Outpatient Use of Ketamine for Mental Health Conditions

Practice Standards Recommendations

Ketamine Assisted Therapy Association of Canada

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Preamble

The Ketamine Assisted Therapy Association of Canada (KATA) is a not-for-profit interdisciplinary organisation originating in British Columbia. Our 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. **Our intention is that these practice standards recommendations will facilitate physicians, prescribers, and more broadly health-care professionals, to review and update their policies and procedures to provide ketamine treatment in a safe and effective manner.**

In August, 2021, the CPSBC released an Interim Guidance document on the use of non-intravenous ketamine in the community setting. This document clarifies that non-intravenous routes of ketamine 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. Additional to the Interim Guidance are other CPSBC, College of Physicians and Surgeons of Alberta (CPSA) and College of Physicians and Surgeons of Saskatchewan (CPSS) resources that 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.

The impact of mental health conditions on British Columbians is significant with approximately 17% of the population experiencing mental illness (CMHA, 2021). Major depressive disorder (MDD) ranks as the second leading cause of disability in the world (Matveychuk et al., 2020), affecting some 280 million people according to the World Health Organization (WHO, 2021). Studies indicate that up to 30% of patients will not respond to optimised standard medical and non-medical interventions for depression. In addition, up to 40% of patients with treatment-resistant depression (TRD) do not respond to electroconvulsive therapy (ECT) (Haq et al., 2015). In addition, the commonly used serotonin, norepinephrine, and dopamine reuptake inhibitors have a delayed onset of action by several weeks, which is not ideal in patients who are often in crisis and suicidal (Witt et al., 2020).

As such, KATA recognises that there is an urgent need for access to rapid acting treatment for patients with treatment resistant depression. KATA also recognises that effective treatment for mental health conditions requires a coordinated and multidisciplinary approach that is based upon a thorough assessment, and a comprehensive treatment plan that includes both pharmacological and non-pharmacological components encompassing a complete biopsychosocial approach.

Ketamine offers hope as a safe, rapid-acting antidepressant (RAAD) that can be administered in community settings intramuscularly (IM), intranasally (IN), sublingually (SL) and orally (PO) to manage treatment-resistant depression (McIntyre et al., 2020), depression with suicidality (Grunebaum et al., 2018; Thomas et al., 2018), bipolar affective disorder (Kryst et al., 2020), and potentially, post-traumatic stress disorder (Feder et al., 2021).

Although much of the data on the effectiveness of ketamine has been done using intravenous infusions, KATA advocates 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 and other treatments such as electroconvulsive therapy (ECT). Evidence is mounting that non-intravenous ketamine is safe and effective. We advocate for its use as an alternative to current pharmacologic and non-pharmacologic standards of care as well an additional therapeutic modality for treatment-resistant cases

These practice standards recommendations intend to support safety, 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, 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 often requires 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, organisation, leadership, appropriate personnel, and physical resources to provide optimal care.

In summary, our goal is to educate, advocate for, and advise prescribers on the safe and effective use of ketamine in community settings for mental health conditions. We hope that this document may serve as a guide for prescribers and health-care professionals to use as a resource in the delivery of ketamine for mental health conditions in outpatient settings. These recommendations will be revised over time and on a regular basis as new evidence emerges.

Discussion and Recommendations

Introduction to Ketamine-Assisted Therapy

Ketamine-assisted therapy (KAT) is defined as the combination of the administration of ketamine with an additional non-pharmacological component to treatment such as psychotherapy typically done before 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 behavioural therapy, interpersonal therapy, insight-oriented psychotherapy, and somatically-focussed therapies (Dore et al., 2019).

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 optimise 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. This may reduce the risk of agitation while the patient is in the dissociative state (Hartogsohn, 2017).

Ketamine causes dissociation through complex neurochemical actions that are not yet well understood. 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 (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. In 2000, Berman published the first study about the use of ketamine infusions to treat patients with 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 anaesthetic 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 should include (R)-ketamine” (Passie et al., 2021). 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 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.

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), 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) after administration (Mihaljecić et al., 2020). 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.

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 summarises 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 in North America is common and has often been associated with new and innovative 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 randomised 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 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]

Additional off-label therapeutic uses for 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/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 we recommend that patients are screened and assessed by several medical professionals (e.g., general practitioner, psychiatrist, psychologist, specialist, registered nurse, registered therapeutic counsellor, registered clinical counsellor) and that old records are requested and examined. 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.

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

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.

The patient should be thoroughly apprised of their treatment options for their disorder(s). Such non-pharmacological options should 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 physicians 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.

Appropriate patient selection and screening is of utmost importance in ensuring the safety of KAT. Prescribers should always use their clinical judgement 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 ketamine-assisted therapy should meet all of the following criteria:

- Be of age 19 years or older
    - If the patient is under 19 years of age, they may be considered as a candidate using clinical judgement; taking into account past medical history, treatments and shall be in consultation with the primary care team
- Have participated in a comprehensive 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
- Be capable of participating in ongoing treatment as needed
- Have adequate existing or arranged supports to ensure safety during treatment process including safe transportation and access to emergency therapeutic support

Medical Considerations

- Contraindications:
    - Patients presenting to the clinic intoxicated
    - ASA ≥3 (ASA Physical Status Classification System) - see Appendix D
- Caution should be taken with:
    - BMI ≥45
    - Obstructive sleep apnea
    - METS Classifications <4 (see Appendix E - patients should have the cardiac fitness to perform light housework)
    - Patients who are otherwise cardiac or respiratory limited

Psychological/Psychiatric Considerations

Ketamine-assisted therapy 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 episode
- Caution should be taken with:
    - History of psychosis–referring or treating clinician needs to 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, psychiatric disorders (especially when the patient is unwilling to engage in psychological therapies), acute psychosocial stressors
    - 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

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 Spratato®. 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.

> "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."

In the doctor-patient therapeutic relationship, the patient has the right to make decisions about their health-care including choosing complementary or alternative therapies instead of, or as an adjunct to, conventional medicine. With regards to patient autonomy, our opinion is that adequately informed patients are not required to have failed standard therapies prior to receiving ketamine for mental health conditions.

> "The physician-patient relationship is the cornerstone of psychiatric practice, and its goal is to promote patient health and well-being, embodying the key ethical considerations of respect for persons, fairness, and beneficence. Patients often lack medical expertise and sometimes struggle with symptoms that adversely affect their autonomous decision-making. The psychiatrist is responsible for rendering medical care in the patient's best interest while respecting the patient's goals and autonomy." [2]

Physicians and prescribers must balance the ethical principles of patient autonomy with their professional obligations of providing effective – or at least non-harmful, care.

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 sedation 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 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 Physician Competencies and Training. A clinician should always use their best judgement 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

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

1. Before the session:
    a. Compare with intake blood pressure and make allowances for situational hypertension. Clinical judgement 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.

[2] American Psychiatric Association (APA). 2015. "APA Commentary on Ethics in Practice."

2. At peak drug effect: hold if not clinically indicated (indicated if signs of dyspnea, chest pain or mental status changes not consistent with expected treatment effects). See Appendix F on Blood Pressure Considerations).
3. Before discharge: hold if not clinically indicated.

Pulse oximetry is recommended if clinically indicated:

1. Before the session: in patients with increased risk of respiratory issues.
2. 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.
    a. In patients with obstructive sleep apnea, consider having the patient's head raised above 45°
3. Before discharge if clinically indicated.

Mental Health/Psychological Monitoring:

1. Before session: mental status exam, any changes since last assessed, current SI, symptoms, review informed consent.
2. During Session: dissociation is a part of the treatment process. The degree of dissociation is not critical unless accompanied by significant emotional distress. Sedation should be monitored indirectly with observation and oximetry (if indicated).
3. Post Session: confirm the patient meets physical and psychological discharge assessment criteria.

Discharge Planning and Assessment:

1. Assess the degree of dissociation, consider using a scale such as the Clinician Administered Dissociative States Scale (CADSS).
2. Reassess mental health status, reassess SI if present.
3. Assess for any medical changes.
4. Ensure safe ambulation without assistance.
5. Make a follow-up plan, give contact phone numbers, discharge instructions and discharge the patient into the care of a responsible adult.
6. Patients should be made aware that they should not operate a motor vehicle or hazardous machinery for 24 hours after treatment.

Staffing and Session Requirements

At sub-anesthetic doses in properly selected patients, ketamine is safe and does not require 1:1 monitoring of a critical care trained health professional or anesthesiologist. Consideration for staffing requirements should include the dose and route of administration of ketamine, other medications, comorbidities, and the patient's mental health stability.

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

- Ketamine must only be administered by a qualified health-care professional and monitored by a trained care provider with a minimum level of BLS training for the duration of the session. A health-care 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.
- A minimum of one medical health-care professional should be present for every four patients receiving sub-anesthetic ketamine
- The supervising physician or prescriber, if not on site, must remain on-call until the patient has met established discharge criteria.

- Personnel with expertise in mental health conditions and the clinical effects of ketamine should be on site for the duration of the session.
- All physicians must practice within the guidelines of the CPSBC. “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, 2021).

Side Effects and Adverse Effects

Ketamine can cause dose-dependent neurological, psychological, cardiovascular, and other effects. The potential adverse effects must be weighted against the benefits that patients 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). 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 parenteral ketamine to treat depression, 0.5% of patients withdrew treatment due to psychiatric effects (Feifel et al., 2020). Most psychiatric 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).

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 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 or laryngospasm have been reported in procedural sedation doses which are much higher than that used in the office setting (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.

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 are illicit users of ketamine which may contain adulterants or be used concurrently with other substances (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 the 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.

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 less common (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 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 within the guidelines of the CPSBC, which are expected to change over time as this new field of medicine develops. “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, 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 College’s guidelines for 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

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.

We understand that duplicate prescriptions are being studied for BC and are already in place in other jurisdictions (AB, SK). We recommend the following protocols for community settings which include applicable standards from the CPSBC's Non-Hospital Medical and Surgical Facilities Accreditation Program (NHMSFAP) Medication Management Accreditation Standards.

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 standardised protocols to ensure more consistency and objectivity in the medication preparation process.

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 the person who prepared it.
- Medication administration documentation is 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 unauthorised 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.
- 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
- 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 summarised 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 for IN
- 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 summarised 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 occurence. 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 anaesthesia relevant to our discussion, particularly to establish evidence for safety in the higher ranges of sub-anaesthetic 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 standardised questionnaires) for mental status were also applied but were inconsistent.

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
- CPSBC - NHMSFAP AS - Intravenous Use of Ketamine for the Treatment of Mood Disorders DRAFT
- CPSA - Clinical Toolkit - Ketamine and Esketamine: Key Considerations
- CPSS - Position on Ketamine Off-Label Use
- CPSBC - Complementary and Alternative Therapies Practice Standards
- CPSBC - NHMSFAP Medication Management Accreditation Standards

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Appendix B: Ketamine Pharmacokinetics by Route of Administration

Route	Reported Dosing	Bioavailability (%)	Peak (min)	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	15	45-120 min (check)
IN (R/S)	40-160mg, titrate to effect	45-50	5-15	–
SL	100-400mg	30	14-45	–
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

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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 is usually to recruit a homogeneous population, and can have restrictive exclusion criteria in order to minimise 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 prioritised 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 and 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 of prospective patients 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: 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.

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