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THERAPY IN PRACTICE

Non-parenteral Ketamine for Depression: A Practical Discussion on Addiction Potential and Recommendations for Judicious Prescribing

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Abstract

Intravenous (IV) ketamine is increasingly used off-label at subanesthetic doses for its rapid antidepressant effect, and intranasal (IN) esketamine has been recently approved in several countries for treating depression. The clinical utility of these treatments is limited by a paucity of publicly funded IV ketamine and IN esketamine programs and cost barriers to private treatment programs, as well as the drug cost for IN esketamine itself, which makes generic ketamine alternatives an attractive option. Though evidence is limited, use of non-parenteral racemic ketamine formulations (oral, sublingual, and IN) may offer more realistic access in less rigidly supervised settings, both for acute and maintenance treatment in select cases. However, the psychiatric literature has repeatedly cautioned on the addictive potential of ketamine and raised caution for both less supervised and longer-term use of ketamine. To date, these concerns have not been discussed in view of available evidence, nor have they been discussed within a broader clinical context. This paper examines the available relevant literature and suggests that ketamine misuse risks appear not dissimilar to those of other well-established and commonly prescribed agents with abuse potential, such as stimulants or benzodiazepines. As such, ketamine prescribing should be considered in a similar risk/benefit context to balance patient access and need for treatment with concern for potential substance misuse. Our consortium of mood disorder specialists with significant ketamine prescribing experience considers prescribing of non-parenteral ketamine a reasonable clinical treatment option in select cases of treatment-resistant depression. This paper outlines where this may be appropriate and makes practical recommendations for clinicians in judicious prescribing of non-parenteral ketamine.

Key Points

Intravenous ketamine and intranasal esketamine for treatment-resistant depression are not widely accessible to patients and prescribers.

Non-parenteral forms of ketamine may be a reasonable treatment option for more accessible and less supervised ketamine treatment for select patients. Recommendations are made for judicious prescribing.

Clinicians should consider the addiction potential of ketamine when used as an antidepressant, and this should be placed in context of the risk/benefit ratio for individual patients, similar to prescribing of other psychiatric medications with known abuse potential.

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1 Introduction

Major depressive disorder (MDD) is a prevalent and disabling illness associated with substantial personal and societal burden [1]. Traditional antidepressants and psychotherapies require several weeks to elicit a response [1, 2], and if a patient fails to respond/remit to the first or second antidepressant tried, the likelihood of response to subsequent trials of traditional antidepressants drops to around 15% [3]. This poses a need for alternative antidepressant agents, particularly with a more rapid onset of clinical effect. The recent approval of intranasal (IN) esketamine for treatment-resistant depression (TRD) in a number of countries and the recent Canadian Network for Mood and Anxiety Disorders (CANMAT) recognition of intravenous (IV) ketamine's rapid antidepressant effects [4] bring new hope and offer promise for patients who have otherwise failed to respond to traditional treatments.

Despite the therapeutic potential, administration of IV ketamine or IN esketamine presents somewhat of a clinical conundrum. Although effective, both treatments must be delivered and supervised in a healthcare setting, placing them out of reach for most prescribers and their patients. Publicly funded IV ketamine and IN esketamine programs to support observed use are rare even in urban centers, so much of the population is unable to access these treatments. Where public programs do exist, they are limited by regulatory frameworks and resource requirements for treatment, monitoring, and development of treatment models to accommodate patient flow through programs, and concerns about longer-term safety and tolerability. While a number of private clinics (very few in Canada, where the authors clinically practice) offer these sorts of ketamine services, cost is an obstacle to many patients who could otherwise benefit. Additionally, limitations have been further accentuated by the global coronavirus disease 2019 (COVID-19) pandemic, which has shifted a focus to virtual care to limit patient contacts with hospitals, clinics, and any healthcare setting where they could potentially be exposed to, or transmit, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. This paradigm shift may have also decreased patient compliance with face-to-face appointments, as many wish the convenience of a remote appointment, and this seems likely to persist as a shift in care delivery.

Given these constraints, there is an appeal for prescribers to offer IN, oral (PO), and sublingual (SL) racemic ketamine formulations. Generic ketamine is comparatively cost-effective (5 Canadian dollars (CAD$) for a 50-mg vial) compared to IN esketamine (CAD$273 per 28 mg) (SPRAVATO) [5], so compounding ketamine into IN, PO, and SL formulations for use breaks the treatment barrier of drug cost itself. IV ketamine must be monitored due to the IV nature of administration. IN esketamine has monitoring requirement set by regulatory bodies—and these differ globally. For example, a 2-h monitoring period is required in Canada and the USA [6], but the European Union and several other countries do not specify a time, and the language is more loose [7]. This monitoring is due to transient hypertension and dissociative effects, but there are no data to determine whether IN, PO, and SL ketamine should carry the same requirements for supervised administration and monitoring. These requirements may, in fact, be bulky and overcautious. A recent meta-analysis demonstrated that the transient blood pressure increases of ketamine and esketamine brought blood pressures to a transient stage I hypertension level, which is not considered dangerous, and there was no difference between the two drugs [8]. It would appear that ketamine/esketamine overall does not produce dangerous blood pressure changes when used at antidepressant doses in most patients. This study included primarily IV ketamine, and all the esketamine studies included were IN. While keeping in mind the existence of outliers and need for clinical discretion, the fact that blood pressure increases most typically led to a transient level stage I hypertension only could suggest that widespread regulatory requirement policy to monitor blood pressure for IN esketamine may be excessive, and benefits of universal monitoring to catch the rare dangerous event may not outweigh the accompanying limits in access for the greater population of otherwise healthy patients. Similarly, this suggests that route of administration may also not produce differing blood pressure effects despite differences in absorption and kinetics with varying routes. Additionally, IV and IN administration produce the most rapid onset of action, so while more data are needed regarding IN, PO, and SL ketamine, it seems unlikely that IN ketamine would be more dangerous than IN esketamine or IV ketamine, or that PO or SL ketamine would produce greater escalations in blood pressure than more rapidly acting IV or IN ketamine. It is also unclear whether dissociative effects may differ across formulations, but the experience of dissociative effects alone does not clearly preclude home use following psychoeducation for appropriate patients. More research is required regarding these two issues for definitive answers. Another clear limitation to the use SL/PO/IN ketamine is the lack of data on optimal dosing strategies across formulations.

Another major consideration for less supervised use comes from ketamine's history as an illicit drug. The addictive potential of ketamine when used as an antidepressant has been repeatedly raised and cautioned by a number of expert consensus statements worldwide [4, 9–11]. While there is due cause for attention to potential harms, these warnings appear to have been stated repeatedly in the absence of further literature to assess level of risk, and without contextual discussion to place risk of ketamine abuse in context with other potentially abusable yet necessary medications prescribed in psychiatry. The authors of this paper include psychiatrists from multiple centers in Canada with extensive combined expertise in treating resistant mood disorders with ketamine, including prescribing IN and SL formulations for home use. Our group also has specialties in attention deficit hyperactivity disorder (ADHD), addiction, pain, and sleep medicine, with extensive experience in cautious prescribing of potentially abusable therapies such as psychostimulants, benzodiazepines, and even the home use of gamma-hydroxybutyrate (GHB) for narcolepsy. This paper will discuss the relevant literature from psychiatry, anesthesia, and pain medicine surrounding the safety of ketamine use, with a focus on potential risks of misuse and abuse. This will then be placed in context to discuss specific practical clinical implications for psychiatric prescribing of non-parenteral formulations of ketamine that could ostensibly be less supervised.

2 A Summary of Ketamine Use in Psychiatry and Accompanying Clinical Considerations

Ketamine use in psychiatry remains in its infancy. Since the 2016 CANMAT depression guidelines designated it as an experimental treatment, it has rapidly matured to designation as a third-line adjunct for bipolar depression [12] and a third-line treatment for TRD in Canada [4]. Other disorders with published data and growing evidence include obsessive-compulsive disorder, social anxiety, post-traumatic stress disorder (PTSD), substance use disorders (SUD), suicidal ideation, as well as schizophrenia [13–18]. Ketamine has also been used as an adjunctive agent in electroconvulsive therapy (ECT) [16].

Another growing dimension of ketamine use in psychiatry is "ketamine-assisted psychotherapy" (KAP). This is based on the premise that the dissociative effects of ketamine can be harnessed under the guidance of a psychotherapist to help a patient adopt "an openness to the expansiveness of mind with access to self in the larger sense" [19]. For KAP, SL or intramuscular (IM) ketamine is commonly used to induce a more open and vulnerable state that promotes communication with the therapist. Although of limited quality, there has been published case series data on KAP treatment of patients with depression, PTSD, ADHD, anxiety disorders, and SUDs [19].

The usage of ketamine for depressive disorders has been extensively reviewed elsewhere [14, 15, 20–23], including its excellent safety and tolerability [24, 25]. Consensus statements from Canada, the United Kingdom (UK), and USA, as well as a recent international consensus statement, recognize and make recommendations for use of ketamine in depression, with a focus on IV ketamine as this is where most data lie [4, 9, 11]. Current recommendations suggest that ketamine should be considered as a short-term strategy in patients with TRD. Data to guide duration, interval, and frequency of maintenance treatment are sparse [4], as are data on long-term risks, including any addictive potential when used longer term even in a controlled environment for IV administration. Despite the lack of data, it is known that patients tend to relapse within weeks [4], and the notion of discontinuing an effective treatment, particularly for treatment-resistant patients, runs contrary to the clinical gestalt and guideline recommendations that advocate for a chronic disease management model for depression [26]. Once again, we face a ketamine conundrum: the patient has responded to a treatment that requires monitoring in a healthcare setting; how can this be delivered on an ongoing basis to maintain treatment response? The product monograph for esketamine nasal spray advises induction therapy with twice weekly treatments for 4 weeks, followed by step-down to weekly maintenance for four treatments, then to continue weekly or every other week, based on clinical response [6]. With caution, a similar model could be considered for IV ketamine, and this has been utilized by several of the authors (JS, AK, PC) for patients requiring maintenance IV ketamine treatment (Misericordia Community Hospital and Grey Nuns Community Hospital, Covenant Health, Edmonton, AB, Canada). Notably, this is similar to commonly used maintenance treatment schedules for ECT, for which there is also little data to guide frequency or duration of maintenance treatment [27].

Repeated IV administrations, however, are often impractical for patients and are associated with high resource costs due to the staffing and monitoring required. Often, these costs are passed down to the patient in a private clinic setting. Anecdotally, in the hospital system, authors of this paper have seen publicly funded IV ketamine clinics in which they consult quickly reach capacity due to patients requiring maintenance treatments to maintain a semblance of stability. In the private system, both the initial and especially the ongoing cost for infusions is prohibitive for most patients. Additionally, specialized IV clinics (private or public) are generally not available outside major urban centers. These factors, along with the recent exponential growth of virtual care, leave IV treatments less palatable to many patients and clinicians. Similarly, each IN esketamine treatment must be delivered in a healthcare setting, with requirements to monitor patients for 2 h for each treatment. While evidence for use of SL, IN, or PO formulations of racemic ketamine that could be taken in less stringent settings are limited to small randomized controlled trials (RCTs), case series, and anecdotal reports [4], other authors have discussed the potential utility and safety of PO ketamine [28, 29], which could improve treatment access. These non-IV formulations could also be of particular utility as maintenance ketamine therapy in patients who have previously responded to IV or as initial treatment in patients unable to access IV treatments [30–32]. However, data to guide dose and frequency are lacking, and although previous authors have suggested that after a first observed dose, other formulations may be safely used at home [28, 29], no consensus recommendations have been made for safe prescribing, other than deferring to tertiary centers with ketamine prescribing expertise [4].

With it being a novel antidepressant therapy, clinicians and patients must become familiar with ketamine's safety and tolerability profile. Acute side effects of IV ketamine include sedation, dissociation, increased blood pressure, headache, and dizziness [24]. Dissociation is usually transient and does not typically require clinical intervention as long as appropriate psychoeducation is delivered to patients prior to treatment initiation [4]. Blood pressure changes with IV ketamine are typically mild, transient, and not clinically

significant [25, 33]. This is not dissimilar to blood pressure changes observed with stimulants for ADHD, which are infrequently clinically important [34]. In terms of long-term effects, chronic ketamine abuse has been associated with cognitive deficits, confusion, and cystitis, but to date, this has not been problematic in the literature related to depression [35]. While data on potential long-term side effects of ketamine treatment are needed, it should also be noted that therapeutic ketamine doses are much smaller than is typically used in chronic ketamine abusers.

Given differences in kinetics, dosing, and bioavailability of PO (17%) [36], SL (29%) [37], and IN (50%) [38] ketamine formulations, it is unclear whether the safety and side effect profiles are entirely consistent across various formulations. A systematic review of PO and SL ketamine noted no significant side effects, and no problems with tolerance or substance misuse in any of the studies, which totaled 140 patients who received ketamine up to 3 years in duration [22]. The highest single doses reported were 300 mg PO every 3 days [39], and 7 mg/kg twice weekly to every 2 weeks [40]. In a subsequent RCT of 22 patients, 1 mg/kg of PO ketamine administered thrice weekly demonstrated mild blood pressure elevations that did not require intervention, and overall side effects were not different from placebo [41].

Side effects of IN ketamine have been more variable. One study found a dose of 50 mg was well tolerated [42], while another study of a series of 100-mg doses given over a period of weeks [43] was aborted early due to intolerable side effects of sedation and lack of motor coordination. In contrast, a small case series reported good tolerability of IN ketamine up to 150 mg administered up to twice weekly [31]. IN esketamine has a better documented safety profile, with common side effects of sedation, dissociation, and blood pressure changes that are noted to be mild and transient [6]. Hence, although evidence for PO, SL, and IN ketamine remains limited, no studies have reported concerns of cardiorespiratory compromise or clinically significant elevations in blood pressure that would preclude home use. It would seem logical that if the blood pressure effects of a 100% bioavailable IV formulation are rarely clinically significant, any blood pressure elevation from a less bioavailable non-parenteral formulation may be of variable duration, but not of greater magnitude, so long as approximately equivalent doses are given. No studies addressed the level of concern that would be warranted in regard to addictive potential of these non-parenteral formulations of ketamine, or potential differences in addictive potential given differing absorption and time to onset of dissociative effects. Given the lack of evidence and theoretical concern, it would be advisable to exercise similar caution with home use of ketamine as is given to the home use of stimulants or other sedatives. Indeed, the sedative GHB, a drug with significant side effects, overdose risk, cross tolerance with alcohol, abuse potential, and diversion potential [44], is indicated in a number of countries for narcolepsy with cataplexy and self-administered without medical supervision at home, under a controlled delivery program [44].

3 Ketamine Misuse and Addiction in Society: What Do We Actually Know?

At subanesthetic doses, ketamine can lead to psychoactive effects including perceptual disturbances, derealization, depersonalization, altered body perceptions, and impaired proprioception [45]. These phenomenological effects may be experienced as pleasant or desirable and have contributed to diversion of ketamine for recreational misuse since the 1970s. Notably, recreational users of ketamine have reported that the most appealing aspects of the drug include visual hallucinations and out-of-body experiences; in contrast, others have reported negative effects including memory loss, anxiety, emotional withdrawal, blunted affect, impaired verbal fluency, and physical effects such as palpitations, tachycardia, and blurred vision [45, 46]. The most commonly misused form of ketamine is powder produced by dehydrating ketamine solution, which is usually insufflated or snorted, but has also been smoked or added to beverages [45, 46]. Other misused forms of ketamine include liquid ketamine, which can be injected, added to other substances that are smoked, or consumed in beverages, and less frequently, ketamine is misused by IV or IM injection. Typical doses of ketamine used recreationally start at ~ 100 mg and can reach 500 mg and higher, often delivered multiple times in a single day given the rapid offset of effects [45, 47, 48]. This leads to a potential use of several grams daily, which is much higher than a typical dispensed prescription of ketamine for depression.

The National Institute on Drug Abuse within the United States' National Institute of Health (NIH) designates that presence of any ketamine withdrawal syndrome is "unknown" [49]. However, a recent review cautions ketamine withdrawal symptoms that include craving, palpitations, tiredness, low appetite, low mood, chills, autonomic arousal, lacrimation, restlessness, paranoia, anxiety, hallucinations, and delusions beginning 24 h post-ketamine, and lasting up to 2 weeks [50]. This report, however, was based largely on one case [51] of a single patient who developed these symptoms after 2 years of using 4–7 g of ketamine daily, and two psychotic patients with ketamine dependence admitted to a psychiatric unit [52]. Although interesting neurochemically, withdrawal symptoms do not imbue addictive potential, as it is well known that traditional antidepressants have also been associated with discontinuation/withdrawal symptoms [50]. Concerns for development of psychological

dependence in the absence of a physical withdrawal syndrome have also been based on case reports [53, 54]. Of note, fewer than 15 cases of human ketamine dependence have been described in the literature over the past 20 years [24].

In a comparative ranking of 20 substances with potential for misuse based on a review of the available literature, ketamine was ranked sixth overall, aligned with benzodiazepines and amphetamines. This ranking considered factors reflecting risk of physical harm, dependence, and social harm [55]. With respect to dependence factors specifically, ketamine ranked 11th for physical dependence tied with methylphenidate, and was equal to cannabis at ninth overall for both pleasure and psychological dependence. Overall, this clearly places ketamine as mid-range in terms of theoretical dependence risk, comparable to other drugs commonly used as unsupervised PO medications in psychiatric practice.

The World Health Organization (WHO) lists ketamine as an essential medicine for anesthesia and analgesia and recognizes that there is substantial evidence supporting its clinical effectiveness in depression and other mental health disorders [56]. Despite the known use of ketamine as a drug of misuse, the WHO concluded that "There is no compelling evidence… to suggest that [illicit use of ketamine] is becoming a global trend." Indeed, the misuse of ketamine represents < 1% of international illicit drug use, and there is evidence that rates of ketamine misuse are declining globally [56]. There are strong indications that prevalence of ketamine diversion and misuse is lower than many other substances [56, 57]. Reviews have suggested that the overall prevalence of ketamine misuse in the general population ranges from 0.1% in the USA to 4% in the UK [45]. Prevalence in use among US college students decreased from 2.5% in 2002 to 1.5% in 2012, and decreased in high schoolers from 1.3 to 0.4% [57]. While the British crime surveys of the late 2000s reflected concern with escalating use of ketamine in the UK [58], more recent data suggest the trend is toward decreased ketamine use in the UK, with reductions from 2011 to 2013 of 0.6% to 0.4% in adults and 1.8% to 0.8% in young adults, respectively [57]. However, reported incidence rates and drug seizures point towards potential increases in ketamine misuse and diversion in some Asian countries such as Indonesia, Hong Kong, and Taiwan [59]. Ketamine misuse also appears to be higher in certain populations and situational circumstances. For example, 32–43% of self-described "club drug" users reported having misused the substance [46].

In terms of toxicity, ketamine has consistently accounted for a minority of emergency department visits due to recreational drug use in the USA, with reports ranging from 0.033% in 2005 to 0.12% in 2011 [57]. The risk of fatal intoxication with ketamine is very low, with a total of 12 deaths reported in Europe between 1987 and 2000, among which only three involved ketamine as the sole substance [56]. Interestingly, a review of the changing portrayal of ketamine by print news media in the USA corroborates a change in recent years towards a more favorable view of ketamine as a clinical therapeutic for the treatment of depression rather than as a street drug of misuse [60].

4 Evaluation of Addiction Concerns with Ketamine Use in Anesthesia and Pain Medicine

Ketamine has an overall favorable safety profile in the analgesic setting as meta-analyses have reported no cases of dependence or addiction when IV ketamine was used in the acute or chronic management of pain [61, 62]. Recent large scale national joint guidelines from the USA state that "there is little to no evidence in the literature at this time that suggests that brief exposure to ketamine while in a hospitalized setting increases the chance of addiction to ketamine" [63]. In the setting of chronic pain, these same guidelines do flag active substance abuse as a contraindication for ketamine treatment and note ketamine's potential for addiction and diversion. Nevertheless, these guidelines also recognize PO and IN ketamine for home use as reasonable alternatives to IV ketamine infusions in the ongoing treatment of chronic pain [64]. Careful patient selection and use of opioid screening instruments to detect patients at risk of misuse are encouraged, even in the absence of validated screening instruments for ketamine. The guidelines caution on risks with driving, particularly in patients using ketamine for breakthrough pain. No further recommendations for safety and monitoring of home ketamine use are made [64]. Nonetheless, the US National Pain guideline recognizes take-home ketamine as a viable option for appropriate patients. It seems reasonable for psychiatry to consider this perspective of our colleagues in pain medicine and anesthesia, who have more seasoned experience prescribing ketamine, and follow their lead to consider take-home ketamine as an option in select cases.

5 Is Ketamine Misused in Patients with Depression?

While patients have reported an equal positive drug "liking" for ketamine and esketamine side effects [65], misuse of ketamine or esketamine when prescribed for patients with depression has been rarely reported. Three

published case reports describe the development of tolerance and addiction specifically in patients with depression using ketamine [66, 67]. The first was an untreated patient using ketamine to self-medicate [66], and the second was a patient who had been treated with ketamine for depression with good effect initially [67]. The third involved a patient with depression and lack of remission with prescribed psychiatric medication [68]. In this case, she began using ketamine specifically for mood on the suggestion of an anesthetist and escalated her dose over time. Poor monitoring of ketamine prescribing and inappropriate patient selection were thought to contribute to the misuse [67]. Indeed, despite repeated warnings in the depression literature regarding addiction potential, a systematic review of ketamine side effects found that of 20 RCTs included in the study, none systematically evaluated for dependency as a side effect, and of the 60 total studies included, very few evaluated this [24]. A later systematic review of participant discharge summaries following trial completion in four placebo-controlled, cross-over, single-dose IV ketamine trials and one open-label study for treatment of TRD found no increased ketamine craving, abuse, or possible intent to misuse ketamine 3 months post-administration [69]. Another systematic review, of 13 RCTs, prospective open-label trials, retrospective chart reviews, and case reports of PO ketamine for the treatment of depression, yielded no reports of abuse or dependence, although again, the studies making up these reviews did not systematically evaluate addiction concerns [22]. Likewise, no identified reports of dependence, craving, or addiction with treatment periods up to 28 days were seen in four RCTs of IN esketamine for depression treatment [23].

Although the literature for maintenance ketamine treatment in depression is quite limited, it suggests that misuse and addiction may be rare with long-term use. A small case series of 11 depressed patients who used IV ketamine for up to 49 weeks reported a loss of antidepressant effect in four patients, but no dependence or abuse, although these effects were not systematically assessed [30]. In another subset of a case series, 14 patients were treated for up to 126 weeks with IV ketamine; one patient discontinued treatment due to an inability to abstain from cannabis, but again there were no reports of ketamine dependence or addiction [70]. Further evidence may be gleaned from a 48-week open-label extension phase III esketamine nasal spray trial, where there were no reports of drug seeking, overdose, abuse, or patient requests for dose increases beyond the maximum study dosage of 84 mg once weekly [71]. As such, the requirements for controlled distribution of IN esketamine and administration only in a healthcare setting are based only on the theoretical risk from the view of addiction/diversion potential. Regulatory restrictions in North America [6] for this medication have been placed far above other commonly used psychiatric medications with documented greater misuse or diversion potential, making it untenable for practitioners to deliver it and patients to receive it. The relative scarcity of misuse/diversion reported with maintenance ketamine or esketamine matches the authors' own clinical experience and observations in prescribing compounded SL and IN racemic ketamine over periods up to 3 years [32].

Although studies of low-dose ketamine in depression trials have not identified any cases of dependence, it remains a theoretical risk based on preclinical and clinical studies showing rapid development of tachyphylaxis when used at higher anesthetic doses, as well as the development of tolerance in frequent recreational users of ketamine [24]. It should be noted that recreational ketamine users self-report a high prevalence of depressive symptoms, particularly in users with higher ketamine craving scores [72], and it has been observed that nearly one-third of ketamine abusers have a comorbid depressive disorder [73]. Epidemiologic data have noted that patients with no SUD history are more likely to develop an SUD when they have TRD, particularly for misuse of opioids and sedatives. Interestingly, patients with pre-existing SUD actually appeared to have a lower risk 1 year into treatment than in the first year—it is unclear whether this may have correlated with an improvement in symptoms [74]. While data for ketamine specifically are lacking, it is possible that a dimension of ketamine misuse could be an attempt to self-medicate among persons with depression or at risk for depression, and that screening and management of depressive disorders should be strongly considered in this population. As evidence for ketamine in depression has accumulated, both the continued stigma associated with mental health disorders and limited access to IV ketamine or IN esketamine may limit the ability for patients to seek treatment [78, 79], potentially leading to self-medication with illicitly obtained ketamine. Under this paradigm, appropriate treatment of depression with ketamine when indicated may actually reduce misuse/abuse of substances, including ketamine used to self-medicate [80].

6 Ketamine Pharmacology: What are Potential Mechanisms of Addiction?

Unlike conventional antidepressants that target monoaminergic systems, ketamine primarily affects the glutamate system, notably as a non-competitive blocker of the *N*-methyl-D-aspartate (NMDA) receptor, an effect that is responsible for its anesthetic actions [20]. Although ketamine's antidepressant mechanism of action is not fully understood, there

Table 1 Potential ketamine effects contributing to abuse potential

Action at opioid receptors (reviewed by McIntyre et al. [11])
Dysregulation of stress hormone pathways [78, 79]
Reduction in oxytocin [78] (seen in opioid, stimulant, alcohol, cannabis, and MDMA addiction)
Reduction in orexin-A [79] (linked to addiction via reward and pleasure)
Increased ACTH
Increased cortisol levels
Limbic system activation—dopamine reward pathways [80]
Cortical activation [80]

ACTH adrenocorticotropic hormone, *MDMA* 3,4-methylenedioxymethamphetamine

has been suggestion that its antidepressant effects are contingent on opioid system activation, which could theoretically contribute to abuse potential [81]. A small study showed that pre-treatment with PO naltrexone significantly attenuated the rapid antidepressant effects of IV ketamine in 12 patients [82], but another small study ($n=5$) showed the opposite effect, where co-treatment of naltrexone and ketamine significantly reduced depressive symptoms as early as the first dose [83]. A view of its abuse potential based on opioid activity as stated elsewhere is likely overtly simplistic given that ketamine interacts with a myriad of receptor systems. This is summarized in Table 1.

7 Ketamine May be a Therapeutic Agent for Addictions Treatment

Despite the concerns for addictive potential of ketamine, there is actually preliminary support in the literature that ketamine may be an effective treatment for SUD [84]. There is emerging evidence for a role for ketamine in the management of SUD in patients with and without comorbid depression. It has demonstrated efficacy as an adjunct to naltrexone in MDD patients with alcohol use disorder [83]. There is also evidence for ketamine as either a standalone treatment [85, 86] or as an adjunct to psychological therapy [87] for cocaine use disorder, psychotherapy-assisted management of heroin dependence [88, 89], and opioid withdrawal [90]. Although these studies are limited by small sample sizes and short follow-up, they offer important reassurance to counter concerns that ketamine could induce addictive behavior with other substances when used for the management of depression. Although the mechanism(s) of efficacy in treatment of SUD also remain unclear, several possible pathways have been suggested and are summarized in Table 2 [91].

Table 2 Potential mechanisms of ketamine as a treatment for addiction [88]

Increased neurogenesis and synaptogenesis
Prefrontal cortex
Anterior cingulate cortex
Insula
Rapid antidepressant effects
Minimize self-treatment with substances
Treatment of comorbid conditions like PTSD
Provoking mystical experiences
Improved self-concept
Improved attitudes towards others
Positive changes in life values
Increased motivation for abstinence
Enhanced efficacy of psychotherapy due to enhanced neuroplasticity

PTSD post-traumatic stress disorder

8 Conclusions and Clinical Implications

The emergence of ketamine into psychiatric practice brings clinical questions and conundrums for clinicians who want to offer this treatment to patients. While access to IV ketamine and IN esketamine programs was already limited, the recent pandemic has necessitated adaptation within medicine to find ways to deliver patient care virtually [92, 93]. Moreover, there is increased demand for rapid, effective, and accessible treatments for TRD as societies are now grappling with mental health sequelae of the pandemic. IV ketamine and IN esketamine must be provided in a supervised healthcare setting, and access will likely always be limited due to program capacity, cost (to the system or the patient), and increasing patient reluctance to regularly visit healthcare settings to receive care on the heels of the COVID-19 pandemic. Additionally, these sorts of treatments are available only in specialized centers, limiting the access of much of the population. As such, the ability to offer novel treatments such as ketamine in other formulations that may potentially be prescribed for use in less supervised or home environments in a safe fashion is even more crucial. While more data are needed to guide dosing and frequency of alternate formulations, on review of the limited existing literature, there is no clear evidence that addiction potential of ketamine is more serious than other drugs we prescribe with due caution in psychiatry such as stimulants or sedatives. Serious risk may exist in certain subpopulations, just as it does with other abusable medications, but this warrants a similar approach in cautious prescribing where appropriate, rather than preclude prescribing altogether.

The authors of this paper have several years of experience in the use of PO, SL, and IN ketamine for mood disorders

Table 3 Suggested potential patient profile for less supervised ketamine treatment

High level of treatment resistance—patients who have exhausted other treatment options
Severe symptoms
Significant disability
Suicidality
Has required usage of other off-label treatments in the past
No drug misuse history—substance abuse/misuse screen
No previous history of antisocial/illegal activity/drug diversion
Previous positive response to ketamine
Limited ability to access ketamine treatments with stronger evidence base (i.e., IV ketamine or IN esketamine)
Reliable to attend follow-up appointments
Medically suitable for ketamine treatment, including stable cardiovascular status and controlled baseline blood pressure
Compliant with side effect monitoring
Significant experience with side effects of psychotropics and good judgment on reporting these to the clinician

IN intranasal, *IV* intravenous

[31, 32]. Patients have been highly treatment resistant, and these ketamine formulations have been well tolerated and life saving for many patients who have not responded to other treatments. Based on the authors' collective experience in prescribing non-IV formulations of ketamine, we have suggested potential patient characteristics for physicians to consider when evaluating patients for home use of ketamine (Table 3). Of note, we would agree with previous authors [4, 94] that any ongoing/maintenance use of ketamine for depression should be reserved for patients who have exhausted other treatment options, including multiple trials of antidepressants and other more evidence-based augmentation strategies.

Though systematically obtained real-world data for addiction risk of ketamine when used as a psychiatric medication are lacking, existing knowledge appears not to preclude its use when indicated. Cautious prescribing of this agent is warranted, similar to our approach with substances of potential abuse such as benzodiazepines and stimulants. Clinicians should not be deterred from prescribing ketamine with appropriate cautions when it is reasonably indicated but should maintain an awareness that new information may arise to swing the risk–benefit pendulum, and require adjustment in clinical practice accordingly. Practical suggestions for judicious prescribing are offered in Table 4.

Further to the above clinical recommendations, there is an urgent need for additional high-quality research with systematically collected data to better define the optimal dosing strategies for non-IV formulations of ketamine as an antidepressant, and for longer-term studies that prospectively monitor for safety, dose escalation, and the potential development of craving, misuse, and dependence. Other authors have wisely suggested the need for a registry to monitor use patterns of drugs with abuse potential like ketamine and esketamine [95], and have suggested a ketamine side effects monitoring tool [Ketamine Side Effect Tool (KSET)], which includes measures of drug craving and misuse, but not drug liking [96]. The Food and Drug Administration (FDA) has previously acknowledged drug liking as an important factor in predicting abuse potential [97], and it would be important to evaluate this factor in real-world ketamine or esketamine treatment. Future studies should include measures of drug liking/craving/patterns of misuse. In the absence of any validated tool for this specific purpose, a patient-rated Drug Liking and Craving Questionnaire (DLCQ) for ketamine/esketamine has been created and is in use in several Canadian clinical studies [98]. Naturalistic studies of patients using maintenance ketamine or esketamine therapy could monitor for other red flags of substance misuse such as dose escalation, early refills, and development of other SUD. Similarly, it would be valuable to track data on drug-seeking behavior such as the frequency with which patients request ketamine treatment specifically, ask to prolong treatment for its dissociative effects, or try to convince clinicians of its utility simply to access and abuse it, rather than for its true antidepressant effects. Clinicians prescribing ketamine are advised to clearly assess antidepressant effect in individual patients for efficacy, and not to rely on patient reporting which may be misconstrued as drug liking. Ketamine prescribers are advised to stay abreast of current literature and engage in continuing medical education on this topic.

Table 4 Practical suggestions for prescribing ketamine as an antidepressant for home use

Informed consent—potential risks/benefits
Use of patient contracts
Prescribe in limited quantities and limited refills (i.e., 2- to 4-week supply depending on frequency of dosing)
Prescriber experience with ketamine
Affiliation with a more intensive ketamine program (for further assessment/referral/case discussions)
Consider observing first treatments or dose changes in office to monitor blood pressure and dissociation (i.e., with CADSS)
Educate patients on dissociative symptoms
Advise patients not to drive until next day after use
Dose at night when used at home
Wait until dissociative/sedative effects of ketamine dissipate before using other potentially sedating bedtime medications
Screen for bladder toxicity
Check urinalysis at baseline and every 3–6 months for signs of microscopic hematuria
Ask about urinary symptoms (i.e., frequency, urgency, hematuria)
Monitor for drug liking/signs or symptoms of misuse (e.g., KSET)
Lost prescriptions
Requests for early refills
Requests for dose escalation or increased frequency despite stable psychiatric status
Consider that non-IV forms may require higher doses due to reduced bioavailability, and that documented bioavailability of each formulation is to be considered a rough estimate and may vary
Prescribing clinicians should be informed of current literature and continue medical education on ketamine to learn and adjust prescribing practices as new data become available

CADSS Clinician-Administered Dissociative States Scale, *IV* intravenous *KSET* Ketamine Side Effect Tool

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