REVIEW ARTICLE

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Developing an IV Ketamine Clinic for Treatment-Resistant Depression: a Primer

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ABSTRACT: *The efficacy of subanesthetic intravenous ketamine for treatment resistant depression (TRD) has spurred a growth of clinics nationwide that provide this service. Ketamine is an FDA-approved drug as an anesthetic but remains unapproved for psychiatric indications, and this status raises a number of short- and long-term safety and efficacy concerns that need to be addressed when implementing and developing this type of clinic. Using a framework of systems, provider, and patient domains, we provide a review of the key challenges in providing ketamine infusions and suggest potential approaches. Under systems issues, we highlight broad stakeholder engagement involving cross-departmental and multidisciplinary considerations, business case development, and delineation of administrative standard operating procedures. In the provider domain, we highlight specific roles for different treatment team members as well as suggested training requirements.*

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In the patient domain, we identify a variety of standard operating procedures involving initial patient assessment parameters, ketamine dosing and administration guidelines, and safety monitoring procedures. Together, this review provides key considerations for developing a ketamine clinic for depression, in an effort to meet the pressing demand for this novel treatment option while helping to ensure its safe implementation. Psychopharmacology Bulletin. *2021;51(3):109–124.*

Introduction

According to the World Health Organization (WHO), depression is considered the most disabling illness worldwide afflicting an estimated 300 million people.[1] In addition to emotional distress, the symptoms of depression can lead to unemployment, deteriorating health, premature mortality due to medical illnesses, and deaths by suicide.[1] With the COVID-19 pandemic and subsequent economic crisis, the prevalence of depression symptoms in the US is increasing.[2] Although a wide range of treatments exist for depression, many individuals respond poorly—if at all—to multiple therapeutic trials of antidepressants or mood stabilizing medications. While there are various attempts underway to improve and standardize when to apply and discontinue the term "Treatment Resistant Depression," a simple description is that when two or more trials using evidence-based treatments with adequate duration and dose fail to treat depressive symptoms to the point of response, the depressive episode is defined as "treatment resistant depression," or TRD.[3,4] For the purposes of this article, TRD will be defined as an inadequate response (defined as at least a 50% reduction in symptoms) and/or failure to achieve remission of depression after receiving at least two or more antidepressant treatments at adequate doses and duration in the current episode.[5,6] TRD occurs in approximately 30% of individuals diagnosed with depression.[3,7] Rates of treatment resistant depression may be even higher for patients with bipolar I or II disorder.[8]

Ketamine has been approved by the United States Federal Drug Administration (US FDA) for general anesthesia and procedural sedation since the early 1970s; it has been on the WHO's 100 top essential medicines since 1985.[9,10] This can be attributed to its comparative safety amongst other anesthetic agents, as it does not cause bradyapnea or hypotension, and it does not require invasive airway management or cardiocirculatory support.[10,11] It is unlikely that this drug will receive FDA-approval for use as antidepressant or anti-suicide agent, due to its easy availability and low cost as a generic drug do not interest stakeholders that would bring a new drug indication for regulatory approval in the US or abroad. A similar drug, esketamine, has gone through the

standard approval processes, and demonstrated the safety and efficacy in depression.[12] The process for FDA-approval of esketamine has determined that the drug would not be sold directly to patients, but administered by medical personnel within offices, clinics and hospitals with the requirement of a two-hour (or longer, if needed) observation period post administration. A Risk Evaluation and Mitigation Strategy (REMS) was implemented—a drug safety program for medications with potentially serious safety concerns to help ensure the benefits of the medication outweigh its risks. In contrast, the off-label use of ketamine for depression currently lacks official recommendations for monitoring side effects, abuse potential, and diversion; furthermore, there are no clinical guidelines in acute or long-term use. Therefore, the majority of protocols used in everyday clinical practice for IV ketamine administration in depression have been extrapolated from novel research studies, which typically were designed to demonstrate preliminary efficacy data and recruited only small numbers of individuals.

Research on ketamine has shown that single-dose, off-label use of this drug can provide rapid-acting, relief for patients with TRD.[5,13] Traditional antidepressant treatments may take 4–8 weeks or longer to take effect, while a single dose of ketamine can do so in a matter of hours or days.[13,14] A single IV ketamine infusion has limited duration of efficacy, alleviating depressive symptoms anywhere from several days to two weeks.[6,13,14] Since ketamine's short- and long-term effects for this use are still actively being researched, its widespread use as an off-label medication in the outpatient clinical psychiatric settings remains controversial.[15] The lack of validated clinical protocols, expert recommendations, and the variability of administration of this drug in terms of dosing, frequency of treatment, and method of administration may be expected to increase the risk of potentially serious adverse events.[16] Paralleling researcher and clinician enthusiasm for ketamine has been an enormous amount of attention of media outlets and patient advocacy groups, dwelling on ketamine's attractiveness as a "rapidly-acting antidepressant" that may work where other treatments have failed. However, several considerations must be considered to ensure the safety of ketamine-treated patients with TRD, involving a comprehensive planning process to initiate treatment within a ketamine clinic. One framework that encompasses the key considerations in developing an IV ketamine clinic in psychiatry utilizes the perspective of systems, providers, and patients.[17,18] This article will systematically review each of these perspectives to generate recommendations for starting a ketamine clinic for the treatment of TRD and bipolar depression and conclude with directions for future research.

Systems Issues

When a decision to start a ketamine clinic is made by an institution, all interested stakeholders should be included in the decision-making process. A ketamine clinic will usually benefit from the participation of different departments (primarily psychiatry and anesthesia) along with key administrative committees (such as a Pharmacy and Therapeutics or Medical Practice Committee), and also members of relevant professions. In addition to the department of psychiatry, other key clinical stakeholders will include the anesthesiology department, whose practitioners possess particular expertise and often explicit medical authority over the administration of ketamine; the nursing department that can ensure best practices in nursing are followed during the administration and monitoring of ketamine; and finally the billing and financial departments together with the administrators who will determine the appropriate costs, reimbursements, and administrative operations responsible for space and equipment allocations to allow IV ketamine to be administered. All stakeholders will need to be educated on the purpose of the clinic, the needs of the patient, rules and regulations, medical bylaws and policies, as well as staffing and training requirements necessary to safely run the clinic. For administrative purposes, a feasibility review would include assessment of the financial viability of the clinic, particularly since ketamine for TRD is generally not an insured service. For clinical administrative purposes, a series of detailed standard operating procedures (SOPs), aligned with larger institutional clinical practice committees, will need to be developed to clarify hospital-based vs clinic-based service, the roles and training for all staff, the detailed evaluation of the patient, and specific instructions on administration and monitoring of the ketamine infusions. Examples of such policies currently are not published as peer-reviewed articles but are often available on the internet; additionally, a useful document is the consensus statement on ketamine for mood disorders.[6] Such policies have been designed based on the clinical experience of the providers, often inspired by protocols used in research studies, with incorporation of safety monitoring requirements relevant to clinical rather than research settings. Several such policies from the authors' institutions have been consulted in constructing this article, particularly those from the Mayo Clinic and the University of Michigan. Finally, a robust process must be designed for ensuring proper informed consent, with the development of both a sufficiently detailed consent form as well as patient education materials. Each of these steps in preparing to launch a ketamine clinic, from administrative to clinical, is discussed below.

Building a Business Case

Clinicians naturally gravitate to identification and rapid adoption of new treatments, particularly for refractory disorders. However, use of an off-label medication such as IV ketamine in psychiatry requires substantial negotiation and agreement from the fiscal and administrative authorities within the institution. This includes creating an inventory of all types of anticipated expenses, including costs related to staffing, materials, medications, equipment, and the physical space where the IV ketamine will be administered and post-administration monitoring will occur (if done at a separate location). Cost modeling will also need to account for special tests or procedures (such as blood work, electrocardiograms, and possibly cognitive scales). These may also extend to marketing expenses related to the program as well as any expenses related to potential follow-up of patients post completion of the treatment episode. Since off-label treatments are often not reimbursed, exploration of the patient's options for payment are necessary. Typically, both a projection of the number of patients per week or month over 1–2 years will need to be estimated and their potential costs calculated. Taking the revenue projections from the billing for the procedure, a preliminary cost-benefit analysis can be conducted to determine the estimated return-on-investment. While these calculations may be approximate, they are essential to reassure the institution that it is worthwhile to proceed.

TABLE 1

Typical Staff Roles & Responsibilities in Planning and Delivering Ketamine Infusions

Prior to Administration of IV Ketamine	Administration/ Finance	• Identify key stakeholders, space, clinical indications, etc. • Develop budget, billing charges • To obtain institutional approval, meet with psychiatry, nursing, and anesthesia to plan implementation, evaluation metrics, cost-benefit analysis, analysis of gross and net revenue
	Nursing	• Train in IV ketamine administration & ACLS • Prepare patients prior to procedure, including education prior to procedure
	Psychiatry	• Train in IV ketamine administration and monitoring • Develop inclusion/exclusion criteria and identify patient screening procedures • Delineation of informed consent process and forms

(*Continued*)

TABLE 1 (*Continued*)

Typical Staff Roles & Responsibilities in Planning and Delivering Ketamine Infusions

	Anesthesiology	• Collaborate in providing education and training to nurses and psychiatrists in IV ketamine administration and monitoring • Develop monitoring standards, procedures, and discharge criteria
During IV Ketamine Administration	Administrative staff	• Register and admit patient to IV administration space
	Nursing	• Connect patient to IV line, heart rate, blood pressure, pulse oximetry, and cardiac monitors • Provide appropriate monitoring of patient
	Psychiatry	• Assess interim history, perform mental status exam, measure depressive symptoms using a depression scale (e.g., MÅDRS, QIDS-SR 16 etc.) Availability during infusion to intervene in the case of side effects/intolerability, with possible intermittent monitoring during initial infusion • Assess key side effects with scales (e.g. CADSS) and monitor spontaneous side effect reports
	Anesthesiology (optional/ dependent on institutional requirements)	• Screen patient immediately prior to administration
Post IV Ketamine Administration	Shared Responsibilities of Clinicians	• Documentation and oversight of discharging patient from IV administration space to responsible adult and/or inpatient unit
	Nursing	• Disconnect patient from IV line • Monitor vital signs until discharge (30–60 minutes post-infusion)
	Psychiatry	• Timing of assessment depends on local standards of shared clinical responsibilities • Assess patient's psychiatric status, including measurement of depressive symptoms using a depression scale (e.g., MÅDRS, QIDS-SR 16, etc.) • Ask questions pertinent to side effects • Assess cognitive effects
	Anesthesiology (if applicable)	• Document and discharge patient from treatment room once they meet criteria

Provider Concerns

The off-label use of a medication for purposes other than its original intent is permissible under the FDA guidelines contingent upon its having benefit for the patient.[9] Since the intention is to facilitate the provision of IV ketamine within psychiatry, two main clinician groups are critically important—psychiatrists and anesthesiologists. To start, the psychiatrist or other physicians with expertise in behavioral health should perform a thorough psychiatric assessment and be able to prescribe and oversee initial administration of IV ketamine. To aid the process, psychiatrists should develop and standardize procedures and metrics to properly identify those patients deemed appropriate candidates to receive ketamine treatments, assess the effects of ketamine, and collect long-term data to help inform evidence-based practices of delivering this medication in the clinical setting. These data are required for both for outpatient and inpatient populations. Psychiatrists will need to be trained in the pharmacology of ketamine as they would be for any new medication; but in addition, they will need special training to deal with any potential complications. Managing the potential side-effects will mean that the psychiatrist must be comfortable treating common problems such as an elevated heart rate, elevated blood pressure, and the psychiatric side effects of ketamine, particularly negative experiences including hallucination, nightmares, and dissociation; ideally, there should be a mechanism for rapidly accessing advice from anesthesia for urgent situations. Standardized metrics should also be used at intervals to monitor symptoms and side effects through the course of multiple ketamine infusions, as discussed later. While the use of IV ketamine in TRD remains off-label, substantial research, clinical experience, and expert recommendations provide significant guidance and reassurance. Emerging data shows potential benefit of IV ketamine for other major psychiatric indications such as obsessive compulsive disorder, post-traumatic stress disorder, and even substance use disorder, where both research and experience are slim, so the psychiatrist must be able to carefully document symptom severity, functional impairment, and lack of response to approved treatments, in order to adequately demonstrate proper risk-benefit evaluation in newer indications which will also be "off-label".[19–21] In some settings, advanced practice nurses or nurse practitioners may serve as the prescribing ketamine clinician, and so will need the same training as prescribing physicians.

Nurses administering IV ketamine will also need to be familiar with the basic pharmacology of ketamine and fluent in the use of IV infusion pumps that are used to administer IV ketamine over the 40-minutes

infusion. Since many psychiatric units have nurses who do not routinely administer IV medication, training will be necessary in IV ketamine administration, safety provisions and monitoring of controlled substances consistent with institutional requirements. Finally, in the setting where IV ketamine is administered, there should be the ability to provide resuscitation; at least one of the treating providers should be certified in Advanced Cardiac Life Support, or there should be immediate access to such expertise. In institutions offering electroconvulsive therapy (ECT), the ECT suite is an ideal treatment setting for ketamine administration.

Anesthesia Support. Given that ketamine has traditionally been used for general anesthesia, procedural sedation, acute and chronic pain management, anesthesiologists are most familiar with its use. Ketamine for the treatment of TRD is used at sub-anesthetic doses (typically infused at 0.5 mg/kg over 40 minutes). While this is a different regimen than what is typically employed by anesthesiologists, they can provide expertise regarding appropriate use of low dose ketamine administration in psychiatric settings. Frequent and repeated administration of ketamine may affect heart rate and blood pressure, and can cause liver injury and urological toxicity.[10,11,22,23] Therefore, safety procedures and guidelines for monitoring and intervention in case of adverse effects should be developed and executed in collaboration with anesthesiology. Standardized data collection with validated measures should also be launched to determine consequences of longer-term ketamine administration.

Patient Issues

Initial Patient Assessment

Ongoing research on the safety and efficacy of ketamine used as an antidepressant is critical. Long-term use of ketamine has not been well described in the literature. It is important that clinical practice does not outpace the understanding of the use of IV ketamine for the treatment of depression. Therefore, FDA approved treatments, ideally following current and academically documented treatment guidelines, such as those published by the Canadian Network for Mood and Anxiety Treatments (CANMAT) group should still be considered as first-line prior to the use of ketamine for the treatment of TRD.[24]

For patient selection, an Assessment Standard Operating Procedures (SOP) form should specify procedures and recommended instruments for a full psychiatric evaluation, as well as a time frame for completing the assessment prior to administration of ketamine (e.g., no more than 30 days prior to ketamine initiation). Such a comprehensive diagnostic

TABLE 2

Common Procedures and Scales for Evaluating and Monitoring Patients for Ketamine Infusions

Procedures	CMP & CBC	• Comprehensive metabolic panel & complete blood count prior to receiving ketamine infusions to assess for any abnormalities requiring further investigation
	Drug Screen	• Multi-drug screen test prior to infusions to assess for use of any non-prescribed medications or illicit substances and assess possibility of misuse
	Pregnancy Screen	• Pregnancy test once a week during infusions and prior to initial infusion due to risks of ketamine to fetus
Assessments & Scales	Depression Symptoms	• Montgomery-Åsberg Depression Rating Scale (MADRS) • The Quick Inventory of Depressive Symptomatology (QIDS-SR 16) • Patient Health Questionnaire 9-item (PHQ-9) • Hamilton Depression Rating Scale (HAM-D)
	Suicidality	• Columbia Suicide Severity Rating Scale (C-SSRS) • Beck Scale for Suicide Ideation (BSS)
	Cognition	• Consider Repeatable Battery for Assessment of Neuropsychological Status (RBANS), or similar
	Physical Status	• American Society of Anesthesia ASA Physical Status Classification System at baseline
	Dissociation	• Clinician-Administered Dissociative States Scale (CADSS), or possibly by overall side effect scale
	Overall Side Effects Scale	• Ketamine Side Effects Tool (KSET)

assessment would document clinical features and severity, treatment history (including past treatment failures), medical history, and substance use history. Most commonly, a clinician-administered depression scale such as the Montgomery-Åsberg Depression Rating Scale will be administered as the principal intake and outcome measure, along with scales for suicidality, side effects, and cognition.[25] Physical examination including body weight for dosing and particularly for confirming stable vital signs such as blood pressure and heart rate are crucial, since the principal side effects and contraindications of ketamine relate to its potential cardiac effects. It may be useful to use the American Society of Anesthesiologists Classification (ASA Class) system to identify which patients may need a formal anesthesia consult, typically those in category ASA 3 or higher having moderate to severe medical disease.[26] Examples of moderate to severe medical disease would include poorly controlled diabetes mellitus or hypertension, COPD, morbid obesity

(BMI≥40), active hepatitis, implanted pacemaker, moderate reduction of ejection fraction, patients undergoing renal dialysis, and recent myocardial infarction, TIA, or stroke. Furthermore, patients receiving ongoing ketamine infusions should have a review of any new health problems and physical symptoms prior to each subsequent infusion. Key laboratory studies should be components for medical clearance, including a CBC, basic metabolic profile, liver function tests, TSH, and an electrocardiogram. Additional laboratory tests worth considering include assessments of Vitamin D, Folate, and driven by recent findings, a battery of inflammatory cytokines, since these have been associated with unresponsive depression.[1,27,28]

Clear intake criteria, typically treatment refractory non-psychotic unipolar or bipolar depression, along with consideration of other emerging psychiatric indications where there is evidence for efficacy of subanesthetic IV ketamine, such as suicidality, must be identified. Key exclusionary criteria would include large vessel aneurysms at risk for rupture due to a potential spike in blood pressure, the presence of any psychotic symptoms, insufficient cognitive ability to fully appraise the benefits and risks of the treatment and the presence of active substance use disorder may be considered.

Medication reconciliation and clear documentation of currently prescribed drugs and dosage will be important to assess to rule-out potential drug-drug interactions with ketamine. Key issues include certain types of polypharmacy (e.g., high doses of sedatives at night, stimulants in AM), risk of cumulative side effect burden with ketamine, with particular concern about benzodiazepine daily use.[29,30] A discussion of the risks, benefits, alternatives and obtaining informed consent is also imperative. The informed consent process should emphasize that long term effects of repeated ketamine infusions are not well researched, and thus should specify rare but potentially serious sequelae, such as bladder injury or cognitive impairment.[22,31]

Ketamine Administration

The SOP would need to address the standard practices for starting medication as well as stopping ketamine due to treatment emergent complications (see Table 3), or lack of benefit. Research has identified that the appropriate dose for IV ketamine for depression should begin at 0.5 mg per kilogram given slowly over a 40-minute interval. Customary clinical practice also involves both slowing or accelerating the rate of infusion based on side effects or other clinical concerns. In addition, for safety reasons in individuals with high BMI, it has been suggested to dose using calculated ideal body weight. One clinical

TABLE 3

Common Side Effects & Recommended Management Strategies for IV Ketamine

Medications for nausea & vomiting	• Ondansetron prior to infusion/in PACU/ Recovery • IV dexamethasone at the start of treatment in situations where patient previously had severe nausea from a ketamine infusion • Scopolamine patch (placed behind the ears) if the other options fail
Medication for headaches	• PO or IV acetaminophen • IV or PO ketorolac 30 mg
Other potential side effects that may arise & may require clinician intervention	• Significant tachycardia (Consider slowing infusion) • Significant hypertension (consider beta blockers or slow infusion) • Increased salivation • Agitation, hallucinations, nightmares

suggestion would therefore be to limit the initial dose of IV ketamine to 50 mg for the first infusion, with cautious increase in dosing based on refractoriness of response and safety for subsequent infusions, with perhaps 100 mg as an upper limit. In clinical practice, ketamine dosing is increased if lack of clinical benefit is found. An approach used in clinical practice based on limited research evidence suggests that after three infusions, the dose may be increased in the case of an inadequate treatment response. Dose titration should be directed to target antidepressant efficacy (not just the reported psychotomimetic experience during the infusion). With each dose increase, additional attention to tolerability is necessary, with a focus on dissociation, vital sign stability, and sedation. One frequent clinical approach includes increasing the dose to 0.6–0.8 mg per kilogram or directly to 1.0 milligrams per kilogram while taking care not to exceed 100 mg per infusion. In addition to specific dosing standard operating procedures, each clinic will need to establish the appropriate frequency and timing of administration of IV ketamine. Common practice is to administer the IV ketamine twice or thrice weekly, with no clear superiority between the two different frequency recommendations.[32] No research-based consensus on what constitutes an adequate trial of ketamine for TRD has emerged. By common clinical experience, up to six infusions given over 2–3 weeks probably constitutes a reasonable therapeutic trial.

Different clinical settings will mandate different levels of psychiatric and nursing involvement in the administration of intravenous ketamine. One suggestion would require that a psychiatrist be present at the

initiation of the first infusion and be immediately available during the administration of subsequent infusions. A nurse should be available for close monitoring of the patient during the infusion, with an appropriate nurse-patient staffing ratio that would allow for immediate attention if needed. New patients usually require more focused attention than patients who have been receiving ketamine infusions for longer periods, as the infusions tend to have similar side effects in the same patient. Specifically, vital signs including blood pressure, heart rate, and oxygen saturation should be monitored closely during ketamine administration and every 15 minutes for a minimum of one hour after the completion of the infusion. A specific SOP should be established for notification of the physician, and potential slowing or stopping the ketamine when the blood pressure is 20% above the patient's baseline, or reaches either 160 systolic or 100 diastolic. Additional stop criteria may include, but are not limited to, symptoms of hypertensive urgency; presence of shortness of breath, pallor, cyanosis, chest/jaw/arm pain; and the patient's desire to stop. Often the rate of ketamine infusion can be slowed or temporarily stopped to resolve elevated blood pressure. However, additional criteria should be established for what medication may be administered in case of hypertensive crisis or with evidence of complications from the elevated blood pressure or heart rate. Criteria for administration of lorazepam to treat anxiety or unpleasant dissociative states should be delineated (usually 0.5 mg IV as needed, monitoring for sedation). Prior to discharge, the patient must have returned to a stable medical and psychiatric status. In view of the psychotomimetic and cognitive effects of ketamine, patients must leave the ketamine clinic accompanied by someone else with standard instructions not to drive or operate equipment or heavy machinery for the rest of the day.

Protocols incorporating limited evidence for research together with clinical experience need to be integrated to establish parameters for follow-up treatment protocols. Such protocols would typically establish frequency of future ketamine administrations, identification of who is the primary treating clinician, and the creation of strategies for medication during the maintenance phase for ketamine responders, as summarized by Bobo and colleagues.[33] Typically, the patient will return to the referring psychiatrist, who will collaborate with the patient in making final maintenance treatment plans.

Evolving Issues

While numerous studies have established the efficacy of acute IV ketamine treatment for severe TRD, the long-term (maintenance)

efficacy and adverse effect profiles of IV ketamine for this indication are unknown. Common clinical practice dictates that some patients continue to follow a maintenance strategy with repeated ketamine infusions occurring less-frequently than for acute treatment, an approach that mimics the practice of maintenance ECT following a positive acute treatment response. It is also unknown whether the dose of IV ketamine will need adjustment over time.

We recommend, therefore, that each institution create a ketamine registry in order to track long-term benefits and adverse effects associated with this treatment. Ideally, there would be agreement among institutions on a core of common data collection, such as those established recently by the National Network of Depression Centers (NNDC) as part of an NIMH grant to study the genetics of ECT.[34] Based on the rapidly evolving evidence for acute IV ketamine and the slowly accumulating evidence for ongoing IV ketamine treatment, it is reasonable for institutions to provide advocacy to insurers for the provision of IV ketamine. An additional key resource for planning a ketamine clinic is the recent statement from CANMAT.[35] Finally, an ideal solution to the many challenges of IV ketamine treatment would be the development of specific biomarkers which could both help identify appropriate candidates for IV ketamine treatment as well as to predict response and ongoing benefit. Our Bio-K study (ClinicalTrials.gov Identifier: NCT03156504), among others, have conducted emerging research on the appropriate role for biomarkers in the management of IV ketamine administration. Preliminary results from this study are anticipated in early 2021.[36]

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