Ketamine: What Prescribers & Pharmacists Need to Know

Ketamine continues to be a commonly used medication in anesthesia, emergency medicine, chronic pain management, and palliative care.

CPSM and College of Pharmacists of Manitoba (CPhM) are aware that ketamine is increasingly being prescribed off label, including for treatment resistant depression. Other regulatory jurisdictions across North America are reporting the same trend.

CPSM connected with registrants from various disciplines to better understand the evolving clinical use of ketamine in routine practice, as well as in patients with exceptional and complex care needs. **We sincerely thank all registrants who shared information about their practice**.

Key Ketamine Safety Points

Key safety points emerged from collaborating with registrants and CPhM. The **Key Points** below outline considerations for **patient safety**, **quality care**, and recommendations for **best practice** and **collaborative care**. Note that this article excludes topical (cream/ointment) ketamine products.

1) **Intravenous ketamine administration by non-hospital medical or surgical facilities must be accredited.**

2) **Health Canada has only approved ketamine as an anesthetic agent, or as intranasal ketamine (Spravato®) for treatment of severe major depressive disorder.**

3) **Unclear ketamine prescription writing is common and can delay patient care.**

4) **Collaboration is key to ensure shared understanding of the intended prescription.**

5) **Consistency and clarity are safeguards for prescribing intravenous (IV) formulations of ketamine, regardless of administration route.**

6) **Physicians must ensure they have the knowledge, skill, and clinical judgement to prescribe ketamine safely.**

7) **Monitoring and precautions are key to mitigate ketamine associated risks, like other controlled medications.**

8) **Comprehensive Urine Drug Screening (C-UDS) is a universal safety precaution.**

9) **The Prescribing Practices Program (PPP) can help. Phone (204) 774-4344 and ask for PPP.**

Key Ketamine Safety Points

1) Intravenous ketamine administration by non-hospital medical or surgical facilities must be accredited.

Registrants are reminded that any non-hospital medical or surgical facility administering **intravenous** ketamine must be accredited under the Accredited Facilities Bylaw.

2) Health Canada has only approved ketamine as an anesthetic agent, or as intranasal ketamine (Spravato®) for treatment of severe major depressive disorder.

Health Canada approved ketamine for use as an anesthetic agent. Ketamine is also used off label in the management of acute and chronic pain. It is a controlled substance under Schedule I of the *Controlled Drugs and Substances Act*, meaning that it has been classified as having a **high potential for harm and abuse**.

The off-label use of ketamine is regulated by provincial medical regulators (CPSM in Manitoba). In many jurisdictions, its use falls under regulations and guidance for Alternative and Complementary Medical Treatments – this guidance varies among different medical regulators.

In 2018, intranasal ketamine (brand name Spravato®) was approved by Health Canada for the treatment of severe major depressive disorder. Spravato® is only available to physicians and pharmacies who have completed a specialized training program. Spravato® must be administered under supervision, with 2-hour post-dose mandatory monitoring by a healthcare provider. Considering these barriers to access, compounded ketamine products have emerged as a more accessible and cost-effective option. However, compounded ketamine products are not without risks.

3) Unclear ketamine prescription writing is common and can delay patient care.

Ketamine is an M3P prescription. It is important to ensure that ketamine prescriptions are written clearly with the **desired formulation**, **quantity**, and **route** of administration.

In reviewing the ketamine prescriptions submitted by registrants in collaboration, CPSM saw a broad range of terms used for ketamine formulations. These included “compound”, “capsules”, “injection vials”, “oral liquid”, “solution”, and “syrup”, among others. In some cases, more than one term was used on the same prescription, causing further confusion. Additionally, it was not always clear on prescriptions that the expectation was for the ketamine to be compounded, e.g., as an oral liquid, sublingual liquid, or oral capsule.

4) Collaboration is key to ensure shared understanding of the intended prescription.

Health Canada describes compounding as, "The combining or mixing together of two or more ingredients (of which at least one is a drug or pharmacologically active component) to create a final product in an appropriate form for dosing" (as per the Policy on Manufacturing and Compounding in Canada). Otherwise, there are no standard definitions for the various formulation terms being used. Therefore, it is important for all parties involved in prescribing and dispensing ketamine to **ensure common understanding** of the intended prescription.

There are generally four parties involved in each compounded prescription:

- The **prescriber**,
- The **dispensing pharmacy**,
- The **compounding pharmacy** (if the dispensing pharmacy does not have the facilities to compound ketamine or other sterile or hazardous substances, they may outsource to a compounding pharmacy), and
- The **patient**.

It is a shared responsibility for all parties involved to confirm the correct ketamine formulation and strength that is required for the patient. Clearly written prescriptions, with all required information as per M3P requirements, will ultimately require less pharmacist-prescriber correspondence to clarify. However, each **new** ketamine prescription may require some degree of clarification to confirm that the necessary formulation is ordered and dispensed to the patient. In cases where discussion is warranted, CPSM and CPhM strongly encourage direct prescriber-pharmacist collaboration.

Compounding pharmacies must ensure they have the appropriate facilities and expertise to compound ketamine in accordance with the National Association of Pharmacy Regulatory Authorities (NAPRA) standards and use appropriate protective equipment.

5) Consistency and clarity are safeguards for prescribing intravenous (IV) formulations of ketamine, regardless of administration route.

CPSM and CPhM are aware that patients are using IV formulations of ketamine via different routes, including oral, sublingual (SL), subcutaneous (SC), intramuscular (IM), and via percutaneous endoscopic gastrostomy (PEG) tube/line. It is imperative that registrants clearly specify the ketamine **strength**, **formulation**, and **route** of administration on prescriptions. It is also important to clearly specify if a compound is being prescribed.

IV ketamine vials are currently commercially available in two different strengths (10 mg/mL and 50 mg/mL). When prescribing IV ketamine, you must clearly specify the strength. Once the strength is specified, all other M3P parameters should be expressed in **total milligrams (mg)**. This includes the total quantity, the quantity of part fills, and the dosage instructions.

Using terms such as **milligrams (mg), milliliters (mL),** and **unit** interchangeably can be confusing and will require pharmacist clarification, delaying patient care.

When registrants prescribe ketamine injection vials, it will be dispensed as actual IV vials. If the intent is for oral, SL, or PEG line use, additional instructions must be provided on the prescription. This may include one of the following:

- Compounded oral capsules
- Compounded oral liquid
- Repacking IV vials for oral or SL use (e.g., pharmacist transfers IV liquid into an amber bottle or pre-filled syringe)

When **compounded oral liquid** ketamine is prescribed, pharmacists are reminded that the addition of an excipient should be considered and documented in the compounding record. An excipient is a non-medical ingredient that improves the taste of ketamine. It also reduces the risk of potential misuse via IV or other injectable routes. An excipient may also need to be prescribed/listed on the prescription. Again, prescriber-pharmacist collaboration is key.

Transferring IV liquid ketamine into an amber bottle or pre-filled syringe for oral or SL administration falls under **repacking**, defined by NAPRA as, “the process of packing again or the action of repacking (reprocessing)”. However, compounding standards still apply. (See NAPRA Standards for Pharmacy Compounding of Hazardous Sterile Preparations.)

6) Physicians must ensure they have the knowledge, skill, and clinical judgement to prescribe ketamine safely.

While no special CPSM permission/approval is required, **physicians must ensure they have the knowledge, skill, and clinical judgement to prescribe ketamine safely**. Registrants who administer ketamine in their practice must also have the necessary training and equipment to monitor for, and appropriately manage, any adverse reactions.

Physicians are further reminded that off label prescribing of ketamine is a non-conventional treatment option. Registrants must adhere to all provisions in the CPSM Standard of Practice for Good Medical Care and ensure that informed consent is documented in the patient’s medical record. Patients must be fully informed of the risks and benefits of treatment with ketamine

(and the unknown nature of some risks and benefits). Thorough documentation of the diagnosis, the rationale for treatment with off-label ketamine, details of previously attempted interventions, and the treatment response should all be captured in the medical record.

7) Monitoring and precautions are key to mitigate ketamine associated risks, like other controlled medications.

The **risks** and **adverse effects** associated with ketamine are dose dependent. The unsupervised use of ketamine also carries a risk of misuse and diversion. For example, individuals could use prescribed ketamine via unintended routes (e.g., by IV or IM injection despite being prescribed orally). This carries significant cardiovascular, neurological, and psychiatric risks. These risks are magnified when ketamine is prescribed without close monitoring or universal safety precautions, such as DPIN review and comprehensive urine drug screening (C-UDS).

Ketamine should be approached with the same monitoring as any other controlled medication (e.g., opioids) to minimize the risk of adverse effects, misuse, and diversion. This includes implementing universal safety precautions when prescribing all non-topical ketamine products, such as DPIN review, periodic C-UDS, and limited dispensing intervals.

Data about the abuse and diversion of compounded ketamine is limited. However, a 2023 ketamine therapy survey by All Points North (APN), reported that more than half of those using at-home ketamine therapies had either accidentally or purposefully used more than the recommended dose.

8) Comprehensive Urine Drug Screening (C-UDS) is a universal safety precaution.

C-UDS is a useful clinical assessment tool and an important universal safety measure. We recommend periodic C-UDS for all patients on prescribed ketamine. Results should be reviewed/discussed with patients (non-punitively and non-judgmentally), and we do not generally recommend making medication changes based on a single unexpected result.

The intention is to facilitate clinical conversation about safety, not to 'police' patients. Briefly, a C-UDS will allow you to:

- Ensure a patient is adherent to prescribed medications.
- Identify potential non-prescribed medication for clinical discussion.
- Identify over-the-counter medications for clinical discussion that may increase the risk of accidental medication overdose (i.e., dimenhydrinate, diphenhydramine, etc.)

It is important to cross reference the patient's medications with the list of medications identified on C-UDS by Shared Health. Write all prescribed medications on the requisition form. Prescribers must specifically ask for medications to be included on the testing panel if not on the list. The current requisition form is available here: UDT Requisition (2024). The reason for C-UDS can be written as, "to assess adherence to medication regimen". Registrants call PPP and/or diagnostic services (Duty Chemist on call at 431-276-0131) for assistance with interpreting results.

9) The Prescribing Practices Program (PPP) can help. Phone (204) 774-4344 and ask for PPP.

PPP works collaboratively with registrants to ensure quality care and to support safer prescribing practices. Please call us for guidance as needed with ketamine prescriptions, risk mitigation strategies, or for complex patient care.