.5 %) signatures were less commonly included. While most forms communicated off-label use of drug (21/23, 91.3 %), only two (8.7 %) acknowledged a difference between ketamine and esketamine. No forms (0/23, 0 %) were considered adequate for the U.S. adult average reading level of 8th grade (score 8.0–8.9). Mean readability was 13.2 (standard deviation [*SD*] = 1.8) as measured by the Flesh-Kincaid scale, 15.6 (*SD* = 2.0) by Gunning-Fog and 15.5 (*SD* = 1.5) by SMOG, approximating collegiate levels of education.

3.5. IC-Docs: summary measures

IC-Docs on average achieved 64.6 % (*SD* = 12.3), 49.6 % (*SD* = 30.2), and 58.4 % (*SD* = 17.8) of possible points for the domains of clinical content, procedures, and syntax, respectively. For all items across domains, IC-Docs averaged 58.6 % (*SD* = 14.0) of total points achievable.

3.6. IC-Docs: additional measures

Though not included in the formal grading rubric, we examined several additional items relevant to the psychiatric use of ketamine. Ten out of 23 forms (43.5 %) addressed the possibility of worsening suicidality with treatment. Special psychiatric populations listed as contraindications for or necessitating further evaluation prior to treatment included patients with psychosis (5/23, 21.7 %), substance use (1/23, 4.3 %), and bipolar disorder in a manic/mixed state (1/23, 4.3 %). Finally, eight out of 23 forms (34.8 %) discussed the dissociative- and psychedelic-type effects in a context other than as an adverse treatment event. While wording for this varied between forms, this included discussing "dissociation/perceptual changes" as a "routine" and "instrumental" part of treatment, "a minimal trance state" as "essential to successful treatment," the "dose-dependent psychoactive effects" as "potential treatment mechanisms" and "transpersonal" or "mystical experiences" as possibly facilitating shifts in "perspective and emotional state."

4. Discussion

This study reports an exploratory analysis of IC-Docs from community practitioners administering ketamine for outpatient psychiatric use. An analytic framework for considering key elements of this informed consent process was developed using available best-practice guidelines. The final grading rubric encompassed general principles for medication consent and more specific recommendations for ketamine administration. We found that participating clinics addressed a majority of items relevant to medication consent, though did so variably for unique aspects of psychiatric ketamine use across the proposed domains of clinical content, procedures, and syntax.

Regarding clinical content, most IC-Docs included some review of risks (for short-term more so than long-term adverse effects), benefits, and the voluntary nature of treatment. IC-Docs inconsistently addressed the growing concerns around treatment-emergent suicidality (Gastaldon et al., 2021). Broader communication of potential long-term adverse effects of ketamine may have been limited by the lack of extensive study in this area. While risks of urological and gastrointestinal toxicity, neurotoxicity, and dependence have been described in populations with heavy, chronic recreational ketamine use (Short et al., 2018), it is unclear how these data inform the medical risks associated with repeated use of ketamine in the therapeutic context, where dosing parameters are expected to be quite different. Indeed, emerging data suggest that many of the long-term risks identified in heavy ketamine users are mitigated when ketamine is administered in controlled clinical settings (Wajs et al., 2020).

Clinics examined here inconsistently presented alternatives to ketamine or considerations relevant to pursuing alternative treatment, though a discussion of these factors is included in the best practices of informed decision-making for patients (Paterick et al., 2008). This trend may reflect relative lack of equipoise in considering and promoting other research-based interventions, which has been an issue raised (Zhang and Ho, 2015). Providing this broad context may have even greater significance when considering psychological harms involving

therapeutic idealization and thwarted expectations that can occur with medical hallucinogens (Gorman et al., 2021).

In the absence of legal requirements around treatment delivery, the prevailing standard for acceptable procedure is often that of the "reasonable physician," reflecting clinical decision-making that might be expected from others with comparable training working in a similar community (Paterick et al., 2008). Although biomedical research has focused predominantly on IV or IN forms of ketamine, the documents we examined indicate that many clinicians are providing ketamine therapy via other ROAs. This practice is supported by good evidence for the safety and antidepressant efficacy of IV, IN, and PO formulations of ketamine (McIntyre et al., 2020), as well as growing evidence in favor of IM ketamine (Dore et al., 2019; Kheirabadi et al., 2020; Loo et al., 2016). In addition to clarifying ROA, the IC-Docs assessed here generally provided information on ketamine administration protocols, including the approximate number of treatments, dosage, and rationale for adjustments. However, the role of comprehensive medical and psychiatric evaluation prior to treatment, on-site availability of medical and psychological support during treatment, or the potential for adjunctive psychological interventions with ketamine were less commonly or thoroughly described.

For syntax, the IC-Docs often communicated off-label applications of the drug, though specific distinctions between ketamine and esketamine were rarely made, which might be confusing, and even misleading, to patients. Also concerning is the fact that overall readability was graded as poor for all IC-Docs, suggesting that the written information provided might be misunderstood or ignored by patients. Given its relevance to the concept and practice of shared decision-making, comprehension should be a high-priority area for improved consent procedures (Fedson et al., 2018).

While there is a role for the off-label use of medication given scientific rationale and sound clinical judgment, such approaches require careful consideration, given the potential for negligence and harm to patients when risks and benefits—which may vary depending on clinical indication and other factors—are not adequately discussed (Gupta and Nayak, 2014). For ketamine, it is especially worth considering the possibility of exaggerated therapeutic effects (Zhang et al., 2017; Zhang and Ho, 2015), abuse liability (Le et al., 2022), and other harms when administered repeatedly and in contexts deviating from well-established procedure (Zhang et al., 2016). Many IC-Docs stated the utility of ketamine for diagnoses other than depression, such as anxiety disorders or OCD, which have a less robust evidence base. This limitation should be acknowledged in the consent process, as it could affect shared decision-making around whether potential benefits outweigh the medical and psychiatric risks of ketamine treatment for these disorders. Likewise, other factors (e.g., psychiatric comorbidities, personal and/or family history of psychosis) might affect the likelihood of adverse events, which could in turn alter the risk-benefit ratio of treatment. Unfortunately, exclusionary criteria were rarely delineated in IC-Docs. This may be because clear guidelines around psychiatric exclusion factors have not been firmly established, given the insufficient evidence base (McIntyre et al., 2021).

Since consent requires a clear discussion of adverse events, it was notable how IC-Docs varied in their description of dissociative/psychedelic effects of ketamine. Within a traditional biomedical model, these effects are reported as adverse events (Bennett et al., 2022; McIntyre et al., 2021). However, some IC-Docs described dissociative- and psychedelic-type effects as potentially therapeutic. There is certainly some evidence to support this theoretical orientation. Dose-dependent, subjective qualities of drug effect have been linked with therapeutic outcome for highly psychoactive therapies such as MDMA and psilocybin (Breeksema et al., 2020; Vollenweider and Preller, 2020) and are being explored once more for ketamine (Chen et al., 2022; Dakwar et al., 2018; Mathai et al., 2020; Rothberg et al., 2021; Sumner et al., 2021). The way that subjective effects are framed—i.e., as potential therapeutic mechanisms vs. adverse events—might affect how patients and providers weigh risks and benefits as part of the shared decision-making process. The treatment frame may also influence how ketamine is delivered, experienced, and perhaps even the degree to which it is efficacious, as has been the case for classic hallucinogens, for which exist guidelines acknowledging the impact of contextual variables on psychological and physical safety (Johnson et al., 2008). Preliminary data on the unique benefits of ketamine when combined with psychotherapy (Dore et al., 2019; Mathai et al., 2022) further suggest the value of a more nuanced therapeutic context than is currently routine.

Professional organizations have signaled the need for careful medical and psychiatric supervision of ketamine use; however, there is no clear consensus on what adequate supervision entails. Clinics participating in this study varied widely in terms of constitution, clinician training, and services provided, with all clinics consisting of a medical prescriber and a slight majority including a mental health clinician. Best practices in these domains have not been defined, and in some cases, may be controversial. For example, insofar as ketamine is being provided off-label for psychiatric treatment, one might argue that a mental health practitioner is best suited to supervise its use in that context. However, use of ketamine or other hallucinogens is not a standard component of psychiatric training, whereas anesthesiologists might be reasonably assumed to have utilized significantly higher, anesthetic doses of ketamine in their training. Relative to an anesthesiologist or an emergency medicine physician, a psychiatrist might be less experienced managing potentially significant medical adverse events, but more experienced assessing and managing acute psychiatric events. Ketamine certification programs appear to be growing and may address unmet training needs, though professional competencies relevant to working with medical hallucinogens are still being defined (Phelps, 2017; Tai et al., 2021). Unlike the case with esketamine, ketamine is not managed by a Risk Evaluation and Mitigation Strategy (REMS) drug safety program, which may decrease administrative burden on healthcare systems (Wilson and Milne, 2011) but could also increase the possibility of risks associated with deregulated prescribing (Ho and Zhang, 2016). These topics warrant careful consideration as part of the broader discussion of best practices involving ketamine.

There are several limitations of this study. Our sample size was small and, though reflective of broad US geographical regions, may be poorly representative of the larger population working with ketamine in a psychiatric context. While response rates to e-mail surveys are known to be low and appear to be decreasing with time (Fincham, 2008), clinics that were contacted in this study could have been reluctant to share documents with legal and professional implications, despite the assurance of anonymity. The ASKP[3] member clinics that elected to participate represent a narrow sampling of community-based settings and are possibly biased toward those with a more deliberate consent process. As such, our findings might underestimate deviations in the field more broadly. Such deviations might range from minor differences in the interpretation of current evidence to egregious medical negligence. It is also possible that our findings underestimate the comprehensiveness of the IC process in the clinics represented here. In clinical medicine, the verbal consent process is essential when initiating pharmacotherapy, but written consent is often not required (Mithani, 2012). Because IC-Docs do not capture verbal consent, they serve at best as an approximation of the provider-patient exchange. Relevant patient education can also occur by use of information leaflets, which are not considered legal documents. As such, it is possible that items marked "missing" or "incomplete" in our assessment of IC-Docs were adequately addressed in other exchanges prior to treatment.

Our initial findings point to several promising avenues for future investigation. First, these analyses should be replicated using data from a larger sample of ketamine providers, drawn from a broader range of healthcare settings, including academic and government-owned practices. The use of more traditional survey methods could facilitate higher response rates, improve external validity, and allow for better characterization of verbal consent procedures not measured here.

Furthermore, while not addressed in this paper, the details of ketamine consent may meaningfully vary as a function of practice characteristics, such as the specialty training of clinical staff, and these relationships could be explored further in a larger study. Another question to examine in future studies is whether variations in consent parameters impact patients' expectations and/or their clinical outcomes. Given the burgeoning interest in psychedelic medicine, it would be of particular interest to determine whether the way that the dissociative/psychedelic effects of ketamine are framed (i.e., as a therapeutic mechanism vs. adverse event) and whether ketamine is provided within a psychedelic-assisted psychotherapy model, is relevant to treatment.

5. Conclusions

As a psychiatric treatment, ketamine may be life-changing for some patients—and in some cases, even lifesaving. However, it is not without the potential for adverse events. As such, patients and providers alike will benefit from shared decision-making prior to the initiation of treatment. This process should begin with a careful discussion of ketamine's potential risks and benefits, informed by scientific, ethical, and pragmatic factors. The variability of written consent identified in this study points to the utility of standardized IC-Docs that could be developed and distributed to ketamine prescribers. The rubric (see Supplement) and findings presented here lay the groundwork for such a document, which may be developed in the future. In the meantime, we hope that ketamine providers will examine their own consent procedures in relation to our rubric, striving for an informed consent process that is as clear, thorough, and substantive as possible.

Contributors

DSM designed the study, wrote the protocol, conducted the primary literature search, supervised the analysis, and was primarily responsible for developing the manuscript. SML assisted with development of the protocol, data collection, and conducted the primary analysis with support from VM. Authors KCO, AGR, and EAS supervised the project and contributed to writing of the manuscript. All authors contributed to and have approved the final versions of the manuscript.

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Appendix A. Supplementary data

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