Outpatient Use of Ketamine for Mental Health Conditions

Practice Standards Recommendations

Ketamine Assisted Therapy Association of Canada

Version 1: September 23, 2020
Revised, Version 2: December 20, 2021
Revised, Version 3: October 10, 2022
Revised, Version 4: December 6, 2023
In collaboration with Ontario Medical Association (OMA) Psychedelic Medicine Medical Interest Group

KATA Authors: Dr. Neil Hanon, Dr. Anthony Barale, Dr. Ian Mitchell, Dr. Sukh Dhiman, Dr. Joel Kailia, Madison Nobbs RN
Reviewers: Lynn Pollock, Dr. Chris Spooner, Dr. Matt Halstead, Dr. Rielle Capler, Melissa Mazereeuw RN

OMA Psychedelic Medicine MIG Contributors: Dr. Jinous Hamidi, Dr. Emma Hapke, Dr. Sean O'Sullivan, Dr. Ryan Marble, Dr. Mark Cornfield, Dr. Adam Blackman (Chair)

CONTENTS:

Preamble
Discussion and Recommendations
  Introduction to Ketamine-Assisted Therapy
Ketamine Introduction, Pharmacology & Pharmacokinetics
Summary Guidance on Ketamine's Off-label Use in Mental Health Conditions
Patient Selection and Screening
  Medical Considerations
  Psychological/Psychiatric Considerations
Off-Label Use and Informed Consent
Patient Care and Monitoring
Staffing and Session Requirements
Emergency Management
Prescriber Competencies and Training
Medication Management and Administration
Additional Recommendations:
Summary of the Evidence
Appendix A: College of Physicians and Surgeons Regulatory References
Appendix B: Ketamine Pharmacokinetics by Route of Administration
Appendix C: Summary of Contraindications and Exclusion Criteria Used in Clinical Trials
Appendix D: American Stroke Association (ASA): Physical Status Classification System
Appendix E: Metabolic Equivalents (METS) Classifications
Appendix F: Blood Pressure Considerations
Appendix G: Side Effects and Adverse Events Reported in the Evidence
Appendix H: Ketamine and the Paucity of Apnea
Appendix I: Training Requirements

Preamble

Disturbances of mental health exert a profound toll on populations world wide, and Canada is no exception. In one study, the lifetime prevalence rate of depression in Canada was 11.5% (Knoll A. D., 2017).

Problematically, the mainstay of treatment, the serotonin, norepinephrine, and dopamine reuptake inhibitors, exhibit a significantly delayed onset of action, weeks and sometimes months, - which is not helpful for patients in crisis, who may be suicidal (Witt et al., 2020).

Ketamine, historically known as a non-sedating dissociative anesthetic, has recently been re-purposed and reprofiled as an antidepressant medicine with rapid and robust anti-depressant attributes, and may offer a readily available treatment option in both acute and chronic conditions and situations.

Within an appropriate dosage range, ketamine, in its role as a safe and rapid-acting antidepressant (RAAD), can be administered in community settings, intramuscularly (IM), intranasally (IN), sublingually (SL), subcutaneously (SQ) and orally (PO), to manage treatment-resistant depression (McIntyre et al., 2020, Loo et al. 2023), depression with suicidality (Grunebaum et al., 2018; Thomas et al., 2018), bipolar depression (Kryst et al., 2020), and potentially, post-traumatic stress disorder (Feder et al., 2021) and substance use disorders (Dakwar, 2020).

In recent years, several jurisdictions have issued guidelines for such use. For example, in August, 2021, the College of Physicians and Surgeons of British Columbia, (CPSBC), released an Interim Guidance document on the use of non-intravenous Ketamine in the community setting. This document clarifies that intramuscular ketamine in appropriate, sub-anesthetic doses, can be appropriately administered in community settings if prescribers have the knowledge, skill, and judgment to do so safely and effectively, have appropriate training and competence, and have immediate access to equipment used to manage adverse events.

These current updated practice standards recommendations were co-developed with the Ontario Medical Association's Psychedelic Medicine Medical Interest Group (MIG), in collaboration with the Ketamine Assisted Therapy Association of Canada (KATA), from whose comprehensive document much of this material originated.

KATA is a not-for-profit interdisciplinary organization originating in British Columbia. Its physician members have diverse backgrounds in emergency, family medicine, psychiatry, anesthesia, and other specializations, and many have extensive experience administering non-intravenous sub-anesthetic ketamine in outpatient settings. KATA's Policy Working Group has recruited physician and non-physician health-care professionals, researchers, and policy makers to compile evidence and develop recommendations to the College of Physicians and Surgeons of British Columbia (CPSBC) for the community use of ketamine for mental health conditions.

Additional guidance documents have been developed by the College of Physicians and Surgeons of Alberta (CPSA) and College of Physicians and Surgeons of Saskatchewan (CPSS). These resources provide guidance addressing patient safety in the delivery of ketamine. (See Appendix A for College of Physicians and Surgeons resources that were reviewed while writing these recommendations.)

Although much of the data on the effectiveness of ketamine in mental health has been based on studies utilizing intravenous infusions, KATA, the OMA psychedelic MIG and these practice standards advocate for non-intravenous administration of sub-anesthetic ketamine as a way of increasing patient access by reducing the level of health-care resources required to monitor patients when compared to intravenous administration, as well as other treatments such as electroconvulsive therapy (ECT). Evidence is mounting that non-intravenous ketamine is safe and effective (Dore, 2019). A recent study found ketamine "not inferior to" ECT for treatment resistant depression (Anand, 2023). We advocate for its use as an alternative or adjunct to current pharmacologic and non-pharmacologic standards of care for moderate to severe mood disorders as well as an additional therapeutic modality for treatment-resistant cases amongst a number of evolving diagnoses.

Our hope is that these practice standards recommendations, presented here, will facilitate physicians, prescribers, and other health-care professionals, to review and update their policies and procedures in order to provide ketamine treatment to patients in a safe and effective manner in a community setting.

These practice standards recommendations are intended to support safety, appropriateness, quality, and consistency of patient care; they are not meant to replace the professional clinical judgment of physicians, prescribers and other health-care professionals, but rather incorporate current evidence, consensus-based practices, and appropriate off-label clinical information into a safe, reasonable, and acceptable framework for patient care that promotes the best possible outcomes.

The decision to recommend ketamine should ideally involve multidisciplinary input to evaluate the indications for treatment and to both define and determine the most effective pharmacological and non-pharmacological interventions, management strategies, and both current and future primary treatment goals. Teams of health-care professionals involved in delivering ketamine must ensure commitment, organization, leadership, appropriate personnel, and physical resources to provide optimal care.

Discussion and Recommendations

Introduction to Ketamine-Assisted Therapy

Ketamine-assisted therapy (KAT) is defined as the combination of the administration of ketamine with psychotherapy typically done **before, during** and **after** the session. Ketamine

has been used as an adjunct to psychotherapy since the 1970s (Clark, 1977). It was initially employed as a tool for shortening the time involved in psychoanalysis. In a study by Wilkinson et al., it was found that concurrent CBT prolonged the therapeutic effects of ketamine for the treatment of mood disorders (Wilkinson et al., 2018). Furthermore, there is an ever growing list of therapies that work alongside of KAT including dialectical behavioral therapy, interpersonal therapy, insight-oriented psychotherapy, and somatically-focused therapies (Dore et al., 2019), transpersonal therapy, (Grof et al., 1973) Somatic Experiencing, and Internal Family Systems (Bathje et al., 2022; Morgan et al., 2020).

The delivery of KAT produces a non-ordinary state of consciousness which is a phenomenon well documented and is understood through a multitude of lenses. Clinical studies have employed a variety of psychotherapeutic models utilizing common factors such as a non-directed, person centered supportive approach as well as applying more specific evidence based psychotherapies such as Cognitive Behavioural Therapy, and Acceptance and Commitment Therapy (Brennan & Belser, 2022; Mathai et al. 2022). In addition to the more standard cognitive-affective and relational approaches employed in therapy working with ordinary states of consciousness, it has been suggested that the clinician have comfort in other therapeutic areas such as existential-spiritual, mindfulness, and somatic awareness (Brennan & Belser 2022; Grof et al., 1973).

The planning and delivery of KAT requires special attention to the dose, route of administration, and support for the patient throughout the treatment process. These and additional considerations, which are discussed throughout this document, are essential to optimize the efficacy of KAT and its duration (Schenberg et al., 2018). The care setting is also important for the outcome of the therapy, and it is accepted that KAT, in general, requires a quiet, calm and low stimulation environment.

Ketamine causes dissociation through complex neurochemical actions that are not yet well understood. The role and utility of dissociation as a marker of therapeutic response is still debated in the field (Mathia et al., 2023) however, some studies suggest the dissociative aspect of ketamine may be required for its therapeutic effect (Ballard & Zarate, 2020). According to Dore et al., dissociation is therapeutic because it allows a "time-out" from ordinary, usual mind, relief from negativity, and an "openness" to new ways of thinking and behaving (Dore et al., 2019). **Due to the unique dissociative effects of ketamine, it is our recommendation that clinicians receive appropriate training and education on how to care for patients in a way that maintains the patients' safety from a medical perspective as well as the patients' psychological safety**. See below for further recommendations on appropriate Prescriber Competencies and Training as well as discussion on dissociation in the Side Effects and Adverse Events section.

Ketamine Introduction, Pharmacology & Pharmacokinetics

Ketamine was developed as CI-581 in 1962, a molecule with similar dissociative anesthetic properties to phencyclidine but with an improved side effect profile and much shorter half-life (Domino et al., 1965). It was first tested on inmates and then on soldiers on the battlefield during the Vietnam War. Evidence for its safety accumulated, and it was noted to produce analgesia and anesthesia *without*

respiratory depression. It is important to note that, in contrast to all other anesthetics, ketamine is not a sedative (as sedatives lower blood pressure, reduce heart rate, depress respiration and suppress the gag reflex) but rather ketamine is a stimulant which transiently elevates blood pressure and increases heart rate without depressing respiration or suppressing the gag reflex. These features contribute to ketamine's remarkable safety profile in comparison to other anesthetics.
In 2000, Berman published the first study about the use of ketamine infusions to treat patients with Major Depressive Disorder (MDD). Since then, many studies have been done that help us understand pharmacodynamics of ketamine and its usefulness in mental health conditions. There is ongoing research to clarify which patients are most likely to benefit from treatment. Similarly, there are ongoing studies examining methods to mitigate risks as well as methods to prolong treatment benefit.

As a racemic mixture of (R) and (S) enantiomers, ketamine has been available in Canada since 1972 (Government of Canada, 2021), mainly for its anesthetic qualities in the operating room and for procedural sedation in the emergency department. In 2020, Janssen Pharmaceuticals released a proprietary intranasal (S)-ketamine (esketamine) preparation that they named SPRAVATO®. There remains debate in the literature as to the similarities and differences of racemic and esketamine. A recent study concluded that "the ideal ketamine preparation used to treat TRD (treatment resistant depression) should include (R)-ketamine" (Passie et al., 2021). Additionally, a more recent study documents that racemic ketamine produces superior results compared to esketamine (SPRAVATO®) "Ketamine for the treatment of major depression: a systematic review and meta-analysis" (Nikolin et al., 2023). A majority of the data we have on the efficacy, safety, and effects has been with racemic ketamine.

The mechanism by which ketamine exerts its RAAD effects is the subject of much debate and research and a brief summary is as follows; ketamine releases glutamate in the central nervous system by binding to the NMDA-receptors of inhibitory, GABAergic interneurons (Matveychuk et al., 2020). The disinhibition of these inhibitory interneurons, leads to a glutamate surge in many brain areas including the prefrontal cortex (decision making), hippocampus (memory), and cingulate gyrus (attention) (Wei et al., 2020; Evans et al., 2018; Matveychuk et al., 2020; Moda-Sava et al., 2019).

AMPA receptors are also activated in the cascade, which in turn release BDNF and mTOR (Nowacka & Borczyk, 2019), chemicals that are involved in the neuroplasticity and anti-inflammatory effects of ketamine (Mihaljecić et al., 2020). Ketamine also binds to mu, delta, and kappa opioid receptors as well as monoaminergic, muscarinic, and nicotinic receptors (Matveychuk et al., 2020, Zanos et al., 2018). The unique neurochemistry of ketamine allows it to rapidly interrupt ingrained negative neural pathways, giving the patient a brief respite from their symptoms which can be the first step towards remission (Stippl et al., 2021).

Ketamine induced changes on brain wave activity have been measured using an electroencephalogram (EEG) showing a reduction in alpha waves and an increase in theta waves which has been shown to improve sleep patterns. (Matveychuk et al., 2020; Mihaljecić et al., 2020). As theta wave activity increases, patients enter a state of dissociation with interruption in the

connections between the thalamocortical and limbic regions of the brain.

Ketamine can be administered to patients via the intravenous (IV), intramuscular (IM), intranasal (IN), sublingual (SL), subcutaneous (SC), rectal, and topical routes. In this document we will mostly be discussing IM, SL and IN routes of administration but will often reference IV as this is currently the most researched route. Peak plasma concentrations occur within one minute (IV), five minutes (IM), and fifteen minutes (IN) and thirty to forty-five minutes (SL) after administration (Mihaljecić et al., 2020)(See Appendix B).

Ketamine has a high rate of clearance through the liver using the P450 enzyme pathways, giving it a relatively short half-life of two to three hours (Zanos et al., 2018). Demethylation by these enzymes converts ketamine to norketamine which is one fifth to one third as potent (Mihaljecić et al., 2020). Norketmine may contribute to the prolonged effects of ketamine especially with repeated treatments as its half life is approximately 100 hours

The pharmacokinetics of ketamine for the use of mental health conditions can be extrapolated from data on its use in chronic pain, anesthesia, and emergency medicine (Ketha et al., 2019; Shimonovich et al., 2016; Peltoniemi et al., 2016; Par Pharmaceutical, n.d., Nowacka & Borczyk, 2019). The table in Appendix B summarizes this data. Where research data was not available (e.g., dosing of racemic IN and PO ketamine), we included evidence from clinical experience.

Summary Guidance on Ketamine's Off-label Use in Mental Health Conditions

Off-label prescribing is not a new phenomenon. In North America, off label prescribing is common and has often been associated with new and innovative/re-profiling uses for medications that are currently licensed by Health Canada (Senate Committee, 2014).

There is existing and emerging evidence for the use of ketamine in the treatment of mental health conditions–specifically MDD and TRD. The data exists in the form of randomized controlled trials (RCT), existing hospital protocols, and observational studies. This is in contrast to typical "off-label" prescribing of other medications, for which data from the Senate Committee of Social Affairs, Science and Technology indicates that 79% of off-label prescriptions do not have even one RCT to support their use. This study also found that off-label prescribing was as high as 26% for central nervous system drugs, 67% for anticonvulsants, 44% for antipsychotics and 33% for antidepressants. It should be noted that the use of racemic ketamine in the management of pain is also an "off-label" prescribing practice as ketamine has only been approved by Health Canada for use as an anesthetic. [1]

[1] [1] Senate Committee on Social Affairs, Science and Technology (2014) "Prescription Pharmaceutical in Canada Off-Label Use"

(S-Ketamine (Spravato), the enantomeric form of ketamine has however been approved by Health Canada for treatment of Major Depressive Disorder).

Additional off-label therapeutic uses for racemic ketamine include post-traumatic stress disorder (PTSD), suicidal ideation (SI), anxiety disorders and substance use disorders (SUD) (e.g., alcohol, cocaine and opioids). Despite positive outcomes for these frequently treatment-resistant conditions, there is limited published evidence for these specific indications (Feder et al., 2021; Dore et al., 2019; Dakwar et al., 2018; Witt et al., 2020).

The Senate Committee suggests collecting data and reporting adverse drug effects when prescribing a medication off-label. We believe that this is reasonable and may be beneficial as it encourages appropriate monitoring and pharmacovigilance (i.e., safety and efficacy) in determining whether off-label therapy should be continued or discontinued based on each individual patient's response.

Patient Selection and Screening

It is important that proper patient screening be conducted to ensure the benefits of prescribing ketamine outweigh the risks, both medically and psychologically. The prescribing physician shall evaluate and assess patients for suitability. Additionally, a psychological and/or psychiatric assessment is recommended to ensure that ketamine therapy is appropriate for the patient. If the prescriber does not have a longitudinal relationship with the patient it is often beneficial that patients be screened and assessed by several healthcare professionals when appropriate as per the knowledge and skill set of the clinicians involved (e.g., general practitioner, psychiatrist, psychologist, specialist, registered nurse, registered therapeutic counsellor, registered clinical counsellor) and that old records are requested and examined, in order to obtain a deeper sense of understanding of the patient. Finally, all patients must have a level of comprehension and capacity to understand the benefits and risks of ketamine as a part of the detailed informed consent process for receiving off-label medications.

We recommend that at minimum there is a medical assessment and clearance for psychological and physical suitability which includes a comprehensive mental health review. In cases where significant trauma is involved we recommend an assessment by a psychiatrist or practitioner who is well versed in the assessment of mental health conditions. It is also recommended that the patient have a pre-established connection with a trauma informed therapist which can be relied upon post treatment.

The majority of research relating to the use of sub-anesthetic ketamine in psychological/psychiatric disorders has been in patients with TRD, arising out of either unipolar or bipolar depression (Sanacora et al., 2017). Definitions of TRD vary considerably across the world. Also, the majority of patients with depression have another concurrent disorder, most commonly an anxiety disorder,

followed by SUDs, obsessive compulsive disorder (OCD), and PTSD. With this in mind, it would be highly restrictive to consider ketamine only in treatment-resistant unipolar depression. There is a need to consider each patient as a unique individual with a constellation of predisposing, precipitating and perpetuating factors leading to their distress and struggles with mood regulation and functioning. The presence of concurrent disorders does not, in and of itself, preclude treatment of such patients with ketamine. However we do not consider use of ketamine as first line treatment and there should be previous reasonable trials of psychotherapeutic and/or pharmacological treatments.

The patient should be thoroughly apprised of their treatment options for their disorder(s). Such additional non-pharmacological and non-psychotherapeutic options include ECT or transcranial magnetic stimulation, if appropriate. In all cases, the patient should be informed that there will be a requirement for a non-pharmacological treatment regimen in parallel with ketamine treatment. Most typically, this would be in the form of a psychotherapy modality which is of particular importance in patients with personality disorders (especially borderline personality disorder). It has been the clinical experience of KATA's physician members that in such patients, the etiology of their struggles with mood regulation and functioning is frequently found in childhood or adolescent trauma with ensuing elements of PTSD. It is our recommendation that patients who have not exhibited adequate response to ketamine as a stand-alone therapy should be considered for adjunctive psychotherapy with ketamine treatment. In patients with trauma and Borderline Personality Disorder (BPD), ketamine should only be offered in a therapeutic envelope (i.e. when there is an established therapeutic alliance in an ongoing psychotherapy practice).

Appropriate patient selection and screening is of utmost importance in ensuring the safety of KAT. Prescribers should always use their clinical judgment and seek expert consultation when needed. Contraindications that would exclude one's eligibility for ketamine therapy have been outlined below as well as cautionary conditions. Please see Appendix C for background and a summary of contraindications and exclusion criteria used in clinical trials.

It is our recommendation that appropriate patients for KAT should meet all of the following criteria:

- Be of age 18 years or older
    - If the patient is under 18 years of age, they may be considered as a candidate using clinical judgment; taking into account past medical history, treatments and consultation with the primary care team. If the patient is a minor, the parents or guardians should be consulted
- Have participated in a comprehensive or enhanced informed consent process for the off-label therapy - see section on Off Label Use and Informed Consent
- Not be put at greater risk than comparable standard interventions or than the absence of treatment to the best of the available knowledge given the novel nature of this treatment modality
- Be capable of participating in ongoing treatment as needed
- Have adequate existing or arranged supports to ensure safety during the treatment process including safe transportation and access to emergency therapeutic support
- In patients with trauma and personality disorders, have a pre-established therapeutic

envelope

Medical Considerations

- Contraindications:
  - Patients presenting to the clinic intoxicated
  - ASA ≥3 (American Society of Anesthesiologists-Appendix D) are generally better suited for treatment in a setting with enhanced continuous monitoring, IV access and advanced resuscitative equipment.[2] There may be some exceptions made to this under the direction of the supervising physician including those with alcohol dependence or other SUDs with no other acute comorbidities.

- Caution should be taken with:
  - BMI ≥40
  - Obstructive sleep apnea
  - ASA 2 patients are suggested to have enhanced monitoring of vitals and oximetry- (see section on Patient Care and Monitoring for further details)
  - Metabolic Equivalents Classification (METS) Classifications <4 (see Appendix E - patients should have the cardiac fitness to perform light housework)
  - Patients who are otherwise cardiac or respiratory limited, should be considered for a cardiac stress test and/or a cardiological consultation when feasible, to establish suitability and safety
  - Women of reproductive age. Consider a pregnancy test on the morning of the session. Women who are breastfeeding, could consider holding feeds for up to 12 hours post-dosing session.

[2] American Psychiatric Association (APA). 2015. “APA Commentary on Ethics in Practice. The use of the American Society of Anesthesiologists scale throughout this document is intended to be used as a guideline and the decision to pursue treatment with ketamine is up to the clinical discretion of the treating physician. There are some comorbidities that are generally not impacted by the administration of ketamine at sub-anesthetic doses, such as alcohol dependence or the presence of a pacemaker.

Psychological/Psychiatric Considerations

KAT has a lot of variance in the model of delivery, and the compilation of health-care professionals involved in its delivery. In the process of patient selection and screening it is important to consider factors related to the setting for the therapy and the competence and training of the health-care professionals delivering the therapy to ensure patient safety and the best possible outcomes.

These considerations are inclusive of the therapeutic context and setting in which the ketamine is administered:

- Contraindications:
    - Current psychotic or manic episode
    - Primary psychotic illness such as schizophrenia (although data may be emerging in this field and may be re-examined in the future).

- Caution should be taken with:
    - History of psychosis – The referring or treating clinician should have a longitudinal psychiatric care relationship with the patient
    - Suicidality
        - If suicide is considered an imminent high risk, such a patient should be treated in an in-hospital setting
    - Significant confounding psychiatric and/or psychosocial factors, e.g., suspected somatoform pain disorder, severe and untreated personality disorders, other severe untreated co-morbid psychiatric disorders (especially when the patient is unwilling to engage in psychological therapies), acute psychosocial stressors – It is recommended that KAT for these conditions be delivered in a therapeutic envelope.
    - Active substance use/dependence – Special consideration needs to be taken into account with recent substance use
        - In those cases consultation with a clinician with expertise in substance use disorders may be useful, as well as a consideration for drug urine testing ahead of treatment.

Off-Label Use and Informed Consent

The use of ketamine for mental health issues is considered to be off-label other than the use of intranasal Spravato® which has been approved by Health Canada for TRD via their Janssen Journey program. Prescribers must be aware of and comply with the College's relevant practice standards including Charging for Uninsured Services, Complementary and Alternative Therapies, Conflict of Interest, and Sale and Dispensing of Drugs.

Ketamine is one of many medications that are frequently prescribed for off-label use. Prescribers of

ketamine must be aware of and comply with the College's relevant practice standards which is not limited to but includes the Complementary and Alternative Therapies Practice Standard (CATPS) in BC and the Complementary and Alternative Medicine Policy (CPSO) in Ontario

> "As with any therapeutic intervention, informed consent is paramount. It is expected that patients be fully informed of the risks, benefits (and unknown nature of the risks and benefits) of any off-label treatments. Particular attention should be paid to informed consent in the off-label use of ketamine, and the details of such discussions should be available in the patient's medical record."

Informed consent should include the following *minimal* requirements:

- Ketamine is a legal drug but used "off label" (explain this term)
- Potential side effects/risks (both transient and long-term) and benefits
- Indications and contraindications
- Alternative treatment choices
- Qualifications of providers
- Preparation for possible dissociative/non-ordinary state of consciousness effects (including possibly recovering memories)
- Sufficient time for a full, documented discussion with all questions answered.

Patient Care and Monitoring

The appropriate level of care and monitoring of patients after the administration of non-intravenous ketamine for mental health conditions has not been clearly defined. The available evidence reports varying degrees of monitoring, personnel used, length of monitoring, and discharge criteria. Given that Health Canada has recently approved SPRAVATO® for use in outpatient settings, guidelines for patient monitoring similar to this medication would be reasonable until further studies are available to guide best practices. Such an approach would balance safety concerns with the need to avoid, as far as possible, onerous, intrusive, and counter-therapeutic monitoring.

For procedural anesthesia with ketamine, it is imperative that continuous cardiovascular monitoring is in place. However, when it is used for the treatment of mental health conditions at lower doses (sub-anesthetic) with non-intravenous administration, the justification for continuous monitoring is less clear as it can disrupt the clinical process. In addition, continuous cardiovascular monitoring increases the cost of treatment substantially due to staffing and equipment costs (Swainson et al., 2020), which could reduce access to ketamine for patients who are in crisis.

Ketamine is a very safe medication in the great majority of cases, especially when patients are carefully selected with medical and psychological/psychiatric screening. Although the scientific literature reveals that ketamine is a generally safe medication, it nevertheless has very uncommonly significant but manageable cardiovascular and psychological effects. A large review of 899 patients showed no significant cardiorespiratory events (Short et al., 2018) in a review of a diverse set of

studies. While nausea and headache are common, ketamine rarely raises blood pressure to dangerous levels. Its dissociative effects can make some patients agitated—a state that is, in most instances, easily managed with the therapist's presence and verbal reassurance. Very uncommonly, the agitation due to dissociation requires the judicious use of a sedative. Health-care professionals delivering this therapy should be skilled and prepared to monitor and manage these and any other emergency situations that may arise. See section on Emergency Management and Prescriber Competencies and Training. A clinician should always use their best judgment to determine when ancillary assessments above routine monitoring including vital signs should be undertaken based on the clinical situation and the condition of the patient.

Cardiovascular Monitoring

Please refer to Appendix B, Appendix D, Appendix E

Vital signs (BP, HR, RR, oximetry) are recommended to be taken:

In patients with ASA 1 Score:

- Before the session:
    - Compare with intake blood pressure and make allowances for situational hypertension. Clinical judgment is required in the total context of the clinical presentation in decisions to move ahead with treatment if the blood pressure is out of range relative to the intake blood pressure.
- At peak drug effect: hold measuring vitals if not clinically indicated. Vital signs are indicated if there are signs of dyspnea, chest pain or mental status changes which are not consistent with expected treatment effects. See Appendix F on Blood Pressure Considerations.
- Before discharge: hold if not clinically indicated.

In patients with ASA 2 Score:

- Before onset of treatment, if a patient has normal vital signs and any regularly prescribed anti-hypertensives have been taken as directed, treatment can proceed.
- At the time of the peak concentration of ketamine (Tmax), which will vary depending on the route of administration (ROA), (please refer to the Appendix B for table) vital signs monitoring is recommended. If vitals are within an accepted range, then it is no longer necessary for further monitoring. If the vitals are abnormal (e.g. elevated blood pressure or dyspnea) and associated with concerning physical symptoms then consider vitals monitoring at 10 min intervals until satisfactory levels or intervention is required. This monitoring frequency relies on the clinical judgment of the medical personnel responsible for the treatment.
- Before discharge: to assure the patient's blood pressure has returned to an acceptable level.
- If hypertension is present for several subsequent readings following the administration of ketamine, the patient should be advised to recheck blood pressure in one week and to seek assessment and possible treatment with their medical practitioner if it is still elevated or at anytime if dyspnea, chest pain or mental status changes occur.

- Pulse oximetry is recommended if clinically indicated:
    - Before the session: in patients with increased risk of respiratory issues (with contributing factors such as: history of sleep apnea with significant oxygen desaturations, facial/neck features suggesting increased risk of airway collapsibility, BMI>30 or age>65).
    - During treatment: if clinically indicated. If oxygen saturation is low during treatment, continually monitor until the patient is no longer at risk for hypoxemia, hold further doses until stable.
        - In patients with obstructive sleep apnea, consider having the patient's head raised above 45°
    - Before discharge if clinically indicated.

Mental Health/Psychological Monitoring:

- Before session: mental status exam, any changes since last assessed, current SI, symptoms, review informed consent.
- During Session:
    - dissociation is a part of the treatment process. The degree of dissociation is not critical unless accompanied by significant emotional distress, that is deemed to be in excess of appropriate reactions. Mental and physical status should be monitored indirectly with observation (respiratory rate and qualities) and oximetry (if indicated).
- Post Session: confirm the patient meets physical and psychological discharge assessment criteria.

Discharge Planning and Assessment:

- Assess the degree of dissociation, consider using a scale such as the Clinician Administered Dissociative States Scale (CADSS).
- Reassess mental status exam, reassess SI if present.
- Assess for any medical changes.
- Ensure safe ambulation without assistance, consider sobriety testing.
- Make a follow-up plan, give contact phone numbers, discharge instructions and discharge the patient into the care of a responsible adult where possible. We recommend a follow up psychotherapy session within 24-48 hours.
- Patients should be made aware that they should not operate a motor vehicle or hazardous machinery for the remainder of the treatment day.

Staffing and Session Requirements

At sub-anesthetic doses in properly selected patients ketamine does not require 1:1 monitoring by a critical care trained health professional or anesthesiologist. All patients receiving sub-anesthetic ketamine must be supervised by a trained health care provider at all times. Consideration for staffing requirements should include the patients' ASA status, dose and route of administration of ketamine, previous treatments with ketamine, other medications,

comorbidities, the patient's mental health stability and is the responsibility of the supervising physician.

During a ketamine administration session, the following staffing requirements must be met:

- Ketamine must only be administered by a qualified and regulated medical professional within their scope of practice(*).
- The prescribing physician should consider cumulative medical comorbidities for patients with an ASA of 2 when deciding whether 1:1 monitoring by a medical professional is required.
- For patients with an ASA of 3 who have been approved for ketamine sessions by the supervising prescriber, 1:1 monitoring is required by a medical professional until the patient meets discharge criteria.
- The supervising physician should be on-site until patients have met established discharge criteria or a physician designate who is a regulated medical professional and has a minimum of active BLS (Basic Life Support) certification and a demonstrated ability to manage airway concerns and other adverse events associated with subanesthetic ketamine administration.
- A minimum of one regulated medical professional should always be present on-site and available to monitor patients directly at all times especially during the peak of the drug effect.
- A regulated medical professional must be present with the patient at all times until patient safety is established after peak drug effects at which time the patient may be supervised by a trained care provider.
- Patients should be monitored by a trained care provider with a minimum level of BLS (Basic Life Support) training for the duration of the session.
- Personnel with proper training and expertise in mental health conditions and the clinical effects of ketamine should be on site for the duration of the session.
- All physicians must otherwise practice within the guidelines of their respective college, CPSBC and CPSO. "It is an expectation of the College that registrants not only observe and monitor the patient, but have the necessary equipment and competence to manage any adverse reactions" (CPSBC, Interim Guidance, 2023).

*Medical doctor, nurse practitioner, physician assistant, registered nurse, or paramedic, who have completed appropriate training

Side Effects and Adverse Effects

Ketamine can cause dose-dependent neurological, psychological, cardiovascular, and other effects. The potential adverse effects must be weighed against the benefits that patients may receive from rapid improvement of their often intractable mood disorders. A discussion of the known side effects and areas of unknown risks and benefits should be included in the informed consent process for receiving ketamine as an off-label therapy. **In general, the side effect profile of ketamine administration includes a short-term increase in blood pressure, transient neurological symptoms and, in many cases, symptoms of dissociation** (McIntyre et al., 2021; Short et

al., 2018; Szarmach et al., 2019; Singh et al., 2016; Shiroma et al., 2014; Swainson et al., 2020) see Appendix G for Side Effects and Adverse Events Reported in the Evidence. Overall, these effects are short-lived and do not require medical intervention.

In a retrospective analysis reporting on 6630 patients who received parenteral ketamine for depression, only 0.7% of patients discontinued ketamine due to an adverse event, of which the majority were due to psychological distress (Feifel et al., 2020). This highlights the need for care providers and patients to be prepared for the psychoactive effects of ketamine; see the Prescriber Training and Competencies section. **Overall the rate of adverse events in published literature is low, which suggests that long-term treatment of depression with ketamine is reasonably safe** (Riva-Posse et al., 2018; Chilukuri et al., 2014).

Neurologic/Cognitive

Across a variety of routes of administration and doses of racemic or esketamine, the most common neurological side effects found in the literature reviewed were lightheadedness, dizziness, fatigue, and blurred vision (Loo et al., 2016; Daly et al., 2018; Short et al., 2018; McIntyre et al., 2021). In addition, transient anxiety at onset is not infrequent. These side effects were typically of short duration and did not require medical intervention (McIntyre et al., 2021)

The available evidence suggests that the use of ketamine for the treatment of TRD does not cause persistent cognitive dysfunction (McIntyre et al., 2021). For example, Morrison and colleagues tested 24 subjects five times with a battery of cognitive tests over six hours following IN esketamine. Compared with placebo, the ketamine group showed slower performance time and greater error rates 40 minutes after 84 mg of esketamine given intranasally, however, two hours after administration these scores were not significantly different from the placebo group (Morrison et al., 2018). Similarly, no lasting cognitive effects were found by Murrough and colleagues up to seven days after an infusion of ketamine (Murrough et al., 2015).

Cardiovascular

The cardiovascular effects of ketamine in its use for TRD were reviewed by Szarmach and colleagues in 2019. In studies using non-intravenous doses of ketamine, blood pressure increases were generally small (i.e., maximum of 20mmHG increase in SBP and 10mmHG in DBP), transient (usually 10-40 minutes) and generally returned to baseline without intervention. No severe adverse cardiac events such as myocardial infarction were observed in any of the reviewed studies (Szarmach et al., 2019). Riva-Posse and colleagues reported on the cardiovascular effects of sub-anesthetic doses of ketamine for use in TRD in a large case-series and found the blood pressure changes to be clinically insignificant and to resolve within 30 mins after completion of a 40-minute IV infusion.

Psychiatric

Common psychological effects of ketamine include emotional lability (Loo et al., 2016), perceptual alterations, and dissociation (Loo et al., 2016; Xu et al., 2016; Daly et al., 2018; Daly et al., 2019; Fu et al., 2020). Again, these symptoms were generally mild and did not require medical intervention. In a recent review on the use of repeated IV ketamine to treat depression, 0.5% of patients withdrew

treatment due to psychological effects (Feifel et al., 2020). Most psychological side-effects occur as the patient is emerging from the dissociated state (Ballard & Zarate, 2020). The majority of these side effects can be mitigated after careful patient selection, screening, providing adequate levels of trained staff, preparing for possible adverse reactions and providing a comfortable and adaptable environment (McIntyre et al., 2021). In a KAT setting, the altered level of consciousness and non ordinary state of consciousness that is achieved via the use of ketamine is part and parcel of the treatment process. It is only with appropriate training and knowledge that these symptoms can be interpreted through a therapeutic lens for the patient rather than as a side effect.

Dissociation is described by patients as feeling detached from their surroundings or self (Loo et al., 2016; Xu et al., 2016; Daly et al., 2018; Daly et al., 2019; Fu et al., 2020). The dissociation produced by ketamine when used for mental health conditions is controversial, with some studies listing it as an undesirable side effect, while others considering it part of the treatment process and potentially important in the efficacy of the therapy (Ballard & Zarate, 2020; Grabski et al., 2020; Luckenbaugh et al., 2014; McIntrye et al., 2021). Regardless, dissociation is not dangerous or limiting, and proper patient management can limit potential adverse effects.

Respiratory

Ketamine does not produce significant respiratory depression, nor does it lower the medullary response to carbon dioxide making it an ideal anesthetic in a variety of settings (Mihaljević et al., 2020; Bellolio et al., 2016). Although a patient's respiratory rate typically decreases for a few minutes after ketamine administration, only rare cases of apnea or laryngospasm have been reported even in procedural sedation doses which are much higher than that used in the office setting if patients are selected appropriately. (Bellolio et al., 2016). For further discussion on apnea and ketamine see Appendix H.

Gastrointestinal

Nausea and vomiting are two of the most common side effects to ketamine treatment. These effects can be mitigated by maintaining an NPO status. Typically nausea and vomiting are transient, however if not medications should be at hand to manage these effects.

Other

Gastrointestinal, ocular, and urologic side effects are less common in the literature and are of unknown significance (Short et al., 2018). These effects are usually short-lived and are more common in studies using intravenous administration of ketamine (Short et al., 2018). There have been occasional reports of damage to the urinary tract, however the majority of these occur in illicit users of ketamine which may contain adulterants or be used concurrently with other substances, also used at much higher frequency than the medical use (Feifel et al., 2020). Ng and colleagues (2021) recently reviewed the literature on the effect of ketamine on the urologic system and concluded that "there is no evidence that ketamine and/or esketamine treatment in adults with mood disorders is associated with urological toxicity."

Therefore, based on available data, adverse drug events in the use of non-intravenous

ketamine for mental health conditions are minor, of short duration and easily managed within a non-hospital clinic or community setting in properly selected patients

Emergency Management

Ketamine is known for its remarkable safety profile making it the anesthetic, analgesic, and anxiolytic of choice in a variety of medical settings. Since its introduction in 1962, it has been safely used in battlefields (Leslie et al., 2021), operating rooms (Strayer & Nelson, 2008), emergency departments (Bellolio et al., 2016), under-serviced rural areas (Ketha et al., 2019), and now in the office for mental health conditions (e.g., Short et al., 2018; Rodrigues et al., 2020; Xu et al., 2016). **The available literature suggests that although generally safe, ketamine can have potentially significant and dose related cardiovascular and psychological effects which may require emergency intervention (McIntyre et al., 2021). Physicians must ensure appropriate procedures, plans, and emergency equipment are available and reviewed regularly, so that negative patient outcomes can be mitigated.**

The most common emergencies that occur during ketamine therapy for mental health conditions can be broadly divided into cardiovascular and psychological/psychiatric events. Elevated blood pressure and heart rate are the two most common cardiovascular effects of ketamine, however chest pain or pressure, palpitations, orthostatic dizziness, and other effects can occur (but are much less common) and thus will require monitoring by a trained and qualified healthcare provider (Short et al., 2018; Szarmach et al., 2019; McIntyre et al., 2021).

Even with intravenous administration at relatively high doses for procedural anesthesia in the emergency room, respiratory urgencies and emergencies are rare. In a systematic review and meta-analysis on this topic, Bellolio and colleagues reported no cases of aspiration (0/145), four cases of apnea (4/381), one case of laryngospasm (1/563), and no cases of the need for intubation (0/161) in the ketamine-only group (Bellolio et al., 2016); see Appendix G for side effects data. When used at lower doses for management of depression, ketamine does not appear to cause apnea or respiratory depression (Short et al., 2018; Rodrigues et al., 2020; Xu et al., 2016).

The most common psychological/psychiatric effects of ketamine that may require intervention are anxiety, irritability, and agitation (Short et al., 2018; McIntyre et al., 2021). Dissociation is an expected and possibly necessary part of the treatment process and should not be considered an adverse reaction requiring intervention (Ballard & Zarate, 2020).

All prescribers must keep up-to-date with emerging evidence and practice which are expected to change over time as this new field of medicine develops. "It is an expectation of the College that clinicians not only observe and monitor the patient, but have the necessary equipment and competence to manage any adverse reactions" (CPSBC, Interim Guidance, 2021). See section on Prescriber Competencies and Training for further discussion of recommendations.

Emergency Equipment and Procedures

We recommend that physicians and prescribers follow the respective College's guidelines for Emergency Preparedness such as the CPSBC's Emergency Preparedness in the Physician Practice Enhancement Program for necessary equipment and procedure requirements and additionally:

- Clinics providing this medical treatment should have a regularly reviewed Emergency Management Plan, and personnel should be aware of how to implement the plan including emergency contact information for patient transfer.
- A higher level of care should be available within 10 minutes in an urban setting and 20 minutes in a rural setting in case of emergency transfers.
- The facility must have appropriately trained personnel and the appropriate equipment to deal with emergencies that relate to the airway, and to the management of complications of ketamine administration.
- The emergency cart must be:
    - Stocked in accordance with the facility requirements
    - Immediately available
    - Checked on a regular basis for expiry dates and completeness of supplies
    - Checked daily to be in working order prior to ketamine administration
- The following emergency supplies are suggested to be kept on hand:
  AED, rescue medicines (ativan, bp meds, allergy, epi pen, narcan, nitro patch or spray and clonidine) and oxygen

Prescriber Competencies and Training

Prescribers of ketamine for mental health conditions must anticipate and be prepared for the common and less common effects of ketamine including its unique dissociative effects which requires that the supervising health-care professional be attentive to patients' needs. With proper safeguards, screening, and planning, the main adverse effects of ketamine can be mitigated.

An understanding of the unique and complex pharmacology of ketamine, its dosing, route of administration, contraindications, and adverse effects is the key to reducing risk. Prescribers should be comfortable managing treatment-resistant patients, some which will have SI. A multi-disciplinary setting may be advantageous for ketamine therapy given that many patients who are treatment resistant will have complex therapeutic needs. All of these factors are important to consider in the patient screening and selection process to reduce the potential risks.

Although life-threatening emergencies are rare with KAT, prescribers should feel comfortable managing an unstable patient and have the appropriate training. Severe psychiatric side effects should be prevented as much as possible by optimizing the psychological preparation of the patient

and by having a relaxing, comfortable environment for KAT. Prescribers must be familiar with rescue medications for medical and psychiatric emergencies and are encouraged to participate in training programs and continuing education to stay apprised of the most recent evidence-based recommendations.

By following these guidelines, prescribers can actively reduce negative outcomes, which will enhance the opportunity for optimal therapeutic results and lasting therapeutic benefits.

Medication Management and Administration

Ketamine is a controlled substance and therefore must be handled in compliance with federal and provincial regulations and is to be managed carefully and only by regulated health professionals to ensure safe handling and prevention of loss, diversion, or theft.

Ketamine comes in a variety of preparations including commercially and compounded formulations. It is our recommendation that community settings requiring non-commercial preparations of ketamine such as lozenges,
rapid-dissolving tablets, nasal spray or others, work with a compounding pharmacy with experience processing ketamine formulations. Compounding pharmacies can use standardized protocols to ensure more consistency and objectivity in the medication preparation process.

Risk Level: Role of Dosage vs Route of Administration: It is important to note that whatever risks there are in the use of ketamine, they do not vary with the route of administration but, instead, increase as the bioavailable dose increases, no matter what the route of administration.

Helpful Features of the IM Route of Administration:

- Reliable level of absorption (93%)
- After IV, IM has the most consistent and predictable rate of onset and duration of activity
- Significantly more affordable than IV or than routes dependent on compounding.
- Compared to other non-IV routes, the IM route burdens the liver, kidneys and bladder with the least amount of ketamine and its metabolites.

Ketamine Administration:

- Patient-specific medication orders must contain the patient's name, date and time the order was written, medication name, dosage, route of administration, frequency of dosing, prescriber's signature and name.
- The medication is administered by a regulated and qualified health care practitioner who is working within their scope of practice.
- Medication administration documentation must be complete.
- Expiration date is to be checked prior to administration.

Controlled Substances Management In-Office:

- Management of ketamine is to comply with the Controlled Drugs and Substances Act, and Health Canada requirements as well as provincial requirements.
- A regulated health professional is responsible for overseeing medication management.
- Ketamine is stored in a location that is not accessible to patients or unauthorized personnel.
- Ketamine is to be stored in a metal safe that is securely anchored to the building and appropriate prevention measures be taken to prevent loss or theft.
- The keys or code to access the controlled substance safe are carried by and provided to regulated health professionals only.
- The facility should have a policy and procedure in place for medication management, including controlled drugs and substances.
- Controlled drugs and substances are counted by two health professionals concurrently at the start and finish of each day in which medications are administered, if feasible.
- Controlled drugs and substances administered, dispensed, or wasted are recorded in a log and the logs are to be retained for at least three years.
- Records of the purchase of controlled drugs and substances are also kept for a period of a minimum of three years.

Additional Recommendations:

The above is not intended to be a complete list of recommendations for the use of ketamine in community settings, and additional recommendations can be made available for the following topics:

- Additional evidence tables
- More detailed Mood Disorder Assessment & Management Plan (including Psychiatric Assessments)
- Admission & Pre-treatment care
- Patient Intake
- More detailed Contraindications Evidence
- Updated Dosing Guidelines for IM, SC, SL & IN routes
- Home Use of Ketamine
- Clinician Qualifications
- Criteria for qualified and regulated health-care professionals, including nurses
- Facility recommendations for Ketamine Clinics, Ketamine administration area
- Treatment Area Staffing and Session requirements
- Equipment, and Equipment Operation & Safety
- More detailed Patient Discharge Criteria
- Policy & Procedure Manuals
- Quality Improvement Program and Practices

Summary of the Evidence

These Practice Standards Recommendations were written after a thorough review of the current evidence, with particular attention placed on patient selection, safety, and monitoring in order to establish the level of safety for the outpatient use of ketamine to treat mental health conditions. We have summarized information from the highest quality articles using the following categories:

1. Level or quality of evidence
2. Number of patients (N)
3. Indication
4. Route of administration
5. Dosing
6. Contraindications
7. Side effects
8. Monitoring
9. Outcomes

Please note that we analyzed a heterogeneous group of studies and therefore not all of the categories were applicable to all studies. The information collected can be made available in the form of an evidence table if requested.

Level or quality of evidence
More than 25 RCTs, 17 systematic reviews and meta-analyses, four expert opinions, and eight open label trials were reviewed. Product monographs, select hospital studies and protocols as well as product monographs were also analysed.

Number of patients (N)
Numbers of patients treated in studies varied from 7-192 in RCTs and up to 6630 patients in a single report that combined an electronic survey sent to ketamine providers and a review of existing evidence.

Indication
Treatment-resistant depression (TRD) was the most common indication examined which has a robust set of evidence. There is more limited but promising evidence for MDD, bipolar disorder, SUD, social anxiety disorder, OCD, SI and PTSD.

Dosing and Route of administration
The majority of the literature that was available and reviewed were of IV dosing, however there were numerous studies that included a mixed route of administration. Dosing ranged from:

- 0.1 - 4.13 mg/kg IV
- 0.1 - 3.3 mg/kg IM
- 0.1 - 0.5 mg/kg SC

- 28 - 84 mg as per spravato dosing for IN
- Up to 0.5mg/kg IN for racemic ketamine.
- 0.5 mg - 7.0 mg/kg PO

The evidence reviewed showed wide variability in dosing protocols. Some studies used consistent doses over the treatment period, others used predetermined increases in dosing, while others used dose escalation protocols that were based on patient tolerance and clinical effect. Based on the data examined, there is evidence to support the use of IM, SL, IN, and PO ketamine as safe alternative routes of administration for ketamine in a community setting. For the SC route there was limited evidence available.

Contraindications
Data for exclusion criteria for ketamine treatment was extrapolated from expert opinion, pharmacological data, as well as the researched evidence provided and is summarized in Appendix C. Caution should be taken when interpreting contraindications from exclusion criteria for research studies, which are chosen for refining research data rather than what would otherwise be clinically contraindicated.

Side Effects and Adverse Outcomes
Side effects and adverse outcomes data in ketamine treatment were extracted from expert opinion, pharmacological data and research studies based on the frequency of their occurance. The minimal adverse outcomes that were reported were generally seen as insignificant and were often correlated to the patient's pre-existing health status.

Monitoring
Levels of monitoring varied between studies, and included HR, BP, ECG, SpO2 and ETCO2. Very few serious adverse effects were reported. The data supports the favorable safety profile for ketamine, as well as for monitoring requirements that do not include continuous telemetry or ECG monitoring. We have also included references for pain management and anesthesia relevant to our discussion, particularly to establish evidence for safety in the higher ranges of sub-anesthetic dosing, without the need for continuous monitoring.

Outcomes
There were difficulties in assessing overall outcomes due to inconsistencies in how the ketamine was applied (e.g., dosing, frequency, route). However, in general, studies showed favourable outcomes, including rapid, transient, antidepressant effects. Variable assessment methods (i.e., validated standardized questionnaires) for mental status were also applied but were inconsistent.

Conclusion
Rates of depression and other mental health issues are high and increasing. Ketamine, a molecule with a well established safety profile, can be immediately added to clinicians' therapeutic armamentarium, as long as basic knowledge attainment and safety guidelines are adhered to.

Appendix A: College of Physicians and Surgeons Regulatory References

Other CPSBC, College of Physicians and Surgeons of Alberta (CPSA) and College of Physicians and Surgeons of Saskatchewan (CPSS) documents referenced during this process include:

- CPBSC - NHMSFAP Update - Ketamine and Major Depressive Disorder, September 8, 2020
- CPSBC - NHMSFAP Update - Circulated for consultation—Parenteral Use of Ketamine for the Treatment of Mood Disorders, Jan/Feb 2021]
- CPSBC - NHMSFAP AS - Parenteral Use of Ketamine for the Treatment of Mood Disorders DRAFT
- CPSBC - Interim Guidance - Ketamine Administration via Intramuscular, Oral, Sublingual, and Intranasal Routes as Treatment for Mental Health Conditions and Chronic Pain in the Community Setting, August 22, 2023
- CPSBC - NHMSFAP AS - Intravenous Use of Ketamine for the Treatment of Mood Disorders, March 24, 2023
- CPSA - Clinical Toolkit - Ketamine and Esketamine: Key Considerations
- CPSS - Position on Ketamine Off-Label Use
- CPSS - Updated Guidance for Ketamine/Esketamine as treatment for mental health and chronic pain diagnoses in community settings, November 17, 2022
- CPSBC - Complementary and Alternative Therapies Practice Standards
- CPSBC - NHMSFAP Medication Management Accreditation Standards

Appendix B: Ketamine Pharmacokinetics by Route of Administration

Route	Reported Dosing	Bioavailability (%)	Peak (min) Tmax	Duration
IV	0.5-1mg/kg	95-100	1	5-10 min
IM	0.5-1mg/kg*	75-95	22	30-75 min
IN (S)	28-84mg (Spravato)	25-50	20-40	45-120 min (check)
IN (R/S)	40-160mg, titrate to effect	45-50	20-40	–
SL	100-400mg	30	20-45	–
PO	3mg/kg	10-29	60-120	2-4 hrs
PR	100-400mg	24-30	–	–

(Yanagihara et al., 2003; Chong et al., 2009; Cohen et al., 2015; Mihaljević et al., 2020; Chilukuri et al., 2014; Nowacka & Borczyk, 2019; Janssen, 2020; Zanos et al., 2018; Bonnett et al., 2021)

*please note these are doses found in the research, clinical practices that have been surveyed or found in the literature to date have reported doses up to 3.3mg/kg

Appendix C: Summary of Contraindications and Exclusion Criteria Used in Clinical Trials

The ideal candidate for ketamine-assisted therapy for mental health conditions has yet to be determined. There remains much debate in the literature as to both inclusion and exclusion criteria for non-intravenous ketamine in outpatient community settings. For example, although most of the studies reviewed excluded patients with psychosis or suicidal ideation (e.g., Daly et al., 2019; Feder et al., 2014; Schwenk et al., 2018; Bahji et al., 2020), there are others that specifically recruited these patients (Veerart et al., 2021; McIntyre et al., 2021; Diazgranados et al., 2010; Price et al., 2009). Similar statements can be made for patients with a history of bipolar affective disorder (Wilkowska et al., 2020), and substance use disorder (Jones et al., 2018), and other conditions. See the contraindications Table below for additional evidence on contraindications for ketamine used in studies. We strongly advise using the information provided below in combination with good clinical judgement on an individual patient basis.

The exclusion criteria used in research studies are not necessarily applicable to real-world, community-based settings because the aim in such studies is usually to recruit a homogeneous population, and can have restrictive exclusion criteria in order to minimize adverse events. Nevertheless, a risk estimate can be made from the available literature as to the risks of giving ketamine non-intravenously for the treatment of mental health conditions. These can be divided into general, neurologic/cognitive, cardiovascular, psychological/psychiatric, respiratory, and gastrointestinal categories.

General

A documented sensitivity to ketamine, esketamine, or any additives of the compounding process precludes its use. Pregnancy and breastfeeding patients were excluded from all trials reviewed (Bahji et al., 2020; Schwenk et al., 2018; Thomas et al., 2018; Phillips et al., 2019; Krupitsky et al., 2007; Loo et al., 2016; Grunebaum et al., 2018; Ionescu et al., 2019; Evans et al., 2018). However, pregnancy can be considered a relative contraindication as there may be situations where a mother's mental health needs are prioritized over the unknown risks to her fetus.

Neurologic/Cognitive

Dementia or any other condition that affects one's ability to understand and give informed consent to the treatment is an absolute contraindication. Ketamine may increase cerebral blood flow, intracranial pressure, and cerebral oxygen consumption but is understood that hydrocephalus is the only absolute contraindication in these conditions (Green et al., 2014). However it is prudent to use caution and clinical judgement in patients with intracranial pathology (Mihaljević et al., 2020). Ketamine does not seem to cause seizures and, in fact, it has been successfully used to treat refractory status epilepticus (Mihaljević et al., 2020).

Cardiovascular

As reviewed in the Side Effects and Adverse Events Section of this document, ketamine causes a

dose-dependant increase in systolic and diastolic blood pressures by up to 50% over baseline, which peaks at 30-50 minutes after drug administration, then tends to return to baseline by two to four hours post-dose (Szarmach et al., 2019; Riva-Posse et al., 2018). This blood pressure surge is caused by central sympathetic stimulation, which increases blood pressure, heart rate, cardiac output, and myocardial oxygen consumption (Mihaljević et al., 2020).

Therefore, any condition where an increased strain on the cardiovascular system could cause serious negative outcomes is a contraindication. This includes patients with uncontrolled hypertension, severe coronary artery disease, central aneurysms, recent cardiovascular events, intracerebral vascular disease, or a NYHA Class III or IV (Riva-Posse et al., 2018; Szarmach et al., 2019; Feifel et al., 2020).

Respiratory

Ketamine does not produce significant ventilatory depression, nor does it lower the medullary response to carbon dioxide making it an ideal anesthetic in a variety of settings (Mihaljević et al., 2020; Bellolio et al., 2016). Although a patient's respiratory rate typically decreases for a few minutes after ketamine administration, only rare cases of apnea have been reported (Bellolio et al., 2016). Therefore, conditions such severe chronic obstructive pulmonary disease (COPD), asthma, restrictive lung disease, and obstructive sleep apnea should be considered relative contraindications.

Psychological/Psychiatric

There is much debate in the literature as to the specific indications for ketamine in the treatment of psychological/psychiatric conditions. Any condition in which a patient is too unwell to consent to treatment is a contraindication. This may include but is not limited to severe psychotic disorder, schizophrenia, bipolar affective disorder, and others. Active addiction to ketamine is an absolute contraindication. However, other substance use as a contraindication is not well studied, also it has been used effectively to treat certain substance use disorders and for some studies is an indication (Dakwar et al., 2018; Krupitsky et al., 2007).

Gastrointestinal/Genitourinary

Nausea and vomiting were some of the most common side effects found in our review of the literature. Although the risk factors that lead to these effects are not well studied, a nausea risk assessment may be helpful prior to treatment but would not be considered a contraindication. Ketamine induced bladder dysfunction was not listed as a contraindication in studies, however this should be considered a relative contraindication.

Conclusion

In summary, ketamine should not be administered if a patient is at high risk for the complications of hypertension, other serious cardiovascular disease, increased intracranial, or intraocular pressure. Furthermore, some psychological/psychiatric history such as psychosis and SI may be absolute contraindications if the team providing care is not familiar and prepared to deal with the patient's potential response to treatment. Careful screening is imperative in the intake process.

Table: Research Contraindications and Exclusion Criteria

Contraindication	References
GENERAL	
Unstable medical conditions	Evans et al., 2018; Feder et al., 2021; Ionescu et al., 2019; Krupitsky et al., 2007; Morrison et al., 2018; Murrough et al., 2013; Phillips et al., 2019; Popova et al., 2019; Riva-Posse et al., 2018; Sos et al., 2013; Thomas et al., 2018; Diazgranados et al., 2010; Zarate et al., 2012
CARDIOVASCULAR	
Uncontrolled hypertension	Loftus et al., 2010; Subramaniam et al., 2011; McIntyre et al., 2021; Dakwar et al., 2018; Krupitsky et al., 2007; Ochs-Ross et al., 2020; Popova et al., 2019; Riva-Posse et al., 2018; University Health System, n.d.
Uncontrolled cardiovascular disease ie ASA score of 4 or higher. (e.g., heart failure, coronary artery disease, arrhythmias, conduction delay, valvular, congenital disease)	Loftus et al., 2010; Schwartzman et al., 2009; Sigtermans et al., 2009; Subramaniam et al., 2011; Grunebaum et al., 2018; McIntyre et al., 2021; Dakwar et al., 2018; McIntyre et al., 2021; Krupitsky et al., 2007; Morrison et al., 2018; Szarmach et al., 2019; University Health System, n.d.; Kheirabadi et al., 2020
RESPIRATORY	
Uncontrolled cardiopulmonary disease (e.g., COPD/emphysema, asthma, restrictive lung disease)	Subramaniam et al., 2011; Dakwar et al., 2018
Severe Obstructive Sleep Apnea (OSA)	Laskowski et al., 2011; Bell et al., 2005
CENTRAL NERVOUS SYSTEM	
Aneurysm (e.g., Aneurysmal vascular disease including thoracic and abdominal aorta, intracranial, and peripheral arterial vessels or arteriovenous malformation)	McIntyre et al., 2021; Szarmach et al., 2019
Elevated intraocular pressure	Zeiler et al 2014; Drayna et al., 2012; Loftus, 2010
Elevated intracranial pressure	Zeiler et al., 2014; Drayna et al., 2012; Loftus, 2010, Subramaniam et al., 2011; Szarmach et al., 2019
HEPATIC	
Hepatorenal disease	Gorlin et al, 2016; Subramaniam et al., 2011; Krupitsky et al., 2007
Hepatic cirrhosis (i.e., severe hepatic dysfunction)	Noppers et al., 2011; Schwartzman et al., 2009; Sigtermans et al., 2009; Subramaniam et al., 2011; Krupitsky et al., 2007
Moderate hepatic disease	Noppers et al., 2011; Schwartzman et al., 2009; Sigtermans et al., 2009; Subramaniam et al., 2011; Kheirabadi et al., 2020
URINARY	
Renal or urologic disease	Kheirabadi et al., 2020
ENDOCRINE	

Uncontrolled hyperthyroidism	Schwartzman et al., 2009
Diabetes	Riva-Posse et al., 2018
PSYCHOLOGICAL/PSYCHIATRIC	
History of psychosis	Barreveld et al., 2013; Loftus et al., 2010; Sigtermans et al., 2009; Subramaniam et al., 2011; Daly et al., 2019; Popova et al., 2019; Feder et al., 2021; Dakwar et al., 2018; Morrison et al., 2018; Thomas et al., 2018; Murrough et al., 2013; Sos et al., 2013; Kheirabadi et al., 2020
Active psychosis	Grunebaum et al., 2018; Ionescu et al., 2019; Loo et al., 2016; Ochs-Ross et al., 2020; Popova et al., 2019; Riva-Posse et al., 2018; Ross et al., 2019; University Health System, n.d.; Wajs et al., 2020; Diazgranados et al.,2010; Zarate et al., 2012

Homicidal/suicidal ideation	Popova et al., 2019; Feder et al., 2021; Grunebaum et al., 2018; Daly et al., 2018; Daly et al 2019 (suicidal/ homicidal intent); Ionescu et al., 2019 (requiring hospitalization); Lapidus et al., 2014; Murrough et al., 2013 (imminent or serious); Ochs-Ross et al., 2020 (with intent); Popova et al., 2019; Sos et al., 2013; Diazgranados et al., 2010
Bipolar disorder	Feder et al., 2021; Fu et al., 2020; Daly et al., 2018; Daly et al., 2019; Ionescu et al., 2019; Lapidus et al., 2014; Loo et al., 2016; Murrough et al., 2013; Ochs-Ross et al., 2020; Phillips et al., 2019
Schizophrenia	Loo et al., 2016
Obsessive compulsive disorder (OCD)	Fu et al., 2020; Daly et al., 2019; Ochs-Ross et al., 2020; Popova et al., 2019
Anti-social, borderline personality disorder	Fu et al., 2020; Lai et al., 2014; Popova et al., 2019; Thomas et al., 2018
Altered mental status (e.g. dementia, delirium)	Loftus et al., 2010; McIntyre et al., 2021, Riva-Posse et al., 2018; Thomas et al., 2018
Substance-use dependence (most specified alcohol or certain substances)	Daly et al., 2019; Popova et al., 2019; Feder et al., 2021; Fu et al., 2020; Grunebaum et al., 2018; Dakwar et al., 2018; Ionescu et al., 2019; Krupitsky et al., 2007; Loo et al., 2016; Murrough et al., 2013; Phillips et al., 2019; Popova et al., 2019; Riva-Posse et al., 2018; Thomas et al., 2018; University Health System, n.d.; Diazgranados et al., 2010; Kheirabadi et al., 2020; Zarate et al., 2012
Anorexia, bulimia nervosa	Feder et al., 2021
Intellectual disability	Daly et al., 2018; Krupitsky et al., 2007; Lapidus et al., 2014; Murrough et al., 2013; Ochs-Ross et al., 2020; Popova et al 2019
Post traumatic stress disorder (PTSD)	Daly et al., 2018; Lai et al., 2014; Lapidus et al., 2014; Sos et al., 2013
Primary sleep disorder	Morrison et al., 2018
OBSTETRIC	
Pregnancy	Barreveld et al., 2013; Loftus et al., 2010; Subramaniam et al., 2011; Grunebaum et al., 2018; Evans et al., 2018, Ionescu et al., 2019; Loo et al., 2016; Phillips et al., 2019
Breast feeding	Schwenk et al., 2018 (Relative); Grunebaum et al., 2018 (Absolute)

Appendix D: American Society of Anesthesiology (ASA): Physical Status Classification System

ASA Classification	Definition	Examples, including but not limited to:
ASA 1	A normal healthy patient	Healthy, non-smoking, no or minimal alcohol use
ASA 2	A patient with mild systemic disease without substantive functional limitations	Current smoker, social alcohol drinker, pregnancy, obesity (30<BMI<40), well-controlled diabetes mellitus or hypertension, mild lung disease
ASA 3	A patient with one or more severe systemic disease(s) with substantive functional limitations	Poorly controlled diabetes mellitus or hypertension, morbid obesity (BMI ≥40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, end stage renal disease undergoing regularly scheduled dialysis, history (>3 months) of MI, CVA, TIA or CAD/stents

Appendix E: Metabolic Equivalents (METS) Classifications

1 MET	Can you take care of yourself? Eat, dress, or use the toilet? Walk indoors around the house? Walk 1 or 2 blocks on level ground at 3.2 to 4.8 km/h?
4 METs	Do light work around the house like dusting or washing dishes? Climb a flight of stairs or walk up a hill? Walk on level ground at 6.4 km/h? Run a short distance? Do heavy work around the house like scrubbing floors or lifting or moving heavy furniture? Participate in moderate recreational activities like golf, bowling, dancing, doubles tennis, or throwing a baseball or football?
>10 METs	Participate in strenuous sports like swimming, singles tennis, football, basketball, or skiing?

Appendix F: Blood Pressure Considerations

Ketamine provokes a predictable sympathetic response after administration that leads to increased heart rate and blood pressure. Despite concerns regarding this increase in blood pressure, the use of high doses of ketamine in the emergency department and operating room have demonstrated that adverse cardiovascular effects such as stroke and myocardial infarction are exceedingly rare (Rodrigues et al., 2020; Strayer & Nelson, 2008).

In a review on the cardiovascular effects of non-intravenous ketamine in outpatient settings, Szarmach and colleagues found that blood pressure increases were generally small (i.e., maximum increase of 20mmHG systolic and 10mmHG diastolic), transient (i.e., usually lasting 10-40 minutes) and generally returned to baseline without intervention. No severe adverse cardiac events such as myocardial infarction were observed in any of the studies reviewed (Szarmach et al., 2019).

During the intake and screening process for office-based ketamine treatment, patients should be screened with one or more blood pressure measurements and have an assessment of their cardiac reserve, ensuring a METS score of at least 4 prior to treatment.

Immediately prior to ketamine-assisted therapy, it is expected that a patient's blood pressure may be elevated above baseline due to anxiety or other psychosocial factors associated with the treatment. Providing reassurance and
non-pharmacological interventions to support a patient’s mental and emotional status may be effective in decreasing blood pressure.

When given as a single or split dose IM, IN, SL, or PO, ketamine’s hemodynamic effects are transitory and not of clinical significance. Assessment of blood pressure and vital signs during the session should therefore be reserved for those with clinical signs of dyspnea, chest pain, or mental status changes not consistent with expected treatment effects. Consider that when blood pressure is measured during the session, it can effectively disrupt the therapeutic process due to the distraction of the noise and sensation of the inflating cuff.

It is our recommendation that medications to lower blood pressure not be routinely administered as the effects of these medications are likely to persist beyond the ketamine session, with associated side effects and delayed discharge.

Appendix G: Side Effects and Adverse Events Reported in the Evidence

Side effect	More Common	Less Common	Rare	References
CARDIOVASCULAR				
Lightheadedness/dizziness				Loo et al., 2016; Daly et al., 2018; Feder et al., 2020; McIntyre et al., 2021; Wajs et al., 2020; Ochs-Ross et al., 2020; Phillips et al., 2019; Popova et al., 2019
Elevated blood pressure and pulse rate				Short et al., 2018; Belollio et al., 2018; Grunebaum et al., 2018; Fu et al., 2020; Fava et al., 2020; Glue et al., 2017, Krupitsky et al., 2007; Ochs-Ross et al., 2020; Phillips et al., 2019
Hypotension				Belollio et al., 2018
Arrhythmia				Short et al., 2018
RESPIRATORY				
Respiratory depression (dose dependent)				Short et al., 2018; Belollio et al., 2018
Laryngospasm				Belollio et al., 2018
Dry mouth				Loo et al., 2016
EYE				
Blurred vision				Loo et al., 2016; Short et al., 2018; Feder et al., 2021; Phillips et al., 2019; Kheirabadi et al., 2020
GENITOURINARY				
Inflammatory urinary tract, cystitis and fibrosis (with chronic ketamine use				Short et al., 2018; McIntyre et al., 2021
PSYCHOLOGICAL/PSYCHIATRIC				
Emotional lability				Loo et al., 2016; Short et al., 2018
Dissociation				Loo 2016; Xu 2016; Daly et al., 2018; Daly 2019; Fu 2020; Short et al., 2018; Wajs et al., 2020, Ochs-Ross et al., 2020; Phillips et al., 2019; Popova et al., 2019; Kheirabadi et al., 2020
Perceptual alteration				Rosenbaum et al., 2019; Short et al., 2018; Phillips et al., 2019
Anxiety				Fu et al., 2020; Short et al., 2018
Insomnia				Short et al., 2018
GASTROINTESTINAL				
Nausea, vomiting				Niesters 2014; Belollio et al., 2018; Feder et al., 2021; Wajs et al., 2020; Ochs-Ross et al., 2020; Passie et al., 2021; Popova et al., 2019;
GENERAL				
Fatigue				Loo et al., 2016; Feder et al., 2021; Ochs-Ross et al., 2020
Headache				Fu 2020; Feder et al., 2021; Wajs et al., 2020; Ochs-Ross et al., 2020

Appendix H: Ketamine and the Paucity of Apnea

Significant but rare respiratory adverse events occur exclusively with procedural or anesthetic doses which are much higher doses than used for TRD and other mental health conditions.

Incidence of apnea even in relatively high doses in the emergency room is very rare. There is a statistical risk of 4 in 381 for apnea and 1 in 563 for laryngospasm when IV ketamine is used as procedural anesthesia (Belollio et al., 2016).

Ketamine is a respiratory stimulant but produces transient respiratory depression, which may include apnea, usually within the first 2 to 3 minutes of administration. This effect appears to be more likely if ketamine is delivered rapidly by the intravenous route but when used as monotherapy is rarely, if ever, of clinical significance (Strayer & Nelson, 2008).

Outpatient access to NMDA antagonists has changed with the availability of esketamine (SPRAVATO®). This intranasal formulation does not require any monitoring for apnea outside of patients with respiratory comorbidity.

Respiratory depression, apneic episodes and airway complications have been described at doses 5 to 10-fold the usual anesthetic dose, while mild or moderate transient respiratory depression has been reported at anesthetic doses with rapid intravenous administration or high anesthetic doses (Janssen, 2020).

Even with IV administration, apnea in the treatment of depression appears to be rarely if ever recorded. In a 2020 review of side effects during depression treatment of 203 patients at the Canadian Rapid Treatment Center of Excellence, there were no episodes of apnea at 0.5 - 0.75 mg/kg (Rodrigues et al., 2020). Caution is still warranted with this mode of administration as there has been one previously healthy patient requiring manual ventilation after developing apnea during low dose intravenous infusion of 0.5 mg/kg (Gómez-Revuelta et al., 2020).

For procedural sedation with ketamine, it is imperative that cardiovascular monitoring is in place. However, given the lower doses of ketamine given for the treatment of chronic pain and mood disorders, in addition to the preference for non-IV administration, it is less clear that the risks justify continuous monitoring, which adds both expense and disruption to the clinical process.

For example, Short, et al. published a systematic review of the side effects associated with ketamine when used for depression. With over 60 studies and 899 patients, they were not able to report any episodes of respiratory depression or apnea (Short et al., 2018). This confirmed a similar review by Xu and colleagues (2016) of 201 patients, again with no apneic episodes.

The pediatric data supplies more granular data on the risk factors for apnea. In a meta-analysis of 8282 children, Green and colleagues (2009) found an overall rate of apnea of 0.8%. However, these

events occurred only with IV or high dose IM injection. In patients who received low dose IM ketamine, there were no episodes of apnea, with a consequent odds ratio of zero. This is congruent with the adult experience, where IM doses of 4-5 mg/kg are frequently associated with apnea or respiratory depression sufficient to require intubation, however reduced dose IM dosing of 2 mg/kg was not associated with any episodes of apnea or intubation (O'Brien, 2020).

The case of esketamine demonstrates that while this medication can lead to apnea in the same way as racemic ketamine, the risk of this happening with oral, nasal, or sublingual administration is not sufficient to require continuous oximetry. Even with IM administration of doses less than 2 mg/kg, continuous oximetry should be limited to those with respiratory comorbidities. Intermittent oximetry should be available for any ketamine therapy.

Appendix I: Training Requirements

Health care professionals prescribing ketamine for KAT should ideally complete a training program containing the following minimal curriculum components:

- Indications and contraindications of KAT
- Pharmacology, pharmacokinetics, dosing and routes of administration
- Pretreatment medical and psychiatric workup and preparation of patient
- Informed consent and documentation
- Adverse side effects
- Patient safety post-treatment
- Clinical staffing, monitoring and safety equipment
- Potential for abuse and diversion and how to mitigate
- Ethical considerations

Those prescribers who are also providing psychotherapy should have additional training in:

- Role of set and setting
- Integration and ongoing psychological care

If a prescriber is not providing psychotherapy it is still recommended that the clinician has an understanding of the above topics as well as their importance in KAT.

In addition, providers should continue medical education around the use of ketamine on an annual basis.

Ongoing individual and/or peer clinical supervision is also strongly encouraged. It should be worth noting that leaders in psychotherapy working with non-ordinary states have published recommendations on additional core competencies that clinicians should work to develop - some of which may be seen as atypical from a conventional medical point of view (Phelps 2017).

References

Anand, A., Mathew, S., Sanacora, G., Murrough J., Goes, F., Altinay, M., Aloysi, A., Asghar-Ali, A., Barnett, B., Chang, L., Collins, K., Costi, S., et al. (2023). Ketamine Versus ECT for Non-Psychotic Treatment-Resistant Major Depression. *New England Journal of Medicine, May 24 2023,* from https://www.nejm.org/doi/full/10.1056/NEJMoa2302399

ASA Physical Status Classification System. American Society of Anesthesiologists. (2014, October 15). Retrieved July 7, 2021, from https://www.asahq.org/standards-and-guidelines/asa-physical-status-classification-system

Bahji, A., Vazquez, G. H., & Zarate, C. A. (2021). Comparative efficacy of racemic ketamine and esketamine for depression: A systematic review and meta-analysis. *Journal of Affective Disorders, 278,* 542–555. https://doi.org/10.1016/j.jad.2020.09.071

Ballard, E. D., & Zarate, C. A. (2020). The role of dissociation in ketamine's antidepressant effects. *Nature Communication, 11,* 6431. https://doi.org/10.1038/s41467-020-20190-4

Barreveld, A. M., Correll, D. J., Liu, X., Max, B., McGowan, J. A., Shovel, L., Wasan, A. D., & Nedeljkovic, S. S. (2013). Ketamine decreases postoperative pain scores in patients taking opioids for chronic pain: results of a prospective, randomized, double-blind study. *Pain medicine (Malden, Mass.), 14*(6), 925–934. https://doi.org/10.1111/pme.12086

Bathje, G. J., Majeski, E., & Kudowor, M. (2022). Psychedelic integration: An analysis of the concept and its practice. *Frontiers in Psychiatry, 13.* https://doi.org/10.3389/fpsyg.2022.824077

Bell, R. F., Dahl, J. B., Moore, R. A., & Kalso, E. (2005). Peri-operative ketamine for acute post-operative pain: a quantitative and qualitative systematic review (Cochrane review). *Acta anaesthesiologica Scandinavica, 49*(10), 1405–1428. https://doi.org/10.1111/j.1399-6576.2005.00814.x

Bellolio, M. F., Gilani, W. I., Barrionuevo, P., Murad, M. H., Erwin, P. J., Anderson, J. R., Miner, J. R., & Hess, E. P. (2016). Incidence of adverse events in adults undergoing procedural sedation in the Emergency Department: A systematic review and meta-analysis. *Academic Emergency Medicine, 23*(2), 119–134. https://doi.org/10.1111/acem.12875

Berman RM, Cappiello A, Anand A, Oren Da, Heninger GR, Charney DS, Krystal JH. (2000). Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry 47*:351–354

Bonnett, C. J., Jain, R., Wallington, D. A., & Schock, T. R. (2021). Intramuscular ketamine to treat major depressive disorder: a case series of forty patients. *Journal of Psychiatry and Mental Health, 6*(2). https://doi.org/10.16966/2474-7769.145

Brennan, W., & Belser, A. B. (2022). Models of Psychedelic-Assisted Psychotherapy: A Contemporary Assessment and an Introduction to EMBARK, a Transdiagnostic, Trans-Drug Model. Frontiers in psychology, 13, 866018. https://doi.org/10.3389/fpsyg.2022.866018

Canadian Mental Health Association. (2014). Fast Facts about Mental Illness. http://www.cmha.ca/media/fast-facts-about-mentalillness/#.Uw0Eo3lupg0

Chilukuri, H., Reddy, N. P., Pathapati, R. M., Manu, A. N., Jollu, S., & Shaik, A. B. (2014). Acute antidepressant effects of intramuscular versus intravenous ketamine. *Indian journal of psychological medicine, 36*(1), 71–76. https://doi.org/10.4103/0253-7176.127258

Chong, C., Schug, S. A., Page-Sharp, M., Jenkins, B., & Ilett, K. F. (2009). Development of a sublingual/Oral formulation of ketamine for use in neuropathic pain. *Clinical Drug Investigation, 29*(5), 317-324. https://doi.org/10.2165/00044011-200929050-00004

Clark, W. H. (1977). Art and psychotherapy in Mexico. *Art Psychotherapy, 4*(1), 41-44. https://doi.org/10.1016/0090-9092(77)90021-7

Canadian Mental Health Association. (2021, July 19). *Fast facts about mental health and mental illness.* CMHA National. Retrieved November 29, 2021, from https://cmha.ca/brochure/fast-facts-about-mental-illness/

Cohen, L., Athaide, V., Wickham, M. E., Doyle-Waters, M. M., Rose, N. G., & Hohl, C. M. (2015). The effect of ketamine on intracranial and cerebral perfusion pressure and health outcomes: a systematic review. *Annals of emergency medicine, 65*(1), 43–51.e2. https://doi.org/10.1016/j.annemergmed.2014.06.018

College of Physicians and Surgeons of British Columbia. (2023, August 10). *Ketamine Administration via Intramuscular, Oral, Sublingual, and Intranasal Routes as Treatment for Mental Health Conditions and Chronic Pain in the Community Setting*. College of Physicians and Surgeons of BC. Retrieved October 19, 2023, from https://www.cpsbc.ca/files/pdf/IG-Ketamine-Administration-via-Intramuscular-Oral-Sublingual-Intranasal-Routes.pdf

Dakwar, E., Nunes, E. V., Hart, C. L., Hu, M. C., Foltin, R. W., & Levin, F. R. (2018). A sub-set of psychoactive effects may be critical to the behavioral impact of ketamine on cocaine use disorder: Results from a randomized, controlled laboratory study. *Neuropharmacology, 142*, 270–276. https://doi.org/10.1016/j.neuropharm.2018.01.005

Dakwar E, Levin F, Hart CL, Basaraba C, Choi J, Pavlicova M, Nunes EV. A Single Ketamine Infusion Combined With Motivational Enhancement Therapy for Alcohol Use Disorder: A Randomized Midazolam-Controlled Pilot Trial. Am J Psychiatry. 2020 Feb 1;177(2):125-133. doi: 10.1176/appi.ajp.2019.19070684. Epub 2019 Dec 2. PMID: 31786934.

Daly, E. J., Singh, J. B., Fedgchin, M., Cooper, K., Lim, P., Shelton, R. C., Thase, M. F., Winokur, A., Van-Nueten, L., Manji, H., Drevets, W. C. (2018). Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression. *JAMA Psychiatry. 75*(2):139-148.

Daly, E. J., Trivedi, M. H., Janik, A., Li, H., Zhang, Y., Li, X., Lane, R., Lim, P., Duca, A. R., Hough, D., Thase, M. E., Zajecka, J., Winokur, A., Divacka, I., Fagiolini, A., Cubala, W. J., Bitter, I., Blier, P., Shelton, R. C., Molero, P., … Singh, J. B. (2019). Efficacy of Esketamine Nasal Spray Plus Oral Antidepressant Treatment for Relapse Prevention in Patients With Treatment-Resistant Depression: A Randomized Clinical Trial. *JAMA psychiatry, 76*(9), 893–903. https://doi.org/10.1001/jamapsychiatry.2019.1189

Diazgranados N, Ibrahim L, Brutsche NE, Newberg A, Kronstein P, Khalife S, Kammerer WA, Quezado Z, Luckenbaugh DA, Salvadore G, Machado-Vieira R, Manji HK, Zarate CA Jr (2010a). A randomized add-on trial of an

N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. Arch Gen Psychiatry 67:793–802.

Domino, Edward F., et al. (1965). Pharmacologic Effects of CI-581, a New Dissociative Anesthetic, in Man. *Clinical Pharmacology & Therapeutics, vol. 6*, no. 3, 4 Jan. 1965, pp. 279–291., https://doi.org/10.1002/cpt196563279.

Dore, J., Turnipseed, B., Dwyer, S., Turnipseed, A., Andries, J., Ascani, G., Monnette, C., Huidekoper, A., Strauss, N., & Wolfson, P. (2019). Ketamine assisted psychotherapy (KAP): Patient demographics, clinical data and outcomes in three large practices administering ketamine with psychotherapy. *Journal of Psychoactive Drugs, 51*(2), 189–198. https://doi.org/10.1080/02791072.2019.1587556

Drayna, P. C., Estrada, C., Wang, W., Saville, B. R., & Arnold, D. H. (2012). Ketamine sedation is not associated with clinically meaningful elevation of intraocular pressure. *The American journal of emergency medicine, 30*(7), 1215–1218. https://doi.org/10.1016/j.ajem.2011.06.001

Evans, J. W., Szczepanik, J., Brutsché, N., Park, L. T., Nugent, A. C., & Zarate, C. A., Jr (2018). Default Mode Connectivity in Major Depressive Disorder Measured Up to 10 Days After Ketamine Administration. *Biological psychiatry, 84*(8), 582–590. https://doi.org/10.1016/j.biopsych.2018.01.027

Fava, M., Freeman, M. P., Flynn, M., Judge, H., Hoeppner, B. B., Cusin, C., Ionescu, D. F., Mathew, S. J., Chang, L. C., Iosifescu, D. V., Murrough, J., Debattista, C., Schatzberg, A. F., Trivedi, M. H., Jha, M. K., Sanacora, G., Wilkinson, S. T., & Papakostas, G. I. (2018). Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (TRD). *Molecular Psychiatry, 25*(7), 1592-1603. https://doi.org/10.1038/s41380-018-0256-5

Feder, A., Parides, M. K., Murrough, J. W., Perez, A. M., Morgan, J. E., Saxena, S., Kirkwood, K., Aan Het Rot, M., Lapidus, K. A., Wan, L. B., Iosifescu, D., & Charney, D. S. (2014). Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: a randomized clinical trial. *JAMA psychiatry, 71*(6), 681–688. https://doi.org/10.1001/jamapsychiatry.2014.6

Feder, A., Costi, S., Rutter, S. B., Collins, A. B., Govindarajulu, U., Jha, M. K., Horn, S. R., Kautz, M., Corniquel, M., Collins, K. A., Bevilacqua, L., Glasgow, A. M., Brallier, J., Pietrzak, R. H., Murrough, J. W., & Charney, D. S. (2021). A Randomized Controlled Trial of Repeated Ketamine Administration for Chronic Posttraumatic Stress Disorder. *The American journal of psychiatry, 178*(2), 193–202. https://doi.org/10.1176/appi.ajp.2020.20050596

Feifel, D., Dadiomov, D., & C Lee, K. (2020). Safety of Repeated Administration of Parenteral Ketamine for Depression. *Pharmaceuticals (Basel, Switzerland), 13*(7), 151. https://doi.org/10.3390/ph13070151

Fu, D. J., Ionescu, D. F., Li, X., Lane, R., Lim, P., Sanacora, G., Hough, D., Manji, H., Drevets, W. C., & Canuso, C. M. (2020). Esketamine Nasal Spray for Rapid Reduction of Major Depressive Disorder Symptoms in Patients Who Have Active Suicidal Ideation With Intent: Double-Blind, Randomized Study (ASPIRE I). The *Journal of clinical psychiatry, 81*(3), 19m13191. https://doi.org/10.4088/JCP.19m13191

Glue, P., Medlicott, N. J., Harland, S., Neehoff, S., Anderson-Fahey, B., Le Nedelec, M., Gray, A., & McNaughton, N. (2017). Ketamine's dose-related effects on anxiety symptoms in patients with treatment refractory anxiety disorders. *Journal of psychopharmacology (Oxford, England), 31*(10), 1302–1305. https://doi.org/10.1177/0269881117705089

Gómez-Revuelta, M., Fernández-Rodríguez, M., Boada-Antón, L., & Vázquez-Bourgon, J. (2020). Apnea during slow sub-anaesthetic infusion of intravenous ketamine for treatment-resistant depression. *Therapeutic advances in psychopharmacology, 10*, 2045125320981498. https://doi.org/10.1177/2045125320981498

Government of Canada. (2021, November 3). Product information. Maintenance. Retrieved November 13, 2021, from https://health-products.canada.ca/dpd-bdpp/info.do?lang=en&code=1215

Grabski, M., Borissova, A., Marsh, B., Morgan, C., & Curran, H. V. (2020). Ketamine as a mental health treatment: Are acute psychoactive effects associated with outcomes? A systematic review. *Behavioural brain research, 392*, 112629. https://doi.org/10.1016/j.bbr.2020.112629

Green, S. M., Roback, M. G., Krauss, B., Brown, L., McGlone, R. G., Agrawal, D., McKee, M., Weiss, M., Pitetti, R. D., Hostetler, M. A., Wathen, J. E., Treston, G., Garcia Pena, B. M., Gerber, A. C., & Losek, J. D. (2009). Predictors of airway and respiratory adverse events with ketamine sedation in the emergency department: An

individual-patient data meta-analysis of 8,282 children. *Annals of Emergency Medicine, 54(*2), 158-168.e4. https://doi.org/10.1016/j.annemergmed.2008.12.011

Green, S. M., Andolfatto, G., & Krauss, B. S. (2015). Ketamine and intracranial pressure: no contraindication except hydrocephalus. *Annals of emergency medicine, 65*(1), 52–54. https://doi.org/10.1016/j.annemergmed.2014.08.025

Grof, S., Goodman, L. E., Richards, W. A., & Kurland, A. A. (1973). LSD-assisted psychotherapy in patients with terminal cancer. International Pharmacopsychiatry, 8, 129–144. https://doi.org/10.1159/000467984

Grunebaum, M. F., Galfalvy, H. C., Choo, T. H., Keilp, J. G., Moitra, V. K., Parris, M. S., Marver, J. E., Burke, A. K., Milak, M. S., Sublette, M. E., Oquendo, M. A., & Mann, J. J. (2018). Ketamine for Rapid Reduction of Suicidal Thoughts in Major Depression: A Midazolam-Controlled Randomized Clinical Trial. *The American journal of psychiatry, 175*(4), 327–335. https://doi.org/10.1176/appi.ajp.2017.17060647

Haq, A. U., Sitzmann, A. F., Goldman, M. L., Maixner, D. F., & Mickey, B. J. (2015). Response of depression to electroconvulsive therapy. *The Journal of Clinical Psychiatry, 76*(10), 1374-1384. https://doi.org/10.4088/jcp.14r09528

Hartogsohn, I. (2017). Constructing drug effects: A history of set and setting. *Drug Science, Policy and Law, 3*. https://doi.org/10.1177/2050324516683325

Ionescu, D. F., Bentley, K. H., Eikermann, M., Taylor, N., Akeju, O., Swee, M. B., Pavone, K. J., Petrie, S. R., Dording, C., Mischoulon, D., Alpert, J. E., Brown, E. N., Baer, L., Nock, M. K., Fava, M., & Cusin, C. (2019). Repeat-doseketamine augmentation for treatment-resistant depression with chronic suicidal ideation: A randomized, double blind, placebo controlled trial. *Journal of Affective Disorders, 243*, 516-524. https://doi.org/10.1016/j.jad.2018.09.037

Janssen Pharmaceuticals. (2020). SPRAVATO® (esketamine) nasal spray, ciii highlights of prescribing information. https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/SPRAVATO-pi.pdf

Jetté, M., Sidney, K., & Blümche, G. (1990). Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity. Clinical Cardiology, 12(8). https://doi.org/10.1002/clc.4960130809

Jones, J. L., Mateus, C. F., Malcolm, R. J., Brady, K. T., & Back, S. E. (2018). Efficacy of ketamine in the treatment of Substance Use Disorders: A systematic review. *Frontiers in Psychiatry, 9*. https://doi.org/10.3389/fpsyt.2018.00277

Ketha, J. K., Ilumbulumbu, M. K., Valimungighe, M. M., Nzanzu, B. P. F., Bekaert, P., Banguti, P. R., Munyambalu, D. K., Sikakulya, F. K., & Eltringham, R. (2019). Use of Ketamine in Rural Area at the East of the Democratic Republic of the Congo (DRC). *Journal of Anesthesia & Clinical Research, 10*(6), 1000895.

Kheirabadi, D., Kheirabadi, G. R., Mirlohi, Z., Tarrahi, M. J., & Norbaksh, A. (2020). Comparison of Rapid Antidepressant

and Antisuicidal Effects of Intramuscular Ketamine, Oral Ketamine, and Electroconvulsive Therapy in Patients With Major Depressive Disorder: A Pilot Study. *Journal of clinical psychopharmacology, 40*(6), 588–593. https://doi.org/10.1097/JCP.0000000000001289

Knoll, A. D., & MacLennan, R. N. (2017). Prevalence and correlates of depression in Canada: Findings from the Canadian Community Health Survey. Canadian Psychology / Psychologie canadienne, 58(2), 116–123. https://doi.org/10.1037/cap0000103

Krupitsky, E. M., Burakov, A. M., Dunaevsky, I. V., Romanova, T. N., Slavina, T. Y., & Grinenko, A. Y. (2007). Single versus repeated sessions of ketamine-assisted psychotherapy for people with heroin dependence. *Journal of Psychoactive Drugs, 39*(1), 13–19. https://doi.org/10.1080/02791072.2007.10399860

Kryst, J., Kawalec, P., Mitoraj, A. M., Pilc, A., Lasoń, W., & Brzostek, T. (2020). Efficacy of single and repeated administration of ketamine in unipolar and bipolar depression: A meta-analysis of randomized clinical trials. *Pharmacological Reports, 72*(3), 543-562. https://doi.org/10.1007/s43440-020-00097-z

Lai, R., Katalinic, N., Glue, P., Somogyi, A. A., Mitchell, P. B., Leyden, J., Harper, S., & Loo, C. K. (2014). Pilot dose-response trial of i.v. ketamine in treatment-resistant depression. *The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry, 15*(7), 579–584. https://doi.org/10.3109/15622975.2014.922697

Lapidus, K. A., Levitch, C. F., Perez, A. M., Brallier, J. W., Parides, M. K., Soleimani, L., Feder, A., Iosifescu, D. V., Charney, D. S., & Murrough, J. W. (2014). A randomized controlled trial of intranasal ketamine in major depressive disorder. *Biological Psychiatry, 76*(12), 970-976. https://doi.org/10.1016/j.biopsych.2014.03.026

Laskowski, K., Stirling, A., McKay, W. P., & Lim, H. J. (2011). A systematic review of intravenous ketamine for postoperative analgesia. *Canadian Journal of Anesthesia/Journal Canadien D'anesthésie, 58*(10), 911–923. https://doi.org/10.1007/s12630-011-9560-0

Leslie, E., Pittman, E., Drew, B., & Walrath, B. (2021). Ketamine use in operation enduring freedom. *Military Medicine, 186*(7-8), e720-e725. https://doi.org/10.1093/milmed/usab117

Loftus RW, Yeager MP, Clark JA, et al. Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. Anesthesiology. 2010;113: 639–646.

Loo, C. K., Gálvez, V., O'Keefe, E., Mitchell, P. B., Hadzi-Pavlovic, D., Leyden, J., Harper, S., Somogyi, A. A., Lai, R., Weickert, C. S., & Glue, P. (2016). Placebo-controlled pilot trial testing dose titration and intravenous, intramuscular and subcutaneous routes for ketamine in depression. *Acta Psychiatrica Scandinavica, 134*(1), 48-56. https://doi.org/10.1111/acps.12572

Luckenbaugh, D. A., Niciu, M. J., Ionescu, D. F., Nolan, N. M., Richards, E. M., Brutsche, N. E., Guevara, S., & Zarate, C. A. (2014). Do the dissociative side effects of ketamine mediate its antidepressant effects?. *Journal of affective disorders, 159*, 56–61. https://doi.org/10.1016/j.jad.2014.02.017

Mathai, D.S., Nayak, S.M., Yaden, D.B. *et al.* Reconsidering "dissociation" as a predictor of antidepressant efficacy for esketamine. *Psychopharmacology* 240, 827–836 (2023). https://doi.org/10.1007/s00213-023-06324-8

Matveychuk, D., Thomas, R. K., Swainson, J., Khullar, A., MacKay, M., Baker, G. B., & Dursun, S. M. (2020). Ketamine as an antidepressant: Overview of its mechanisms of action and potential predictive biomarkers. *Therapeutic Advances in Psychopharmacology, 10*, 204512532091665. https://doi.org/10.1177/2045125320916657

McIntyre, R. S., Carvalho, I. P., Lui, L., Majeed, A., Masand, P. S., Gill, H., Rodrigues, N. B., Lipsitz, O., Coles, A. C., Lee, Y., Tamura, J. K., Iacobucci, M., Phan, L., Nasri, F., Singhal, N., Wong, E. R., Subramaniapillai, M., Mansur, R., Ho, R., Lam, R. W., … Rosenblat, J. D. (2020). The effect of intravenous, intranasal, and oral ketamine in mood disorders: A meta-analysis. *Journal of affective disorders, 276*, 576–584. https://doi.org/10.1016/j.jad.2020.06.050

McIntyre, R. S. (2021). Ketamine and esketamine for treatment-resistant depression: Response to Reus, mattes, and Schatzberg. *American Journal of Psychiatry, 178*(12), 1130-1132. https://doi.org/10.1176/appi.ajp.2021.21060653r

Mental Health Commission of Canada. (2013). Making the Case for Investing in Mental Health in Canada. http://www.mentalhealthcommission.ca/English/node/5020

Mihaljević, S., Pavlović, M., Reiner, K., & Ćaćić, M. (2020). Therapeutic Mechanisms of Ketamine. *Psychiatria Danubina, 32*(3-4), 325–333. https://doi.org/10.24869/psyd.2020.325

Moda-Sava, R. N., Murdock, M. H., Parekh, P. K., Fetcho, R. N., Huang, B. S., Huynh, T. N., Witztum, J., Shaver, D. C., Rosenthal, D. L., Alway, E. J., Lopez, K., Meng, Y., Nellissen, L., Grosenick, L., Milner, T. A., Deisseroth, K., Bito, H., Kasai, H., & Liston, C. (2019). Sustained rescue of prefrontal circuit dysfunction by antidepressant-induced spine formation. Science (New York, N.Y.), 364(6436), eaat8078. https://doi.org/10.1126/science.aat8078

Morgan N. L. (2020). Integrating psychedelic experiences utilizing the internal family systems therapeutic model. *Int. J. Soc. Sci. Manage. Rev* 3 257–264.

Morrison, R. L., Fedgchin, M., Singh, J., Van Gerven, J., Zuiker, R., Lim, K. S., van der Ark, P., Wajs, E., Xi, L., Zannikos, P., & Drevets, W. C. (2018). Effect of intranasal esketamine on cognitive functioning in healthy participants: a randomized, double-blind, placebo-controlled study. *Psychopharmacology, 235*(4), 1107–1119. https://doi.org/10.1007/s00213-018-4828-5

Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Green CE, Perez AM, Iqbal S, Pillemer S, Foulkes A, Shah A, Charney DS, Mathew SJ (2013). Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. Am J Psychiatry 170:1134–1142.

Murrough, J. W., Burdick, K. E., Levitch, C. F., Perez, A. M., Brallier, J. W., Chang, L. C., Foulkes, A., Charney, D. S., Mathew, S. J., & Iosifescu, D. V. (2015). Neurocognitive effects of ketamine and association with antidepressant response in individuals with treatment-resistant depression: a randomized controlled trial.

Neuropsychopharmacology : official publication of the *American College of Neuropsychopharmacology, 40*(5), 1084–1090. https://doi.org/10.1038/npp.2014.298

Ng, J., Rosenblat, J. D., Lui, L., Teopiz, K. M., Lee, Y., Lipsitz, O., Mansur, R. B., Rodrigues, N. B., Nasri, F., Gill, H., Cha, D. S., Subramaniapillai, M., Ho, R. C., Cao, B., & McIntyre, R. S. (2021). Efficacy of ketamine and esketamine on functional outcomes in treatment-resistant depression: A systematic review. Journal of affective disorders, 293, 285–294. https://doi.org/10.1016/j.jad.2021.06.032

Niesters, M., Martini, C., & Dahan, A. (2014). Ketamine for chronic pain: Risks and benefits. British *Journal of Clinical Pharmacology, 77*(2), 357-367. https://doi.org/10.1111/bcp.12094

Nikolin, S., Rodgers, A., Schwaab, A., Bahji, A., Zarate, C., Jr, Vazquez, G., & Loo, C. (2023). Ketamine for the treatment of major depression: a systematic review and meta-analysis. EClinicalMedicine, 62, 102127. https://doi.org/10.1016/j.eclinm.2023.102127

Noppers, I. M., Niesters, M., Aarts, L., Bauer, M., Drewes, A. M., Dahan, A., & Sarton, E. Y. (2011). Drug-induced liver injury following a repeated course of ketamine treatment for chronic pain in CRPS type 1 patients: a report of 3 cases. *Pain, 152*(9), 2173–2178. https://doi.org/10.1016/j.pain.2011.03.026

Nowacka, A., & Borczyk, M. (2019). Ketamine applications beyond anesthesia - A literature review. *European journal of pharmacology, 860*, 172547. https://doi.org/10.1016/j.ejphar.2019.172547

O'Brien, M. E., Fuh, L., Raja, A. S., White, B. A., Yun, B. J., & Hayes, B. D. (2020). Reduced-dose intramuscular ketamine for severe agitation in an academic emergency department. *Clinical toxicology (Philadelphia, Pa.), 58*(4), 294–298. https://doi.org/10.1080/15563650.2019.1643468

Ochs-Ross, R., Daly, E. J., Zhang, Y., Lane, R., Lim, P., Morrison, R. L., Hough, D., Manji, H., Drevets, W. C., Sanacora, G., Steffens, D. C., Adler, C., McShane, R., Gaillard, R., Wilkinson, S. T., & Singh, J. B. (2020). Efficacy and Safety of Esketamine Nasal Spray Plus an Oral Antidepressant in Elderly Patients With Treatment-Resistant Depression-TRANSFORM-3. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry, 28*(2), 121–141. https://doi.org/10.1016/j.jagp.2019.10.008

Par Pharmaceutical. (n.d.). KETALAR (ketamine hydrochloride) injection. Retrieved November 21, 2021, from https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/016812s043lbl.pd

Passie, T., Adams, H. A., Logemann, F., Brandt, S. D., Wiese, B., & Karst, M. (2021). Comparative effects of (S)-ketamine and racemic (R/S)-ketamine on psychopathology, state of consciousness and neurocognitive performance in healthy volunteers. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology, 44*, 92–104. https://doi.org/10.1016/j.euroneuro.2021.01.005

Peltoniemi, M. A., Hagelberg, N. M., Olkkola, K. T., & Saari, T. I. (2016). Ketamine: A Review of Clinical Pharmacokinetics and Pharmacodynamics in Anesthesia and Pain Therapy. Clinical pharmacokinetics, 55(9), 1059–1077. https://doi.org/10.1007/s40262-016-0383-6

Phillips, J. L., Norris, S., Talbot, J., Birmingham, M., Hatchard, T., Ortiz, A., Owoeye, O., Batten, L. A., & Blier, P. (2019). Single, Repeated, and Maintenance Ketamine Infusions for Treatment-Resistant Depression: A Randomized

Controlled Trial. *The American journal of psychiatry, 176*(5), 401–409. https://doi.org/10.1176/appi.ajp.2018.18070834

Popova, V., Daly, E. J., Trivedi, M., Cooper, K., Lane, R., Lim, P., Mazzucco, C., Hough, D., Thase, M. E., Shelton, R. C., Molero, P., Vieta, E., Bajbouj, M., Manji, H., Drevets, W. C., & Singh, J. B. (2019). Efficacy and Safety of Flexibly Dosed Esketamine Nasal Spray Combined With a Newly Initiated Oral Antidepressant in Treatment-Resistant Depression: A Randomized Double-Blind Active-Controlled Study. *The American journal of psychiatry, 176*(6), 428–438. https://doi.org/10.1176/appi.ajp.2019.19020172

Price, R. B., Nock, M. K., Charney, D. S., & Mathew, S. J. (2009). Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. Biological psychiatry, 66(5), 522–526. https://doi.org/10.1016/j.biopsych.2009.04.029

Riva-Posse, P., Reiff, C. M., Edwards, J. A., Job, G. P., Galendez, G. C., Garlow, S. J., Saah, T. C., Dunlop, B. W., & McDonald, W. M. (2018). Blood pressure safety of subanesthetic ketamine for depression: A report on 684 infusions. *Journal of affective disorders, 236*, 291–297. https://doi.org/10.1016/j.jad.2018.02.025

Rodrigues, N. B., McIntyre, R. S., Lipsitz, O., Lee, Y., Cha, D. S., Nasri, F., Gill, H., Lui, L. M., Subramaniapillai, M., Kratiuk, K., Lin, K., Ho, R., Mansur, R. B., & Rosenblat, J. D. (2020). Safety and tolerability of IV ketamine in adults with major depressive or bipolar disorder: Results from the Canadian rapid treatment center of excellence. *Expert Opinion on Drug Safety, 19*(8), 1031-1040. https://doi.org/10.1080/14740338.2020.1776699

Ross, C., Jain, R., Bonnett, C. J., & Wolfson, P. (2019). High-dose ketamine infusion for the treatment of posttraumatic stress disorder in combat veterans. *Annals of clinical psychiatry : official journal of the American Academy of Clinical Psychiatrists, 31*(4), 271–279.

Sanacora, G., Frye, M. A., McDonald, W., Mathew, S. J., Turner, M. S., Schatzberg, A. F., Summergrad, P., & Nemeroff, C. B. (2017). A consensus statement on the use of ketamine in the treatment of mood disorders. *JAMA Psychiatry, 74*(4), 399. https://doi.org/10.1001/jamapsychiatry.2017.0080

Schenberg E. E. (2018). Psychedelic-Assisted Psychotherapy: A Paradigm Shift in Psychiatric Research and Development. *Frontiers in pharmacology, 9*, 733. https://doi.org/10.3389/fphar.2018.00733

Schwartzman, R. J., Alexander, G. M., Grothusen, J. R., Paylor, T., Reichenberger, E., & Perreault, M. (2009). Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: a double-blind placebo controlled study. *Pain, 147*(1-3), 107–115. https://doi.org/10.1016/j.pain.2009.08.015

Schwenk E. S., Viscusi E. R., Buvanendran A., Hurley R. W., Wasan A. D., Narouze S., Bhatia A. (2018). Consensus guidelines on the use of intravenous ketamine infusions for acute pain management from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. *Regional Anesthesia and Pain Medicine, 43*(5), 456-466. doi:10.1097

Standing Senate Committee on Social Affairs, Science and Technology. (2014, January). Prescription Pharmaceuticals in Canada. Retrieved September 10, 2021, from https://sencanada.ca/content/sen/Committee/412/soci/rep/rep05jan14-e.pdf

Shimonovich S, Gigi R, Shapira A, Sarig-Meth T, Nadav D, Rozenek M, et al. Intranasal ketamine for acute traumatic pain in the Emergency Department: a prospective, randomized clinical trial of efficacy and safety. BMC Emerg Med. 2016 Nov 9;16(1):43.

Short, B., Fong, J., Galvez, V., Shelker, W., & Loo, C. K. (2018). Side-effects associated with ketamine use in depression: a systematic review. The lancet. *Psychiatry, 5*(1), 65–78. https://doi.org/10.1016/S2215-0366(17)30272-9

Sigtermans, M. J., Van Hilten, J. J., Bauer, M. C., Arbous, S. M., Marinus, J., Sarton, E. Y., & Dahan, A. (2009). Ketamine produces effective and long-term pain relief in patients with complex regional pain syndrome type 1. *Pain, 145*(3), 304-311. https://doi.org/10.1016/j.pain.2009.06.023

Singh, J. B., Fedgchin, M., Daly, E. J., De Boer, P., Cooper, K., Lim, P., Pinter, C., Murrough, J. W., Sanacora, G., Shelton, R. C., Kurian, B., Winokur, A., Fava, M., Manji, H., Drevets, W. C., & Van Nueten, L. (2016). A Double-Blind, Randomized, Placebo-Controlled, Dose-Frequency Study of Intravenous Ketamine in Patients With Treatment-Resistant Depression. The American journal of psychiatry, 173(8), 816–826. https://doi.org/10.1176/appi.ajp.2016.16010037

Smith WR, Sisti D. Ethics and ego dissolution: the case of psilocybin. J Med Ethics. 2020 May 27:medethics-2020-106070. doi: 10.1136/medethics-2020-106070. Epub ahead of print. PMID: 32461241; PMCID: PMC9202314.

Sos, P., Klirova, M., Novak, T., Kohutova, B., Horacek, J., & Palenicek, T. (2013). Relationship of ketamine's antidepressant and psychotomimetic effects in unipolar depression. *Neuro Endocrinol Lett 34*:287–293.

Stippl A, Scheidegger M, Aust S, Herrera A, Bajbouj M, Gärtner M, Grimm S. Ketamine specifically reduces cognitive symptoms in depressed patients: An investigation of associated neural activation patterns. J Psychiatr Res. 2021 Apr;136:402-408. doi: 10.1016/j.jpsychires.2021.02.028. Epub 2021 Feb 16. PMID: 33647855.

Strayer, R. J., & Nelson, L. S. (2008). Adverse events associated with ketamine for procedural sedation in adults. *The American Journal of Emergency Medicine, 26*(9), 985-1028. https://doi.org/10.1016/j.ajem.2007.12.005

Subramaniam, K., Akhouri, V., Glazer, P. A., Rachlin, J., Kunze, L., Cronin, M., Desilva, D., Asdourian, C. P., & Steinbrook, R. A. (2011). Intra- and postoperative very low dose intravenous ketamine infusion does not increase pain relief after major spine surgery in patients with preoperative narcotic analgesic intake. *Pain Medicine, 12*(8), 1276-1283. https://doi.org/10.1111/j.1526-4637.2011.01144.x

Swainson, J., McGirr, A., Blier, P., Brietzke, E., Richard-Devantoy, S., Ravindran, N., Blier, J., Beaulieu, S., Frey, B. N., Kennedy, S. H., McIntyre, R. S., Milev, R. V., Parikh, S. V., Schaffer, A., Taylor, V. H., Tourjman, V., van Ameringen, M., Yatham, L. N., Ravindran, A. V., & Lam, R. W. (2021). The Canadian Network for Mood and Anxiety Treatments (CANMAT) Task Force Recommendations for the Use of Racemic Ketamine in Adults with Major Depressive Disorder: Recommandations Du Groupe De Travail Du Réseau Canadien Pour Les Traitements De L'humeur Et De L'anxiété (Canmat) Concernant L'utilisation De La Kétamine Racémique Chez Les Adultes Souffrant De Trouble Dépressif Majeur. Canadian journal of psychiatry. Revue canadienne de psychiatrie, 66(2), 113–125. https://doi.org/10.1177/0706743720970860

Szarmach, J., Cubała, W. J., Włodarczyk, A., & Wiglusz, M. S. (2019). Short-term ketamine administration in treatment-resistant depression: focus on cardiovascular safety. *Psychiatria Danubina, 31*(Suppl 3), 585–590.

Thomas, R. K., Baker, G., Lind, J., & Dursun, S. (2018). Rapid effectiveness of intravenous ketamine for ultraresistant depression in a clinical setting and evidence for baseline anhedonia and bipolarity as clinical predictors of effectiveness. *Journal of psychopharmacology (Oxford, England), 32*(10), 1110–1117. https://doi.org/10.1177/0269881118793104

University Hospital Clinical algorithm for ketamine administration for depression. (n.d.) University Health System. Retrieved from
https://www.universityhealthsystem.com/~/media/files/clinical-pathways/ketamine-administration-guideline-080114.pdf?la=en

Veraart, J., Smith-Apeldoorn, S. Y., Spijker, J., Kamphuis, J., & Schoevers, R. A. (2021). Ketamine Treatment for Depression in Patients With a History of Psychosis or Current Psychotic Symptoms: A Systematic Review. The Journal of clinical psychiatry, 82(4), 20r13459. https://doi.org/10.4088/JCP.20r13459

Wajs, E., Aluisio, L., Holder, R., Daly, E. J., Lane, R., Lim, P., George, J. E., Morrison, R. L., Sanacora, G., Young, A. H., Kasper, S., Sulaiman, A. H., Li, C. T., Paik, J. W., Manji, H., Hough, D., Grunfeld, J., Jeon, H. J., Wilkinson, S. T., Drevets, W. C., … Singh, J. B. (2020). Esketamine Nasal Spray Plus Oral Antidepressant in Patients With Treatment-Resistant Depression: Assessment of Long-Term Safety in a Phase 3, Open-Label Study (SUSTAIN-2). The *Journal of clinical psychiatry, 81*(3), 19m12891. https://doi.org/10.4088/JCP.19m12891

Wei, Y., Chang, L., & Hashimoto, K. (2020). A historical review of antidepressant effects of ketamine and its enantiomers.
Pharmacology Biochemistry and Behavior, 190, 172870. https://doi.org/10.1016/j.pbb.2020.172870

World Health Organization. (2017). *Depression and Other Common Mental Disorders: Global Health Estimates.* Retrieved September 10, 2021, from
https://apps.who.int/iris/bitstream/handle/10665/254610/WHO-MSD-MER-2017.2-eng.pdf

World Health Organization. (2021, September 13). Depression. WHO | World Health Organization. Retrieved October 12, 2021, from https://www.who.int/news-room/fact-sheets/detail/depression

Wilkinson, S. T., Ballard, E. D., Bloch, M. H., Mathew, S. J., Murrough, J. W., Feder, A., Sos, P., Wang, G., Zarate, C. A., Jr, & Sanacora, G. (2018). The Effect of a Single Dose of Intravenous Ketamine on Suicidal Ideation: A Systematic Review and Individual Participant Data Meta-Analysis. *The American journal of psychiatry, 175*(2), 150–158. https://doi.org/10.1176/appi.ajp.2017.17040472

Wilkowska, A., Szałach, Ł., Słupski, J., Wielewicka, A., Czarnota, M., Gałuszko-Węgielnik, M., Wiglusz, M. S., & Cubała, W. J. (2020). Affective Switch Associated With Oral, Low Dose Ketamine Treatment in a Patient With Treatment

Resistant Bipolar I Depression. Case Report and Literature Review. *Frontiers in psychiatry, 11*, 516. https://doi.org/10.3389/fpsyt.2020.00516

Witt, K., Potts, J., Hubers, A., Grunebaum, M. F., Murrough, J. W., Loo, C., Cipriani, A., & Hawton, K. (2020). Ketamine for suicidal ideation in adults with psychiatric disorders: A systematic review and meta-analysis of treatment trials. *The Australian and New Zealand journal of psychiatry, 54*(1), 29–45. https://doi.org/10.1177/0004867419883341

Xu, Y., Hackett, M., Carter, G., Loo, C., Gálvez, V., Glozier, N., Glue, P., Lapidus, K., McGirr, A., Somogyi, A. A., Mitchell,P. B., & Rodgers, A. (2016). Effects of Low-Dose and Very Low-Dose Ketamine among Patients with Major Depression: a Systematic Review and Meta-Analysis. The international journal of neuropsychopharmacology, 19(4), pyv124. https://doi.org/10.1093/ijnp/pyv124

Yanagihara, Y., Ohtani, M., Kariya, S., Uchino, K., Hiraishi, T., Ashizawa, N., Aoyama, T., Yamamura, Y., Yamada, Y., & Iga, T. (2003). Plasma concentration profiles of ketamine and norketamine after administration of various ketamine preparations to healthy Japanese volunteers. *Biopharmaceutics & drug disposition, 24*(1), 37–43. https://doi.org/10.1002/bdd.336

Zanos, P., Moaddel, R., Morris, P. J., Riggs, L. M., Highland, J. N., Georgiou, P., Pereira, E. F., Albuquerque, E. X., Thomas, C. J., Zarate, C. A., & Gould, T. D. (2018). Ketamine and ketamine metabolite pharmacology: Insights into therapeutic mechanisms. *Pharmacological Reviews, 70*(3), 621-660. https://doi.org/10.1124/pr.117.015198

Zarate CA Jr, Brutsche N, Laje G, Luckenbaugh DA, Venkata SLV, Ramamoorthy A, Moaddel R, Wainer IW (2012). Relationship of ketamine's plasma metabolites with response, diagnosis, and side effects in major depression. *Biol Psychiatry 72*:331–338.

Zeiler, F. A., Teitelbaum, J., West, M., & Gillman, L. M. (2014). The ketamine effect on intracranial pressure in nontraumatic neurological illness. *Journal of critical care, 29*(6), 1096–1106. https://doi.org/10.1016/j.jcrc.2014.05.024in