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## Systematic Review

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# Should Ketamine Not Be Banned? A Scoping Review

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## Abstract

**Objectives:** Although the importance of ketamine in clinical practice and in resource-poor settings and disaster zones, several attempts were made to reschedule it because of the issues around its misuse. Resisting future moves to reschedule ketamine is important for its continuous availability where needed. This scoping review addresses the question of whether ketamine should or should not be banned and the state of preparedness of low resource settings if ketamine petitions become successful in the future.

**Methods:** A search was performed using PubMed and Google Scholar to identify articles published in the English language from March 2015 to August 2020. The articles were searched with a wide range of priori search terms related to the research questions. The selection of articles was based on relevance and eligibility.

**Results:** Seventy-five articles were selected and grouped into 4 ethical themes. The search revealed that several articles addressed the importance of ketamine, pharmacology, misuse, supply, and consequences of a ketamine ban; however, none addressed how resource-poor countries should prepare for a future without the overreliance of ketamine.

**Conclusion:** Four ketamine petitions in about 10 years are an indication that another may resurface soon; therefore, it is important to continue to study the clinical importance of ketamine while discouraging its overreliance for clinical practice.

## Introduction

Ketamine, a phencyclidine derivative first commissioned for human use in 1965 by Corsen and Domino is an important resource in resource-limited settings, disaster, and conflict zones where access to basic airway equipment and standard monitoring can be challenging.[1–4] Thus, ketamine is popular in these areas because it does not depress respiration and is noted for increasing blood pressure.[4] Regrettably, it has gained notoriety as either a recreational or club drug posing a serious concern of addiction, especially in high-income countries and in countries or regions where the drug is manufactured.[5]

As a result, the increase in ketamine misuse and the aftermath may have necessitated the repeated calls for its reclassification or ban with numerous unsuccessful attempts made by groups in China to lobby for a global ban on ketamine.[6] These efforts may compromise the legitimate use of ketamine. Therefore, resisting future moves to ban or reschedule ketamine in the face of escalating misuse is pivotal to its continuous availability through scientific evaluation to strengthen the argument that ketamine is an essential medicine.

Some studies have emphasized the importance of ketamine in universal health coverage with little emphasis on preparing low and middle income countries (LMICs) for a possibility of a ketamine ban.[1–3,7] The state of preparedness of LMICs for a clinical practice without the routine use of ketamine is worrisome and often ignored, whereas the ethical dilemma of whether or not to ban ketamine remains, despite the silence that characterizes its proper use presently. The questions – Should ketamine be banned? Should ketamine not be banned? How should resource-poor settings prepare for a ketamine ban in the future? – were addressed in this scoping review.

## Methods

### *Data Sources and Retrieval of Information*

The research questions were addressed with a search strategy that aimed to identify articles related to the themes developed for the review. Relevance to the themes was determined for individual studies. Sorting, identification, and final selection of relevant articles were based according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement on scoping reviews (Figure 1).

A literature search was performed using PubMed (National Library of Medicine, Bethesda, MD) and Google Scholar (Google Inc, Mountain View, CA) to identify relevant articles published

**Table 1.** Eligibility criteria for the study

| Inclusion criteria | Exclusion criteria |
|---|---|
| • Articles on importance and successful use of ketamine<br>• Articles on consequences of rescheduling ketamine or ban<br>• Articles on ketamine misuse and supply<br>• Articles on ketamine pharmacology with emphasis on toxicity<br>• Peer reviewed<br>• Published between 2015 and 2020<br>• All geographical areas but written in English<br>• Relevant articles identified from the review of citations referenced in the titles and abstracts reviewed | • Not peer reviewed<br>• Articles not containing search terms and keywords<br>• Language other than English<br>• Not human<br>• Unrelated to research question |

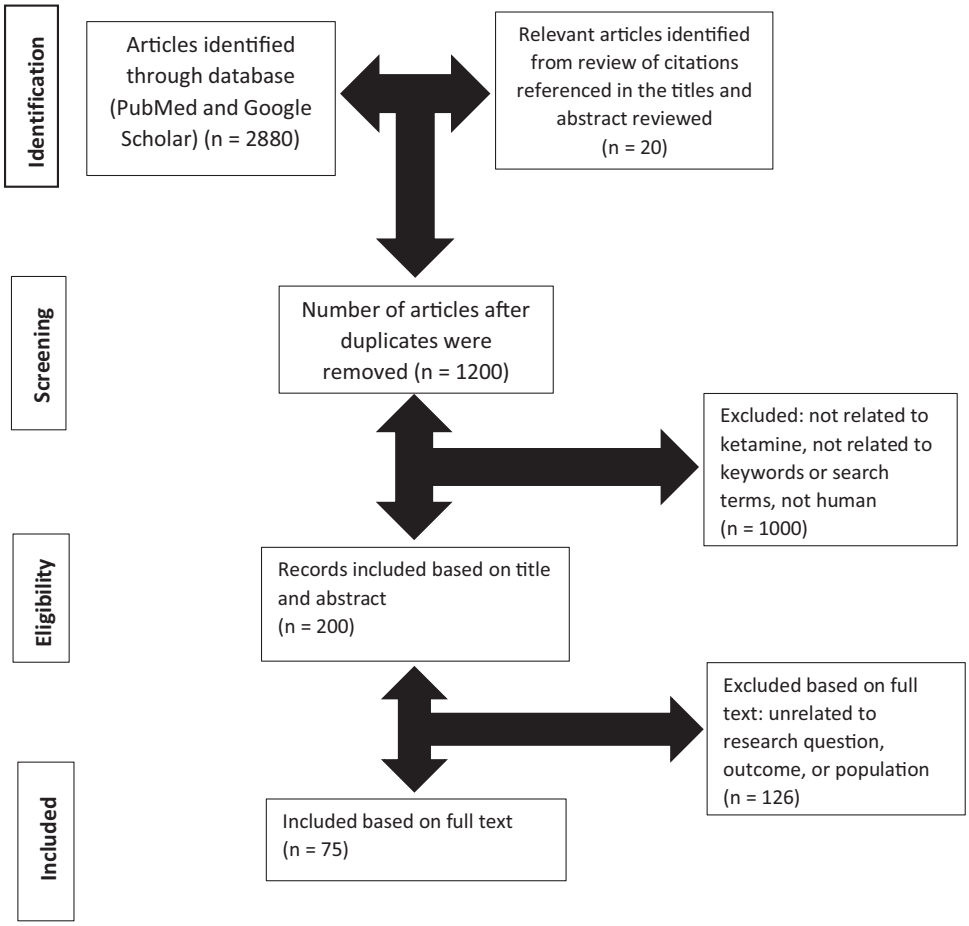


**Figure 1.** Basic flow chart.

in the English language from the time of the last ketamine petition, which was from March 2015 to August 2020. Titles, abstracts, and keywords were screened using the reference manager, Mendeley (London, UK), and relevant citations were reviewed in full text. Additional relevant articles were identified from the review of citations referenced in the titles and abstracts reviewed. Relevant information was extracted and grouped into themes.

### *Search Strategy and Data Collection*

The search terms included the following: *ketamine* AND *addiction, ketamine* AND *misuse, ketamine* AND *toxicity, ketamine* AND *pharmacology, ketamine* AND *trauma, ketamine* AND *pain, ketamine* AND *surgery* "resource-limited setting", *ketamine* AND *global health, ketamine* AND *disaster, ketamine* AND *conflict, ketamine* AND *war* NOT *history, ketamine* AND *humanitarian*. The search was refined to include the following terms: *Ketamine* AND *stability, Ketamine* AND *psychiatry, ketamine* AND *sedation, ketamine* AND *headache, ketamine* AND *uropathy, ketamine* AND *airway diseases* "COPD" (chronic obstructive pulmonary disease) "asthma". Duplicates were removed after a screening of all relevant articles. More articles were excluded after further screening of relevant full-length articles for eligibility, using the inclusion and exclusion criteria stated in Table 1.

### *Risk of Bias*

Each included article was examined for applicability, reporting and conduct of study design including fidelity to the intervention protocol, choice of outcome and outcome reporting, and conflict

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of interest of such article. These were summarized as selection, reporting, performance, or publication bias and presented in Table 2.

Some articles addressed more than 1 theme, while others focused on a few. More frequent discussion of a theme does not necessarily mean such an article is significant. Most articles published after the last ketamine petition may have been influenced by the clamor to resist or assist the ketamine petition, thus increasing the risk of bias. Also, some of the articles reviewed in support of or against not banning or rescheduling ketamine were narrative reviews with a poor outline of methodology and a poor result of literature search, thus increasing risk of bias.

## Results

Seventy-five articles were screened and selected for relevance. The search result along with articles discussing corresponding themes are presented in Table 3. None of the eligible articles directly addressed how LMICs should prepare for a ketamine ban and was subsequently discussed using relevant literature. The selected articles were reviewed under the following themes:

### *Ketamine Pharmacology*

Ketamine is a dissociative anesthetic that acts mainly via the N-methyl-D-aspartate (NMDA) receptor in the brain by inhibiting the reuptake of dopamine, norepinephrine, and serotonin, thus intensifying the effects of these neurotransmitters.[8] Ketamine can be administered via all routes and can be compounded into a flavored drink for oral administration to mask its bitter taste.[9]

Ketamine stability has been reported in some studies. Closset et al. was able to show that ketamine is stable in a Becton Dickinson® (BD) syringe for up to 50 days.[10] Foy et al. was able to determine that ketamine was stable at 33°C for at least 7 days in the patient-controlled analgesia systems between preparation and administration.[11] Huvelle et al. reported that ketamine diluted in 3 mL propylene syringes may be chemically stable for up to 180 days at room temperature at 25°C, while Daouphars et al. demonstrated that ketamine is stable in a polyvinyl chloride bag for 7 days at 23°C, though ketamine was mixed with oxycodone in the latter.[12,13]

Conclusively, ketamine is likely stable over a range of 25 to 33°C for about 7–180 days. This underscores the importance of ketamine in settings where logistics for refrigeration and limited storage, safety of supply routes, lack of timely resupply of medications, and inadequate facilities for cardiopulmonary monitoring post-use are a challenge.[14]

Ketamine stimulates respiration and maintains airway patency during sedation and anesthesia over a wide range of doses due to its bronchodilator effects, thus contributing to its safety in acute pulmonary diseases such as asthma and acute exacerbation of COPD.[1,15] Ketamine also provides amnesia, analgesia, immobility, and loss of consciousness, and can result in centrally mediated dose-dependent fall in body temperature.[1,16] Also, it affects core temperature by reducing the magnitude of redistribution hypothermia.[1,16] Thus, there is often no need for extensive monitoring post-use. Additionally, ketamine is often used for co-induction with other anesthetics such as propofol, thus enhancing their synergistic action and provide cardiopulmonary stability, and can antagonize alfentanil-induced hypoventilation in healthy male volunteers.[1,17]

The enduring sedative, hypnotic, and psychodysleptic effects of ketamine increase the risk of its misuse. Serious adverse effects have been reported in long-term use of ketamine. Adverse effects involving various systems have been reported; however, central nervous system complications are most common. Encouragingly, most of these side effects tend to subside with abstinence because ketamine dependence is rare.[18] Musculoskeletal effects such as myoclonus, twitching, spasms, ataxia, and fasciculation have been reported.[19]

Long-term ketamine use may affect the gastrointestinal system, which may result in epigastric pain, hepatic dysfunction, and impaired gallbladder activity.[19,20] Incidentally, patients inhaling ketamine may be more prone to epigastric pain, recurrent vomiting, and gastrointestinal bleeding, which often precedes genitourinary symptoms.[20] Genitourinary effects of chronic ketamine use such as lower urinary tract dysfunction and increased sexual impulses have been reported.[18] Even though death from acute direct toxicity is rare, ketamine-induced uropathy (KIU) is the most dreaded of ketamine toxicity, and it is seen where ketamine is given as prolong infusion or in chronic abuse.[19,21] KIU may present as hydronephrosis, ureteral stenosis, cystitis, vesicoureteral reflux, bladder fibrosis, severe pelvic pain, and storage symptoms as a result of a loss of bladder control.[1,22–24]

### *Role of Ketamine*

Despite the reported misuse and adverse effects, ketamine is still an important drug in providing essential, non-essential, and specialist medical and surgical care.[25] Ketamine is useful for pain control, sedation, cheap and safe anesthesia in LMICs and in reactive airway diseases. Additionally, it may have a role in patients with sepsis as an immunomodulator and prevention of cancer growth, and it provides hemodynamic stability in hemodynamically unstable or critically ill patients.[1,25–27] Besides, ketamine has been successfully used in sports or trauma medicine, after a sudden onset natural disaster mass casualty incident, crisis or conflict zones, and veterinary medicine as an analgesic or anesthetic.[1,28,29] Ketamine has also been used to supplement the analgesic effect of local anesthetics.[30,31]

### *Ketamine and Resource-Poor Countries*

The burden of disease preventable by surgery is on the increase worldwide, and about 95% of the estimated 4.8 billion people who lack access to safe, affordable surgical and anesthetic care reside in resource-poor countries where the poorest world's population receives only 3.5% of surgical procedures.[32] The risk of financial hardship from medical care is higher in these settings due to out-of-pocket health care spending.[33,34]

In a study by Lin et al.,[33] cost (73%) and lack of providers (8.8%) were reported as the most common barriers to surgical care and outcomes. Regrettably, the physician-to-population densities range from 0 to 4.9 per 100 000 in most LMICs, which worsen the anesthesia workforce crisis.[35] The World Federation of Societies of Anaesthesiologists argued that a minimum of 10 anesthesiologists per 100 000 is required to provide safe anesthesia.[36] Moreover, many anesthesia providers in LMICs are either nurses or clinical assistants with limited formal advance anesthetic training.[7,37,38]

Ketamine use has contributed significantly to improved access to basic surgical and obstetric care in LMICs because its use doesn't require sophisticated equipment for monitoring and expertise. In a survey done in 22 LMICs, availability of ketamine (71.5%) far

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**Table 2.** Summary of the risk of bias in the study

| Author | Publication Year | Article Type | Selection Bias | Reporting Bias | Performance Bias |
|---|---|---|---|---|---|
| Girish *et al.* | 2016 | Narrative Review | ✓ | ✓ | |
| Dohlman *et al.* | 2017 | Narrative Review | ✓ | ✓ | |
| Liao *et al.* | 2017 | Narrative Review | ✓ | ✓ | |
| O'Riordan *et al.* | 2017 | Narrative Review | ✓ | ✓ | |
| Mion *et al.* | 2013 | Narrative Review | ✓ | ✓ | |
| McNulty *et al.* | 2012 | Case Report | ✓ | ✓ | ✓ |
| Closset *et al.* | 2017 | RCT | | | |
| Foy *et al.* | 2015 | PK Study | | | ✓ |
| Huvelle *et al.* | 2016 | PK Study | ✓ | ✓ | |
| Daouphars *et al.* | 2018 | PK Study | ✓ | ✓ | |
| Beiler *et al.* | 2019 | PK Study | ✓ | ✓ | |
| Eikermann *et al.* | 2012 | RCT | ✓ | | ✓ |
| Ikeda *et al.* | 2001 | RCT | | | ✓ |
| Zanos *et al.* | 2018 | Narrative Review | ✓ | ✓ | |
| Bokor *et al.* | 2014 | Narrative Review | ✓ | ✓ | |
| Liu *et al.* | 2017 | Observational Study | ✓ | ✓ | ✓ |
| Jhang *et al.* | 2015 | Systematic Review | | | |
| Castellani *et al.* | 2020 | Systematic Review | | | |
| Orhurhu *et al.* | 2019 | Literature Review | ✓ | ✓ | |
| Li *et al.* | 2019 | Retrospective Cohort | ✓ | ✓ | |
| Gales *et al.* | 2018 | Narrative Review | ✓ | ✓ | |
| Gao *et al.* | 2016 | Narrative Review | ✓ | ✓ | |
| Nowacka *et al.* | 2019 | Narrative Review | ✓ | ✓ | |
| Pribish *et al.* | 2020 | Systematic Review | | | |
| Vo *et al.* | 2012 | Prospective Cohort | ✓ | ✓ | ✓ |
| Abdollahpour *et al.* | 2020 | Systematic Review | | ✓ | |
| Swain *et al.* | 2017 | Narrative Review | ✓ | ✓ | |
| Oham *et al.* | 2020 | RCT | | | |
| Alkire *et al.* | 2015 | Modeling Study | | | |
| Lin *et al.* | 2017 | Prospective Cohort | ✓ | ✓ | |
| Shrime *et al.* | 2016 | Retrospective Cohort | ✓ | ✓ | |
| Hoyler *et al.* | 2014 | Systematic Review | | | |
| Weiser *et al.* | 2018 | View Point | ✓ | ✓ | ✓ |
| Gajewski *et al.* | 2020 | Prospective Cohort | ✓ | ✓ | |
| Masaki *et al.* | 2019 | Prospective Cohort | ✓ | ✓ | |
| Guha *et al.* | 2019 | Prospective Cohort | ✓ | ✓ | |
| Lubega *et al.* | 2018 | RCT | | | |
| Craven | 2017 | Narrative Review | ✓ | ✓ | |
| Trelles *et al.* | 2017 | Narrative Review | ✓ | ✓ | |
| Wedmore *et al.* | 2017 | Narrative Review | ✓ | ✓ | |
| Anagnostou *et al.* | 2020 | Systematic Review | | | |
| Rice *et al.* | 2010 | Report | | ✓ | |
| Ariyo *et al.* | 2016 | Retrospective Cohort | ✓ | ✓ | |
| Torres *et al.* | 2020 | Retrospective Cohort | ✓ | ✓ | |
| Karlow *et al.* | 2018 | Systematic Review/Meta-Analysis | | | |
| Ragazzoni *et al.* | 2019 | RCT | | | |
| Bansal *et al.* | 2020 | Systematic Review | | | |
| Bhadelia *et al.* | 2019 | Report | ✓ | ✓ | ✓ |
| Persson *et al.* | 1999 | RCT | ✓ | ✓ | |
| Robblee *et al.* | 2020 | Narrative Review | | ✓ | |
| Benish *et al.* | 2019 | RCT | | | |
| Schoevers *et al.* | 2016 | Systematic Review | | | ✓ |
| Gautam *et al.* | 2020 | Narrative Review | | | ✓ |
| Feder *et al.* | 2014 | RCT | ✓ | ✓ | |

(*Continued*)

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**Table 2.** (*Continued*)

| Author | Publication Year | Article Type | Selection Bias | Reporting Bias | Performance Bias |
|---|---|---|---|---|---|
| Mion et al. | 2017 | Retrospective Cohort | | | ✓ |
| Jones *et al.* | 2018 | Systematic Review | | ✓ | |
| Slomski *et al.* | 2019 | RCT | ✓ | | |
| Dakwar *et al.* | 2020 | RCT | | | |
| Xu *et al.* | 2016 | Systematic Review/Meta-Analysis | | | |
| Yan *et al.* | 2020 | Narrative Review | | | |
| Farrell *et al.* | 2018 | Narrative Review | ✓ | ✓ | |
| Cohen *et al.* | 2015 | Narrative Review | ✓ | ✓ | |
| Cheung *et al.* | 2019 | Narrative Review | | ✓ | |
| Hayward *et al.* | 2016 | Retrospective Cohort | ✓ | ✓ | |
| UNODC | 2019 | Report | | ✓ | |
| UNODC | 2020 | Report | ✓ | ✓ | |
| UNODC | 2017 | Report | | ✓ | |
| CNNCC | 2019 | Report | | ✓ | |
| Ma *et al.* | 2015 | Narrative Review | ✓ | ✓ | |
| USDEA | 2018 | Report | ✓ | ✓ | |
| UNODC | 2018 | Report | | ✓ | |
| Burke-Shyne *et al.* | 2017 | Narrative Review | ✓ | ✓ | |
| WHO | 2019 | Report | ✓ | ✓ | |
| Klein *et al.* | 2019 | Systematic Review | | ✓ | |
| Lohman *et al.* | 2020 | Narrative Review | ✓ | ✓ | |
| Nickerson *et al.* | 2017 | Systematic Review | | | |

CNNCC = Chinese National Narcotics Control Commission; RCT = randomized controlled trial; UNODC = United Nations Office on Drug and Crime; USDEA = United States Drug Enforcement Administration; and WHO = World Health Organization.

**Table 3.** Characteristics of eligible articles showing themes and number of publications discussing each team

| Themes | Number of Included Publications Discussing Each Theme |
|---|---|
| I. Role of ketamine including subthemes | 57 articles |
| II. Ketamine misuse and supply | 7 articles |
| III. Ketamine pharmacology | 17 articles |
| IV. Consequences of ketamine ban | 8 articles |

Note: Thirty-six articles were considered suitable; reference 21 was relevant in both Themes I and IV.

exceeded the availability of reliable electricity (59%), running water (62.4%), and supplemental oxygen (45.2%).[37]

The successful use of ketamine in LMICs was reported by Masaki et al.; the study typified the feasibility and safety of ketamine for essential surgeries where no anesthetic is available.[39] Similarly, Guha et al. reported how successful it was for non-anesthetists to provide procedural sedation in acutely painful conditions with minimal side effects and no mortality.[40] However, these studies might have overstated the role of non-physician anesthetists in meeting surgical needs in low-resource settings without considering the burden of other surgical care needs where the use of ketamine might not be indicated.

## *Ketamine and Disaster*

Disaster is defined as "a sudden event causing severe destruction of infrastructure, people and the economy and which overwhelms the resources of that country, region or community."[41] These sudden onset disasters may be caused by natural events such as earthquakes, tsunamis, and disease epidemics or man-made disasters such as war and industrial accidents, and often produce mass casualties and later evolve to create complex humanitarian emergencies. Disasters and armed conflicts pose logistical challenges for medical missions managing alternative care sites, hospitals, and clinics, because they are often characterized by high numbers of trauma cases.[41–43] These challenges are more in developing countries where the health care response is already impaired, thus complicating the response.[41–43] Additionally, the presence of other surgical conditions aside from trauma cases often compounds the surgical care needs, as these needs differ from context to context and depend on local means and capabilities.[42]

During these medical missions, absence of anesthesia machines and ventilators, inadequate supply of medical gases, electricity to power oxygen concentrators and medications, and poor state of Post Anaesthetic Care Units (PACU) are common[41] – hence the need for anesthesia techniques that will ensure maintenance of spontaneous respiration that is essential for rapid emergence after anesthesia with the opportunity to bypass the PACU.[41] These challenges make the anesthetist fall back on deep sedation with ketamine with or without regional anesthesia or benzodiazepines such as midazolam for managing the peculiar circumstances during these crises.[41,42,44] Ariyo et al. reported ketamine as essential for medical missions for anesthesia without tracheal intubation in a 6-year review of the humanitarian activities of Doctors Without Borders.[45] Also, the medical mission during the aftermath of the earthquake in Haiti performed 90% of their surgeries under ketamine anesthesia.[41,46] In addition, medical missions often work alongside local nurse anesthetists and health technicians who have vast experience monitoring patients receiving ketamine anesthesia.

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A 10-year review of ketamine administration in prehospital combat patients emphasized the relevance of ketamine in moderate to very severe combat injuries; however, only about 5% of the studied patients received ketamine.[47] Ketamine recipients experienced lower survival rates, perhaps due to the severity of their injuries when compared to non-recipients of ketamine.[47] The possibility of poor record keeping during combat may have affected the study outcome as well.

Challenges, such as distance from suppliers, security of supply routes, availability of cold chain conditions in areas where supply may be held for weeks and unpredictable resupply timing, make ketamine an essential drug that should be stocked in large quantities during disasters and armed conflicts.[41,46] Also, the ability to provide general anesthesia in a spontaneously breathing patient makes ketamine invaluable in disaster and armed conflict zones, as it minimizes the need for sophisticated equipment other than a pulse oximeter and a sphygmomanometer.[2,42,45] In addition, ketamine is reported to be stable in varying concentrations and conditions.[12,14]

### Ketamine and Pain Management

About 50% of the world's poorest countries receive less than 1% of opioid distributed worldwide, where about 61 million people experience about 6 billion days of serious health-related suffering that could be alleviated with access to palliative care and pain relief.[48] This gap can be bridged with ketamine as it is cheap, accessible, easy to administer, highly effective, less addictive (dependence), and can reduce opioid consumption. Low dose ketamine is useful in managing acute and chronic pain, according to existing guidelines.[25,49,50] Also, ketamine may have an important role to play as a part of the opioid-sparing multimodal pain care strategy that could be explored in controlling the opioid crises.[51]

In contrast, Ragazzoni et al. reported that low dose ketamine does not reduce the cost of postoperative pain management after surgery nor does it reduce morphine consumption when a ketamine group was compared with a control group.[49] Despite conducting the study in a resource-limited setting, the use of low dose ketamine and elderly study participants were concerns in the study.[49]

Nonetheless, the consensus is that a sub-anesthetic dose of ketamine has a role to play in the management of pain, especially when used in combination with opioids.[49,52] Additionally, ketamine use has been successful in managing pain crises following sickle cell disease, a commonly seen condition in resource-poor settings due to the poor practice of premarital genetic counseling.[53]

Ketamine is a drug to consider for refractory or severe headache, despite the outcome of the THINK trial by Benish et al.[54,55] In the study, intranasal ketamine was not superior to intravenous metoclopramide in managing refractory headache.[54,55] The intranasal route of administration and small sample size were concerns in the study.[55] Evidence of the efficacy of ketamine in the management of headache is limited and inconsistent; however, it is still considered a second-line choice where headache is associated with significant aura.[54]

### Ketamine and Psychiatry

The role of ketamine in psychiatry has increased in recent years.[50,56,57] Ketamine has been used for treatment-resistant posttraumatic stress disorder (PTSD), substance use disorder, anxiety disorders, alcohol use disorder, refractory status epilepticus, and in treatment-resistant depression, especially with suicidal tendency.[57–62] Low dose ketamine has been reported to be highly beneficial in the management of major depression.[63] Ketamine may be protective or preventive against the development of PTSD in war-wounded soldiers as reported by Mion et al.[59] The early introduction of ketamine in refractory status epilepticus has been advocated and may be more effective when combined with either benzodiazepines, such as midazolam, or hypothermia.[64]

### Ketamine and Sedation

Ketamine is useful for procedural sedation across many specialities.[40,65,66] Despite the controversy surrounding the issue of raised intracranial pressure, current evidence has shown that ketamine may be neuroprotective when used for sedation and perioperative care of patients with acute traumatic brain injury, especially in the presence of inflammation, pain, and stress.[67–69] However, limited evidence revealed increased risk of neurotoxicity in the developing brain, which may result in disturbances in brain development during perinatal and neonatal exposure.[69] There may be a need to reassess the use of ketamine in pregnancy and early neonatal period.

### Ketamine Misuse and Supply

Ketamine misuse affects all countries; however, it is most common in East and Southeast Asia, especially China, Hong Kong, and Taiwan.[70–72] New psychoactive substances (NPS) including ketamine are mostly supplied from East and Southeast Asia, including India; however, supplies have been noted from Europe and other destinations.[71,72] Ninety-six per cent of the ketamine reportedly seized worldwide between 2013 and 2017 was in Asia.[70] Countries of the golden triangle are a major supply of illicit ketamine to China, accounting for the main source of the drug up till 2019.[73] Epidemiology of ketamine abuse revealed it is common among club goers, and addicts are more likely to be younger and of female gender.[70,73]

In 2013, ketamine was reported as the second most abused drug among Chinese populations in a survey done by China's National Narcotics Control Commission (NNCC).[74] Consequently, China and other East and Southeast Asian countries increased crackdown on the supply of NPS and other illicit drugs, thus resulting in a noticeable decline.[71,73] Despite these efforts, trafficking of illegal ketamine continues to be a problem, and it is becoming difficult to retain the achievements, so far.[71,73] Ketamine has been associated with the highest rate of price increase (2016–2018) when compared to other illicit drugs in China, perhaps due to a strong market demand and high profit margins following the increased crackdown.[71]

However, the threat of ketamine abuse is still not widespread compared to cocaine, heroin, or methamphetamine.[75] Although the misuse of NPS, including ketamine, may be as low as 0.03% in Africa, the increasing crackdown on cheap drugs, such as tramadol and codeine, in Africa, may result in drug gangs falling back on drugs, like ketamine, to stay in business.[70,76]

### Consequences of Ketamine Ban

Under the international control system for the manufacture, distribution, transfer, and use of drugs, ketamine is listed as a Schedule III drug (Table 4) due to its potential to cause physical or psychological dependence while it is placed on the World Health Organization essential medicine list.[6,77,78] Scheduling

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**Table 4.** Drug scheduling[a]

| | | |
|---|---|---|
| 1 | Schedule I | Drugs or substances with no currently accepted medical use and a high potential for abuse. For example, Heroin, lysergic acid diethylamide (LSD). |
| 2 | Schedule II | Substances or drugs with a high potential for abuse, with use potentially leading to severe psychological or physical dependence. For example, cocaine, methamphetamine, methadone, fentanyl. |
| 3 | Schedule III | Drugs or substances with a moderate to low potential for physical and psychological dependence. The drug abuse potential is less than that of Schedule I and Schedule II drugs but more than that of Schedule IV drugs. For example, ketamine, testosterone, products containing less than 90 mg of codeine per dosage unit (eg, Tylenol with codeine). |
| 4 | Schedule IV | Drugs or substances with a low potential for abuse and low risk of dependence. For example, Valium, tramadol. |
| 5 | Schedule V | Drugs or substances with lower potential for abuse than that of Schedule IV and consist of preparations containing limited quantities of certain narcotics. These drugs are generally used for antidiarrheal, antitussive, and analgesic purposes. For example, cough preparations with less than 200 mg of codeine or per 100 mL, Lomotil. |

*Notes*: [a]Drugs or substances used to make drugs are classified into 5 distinct categories or schedules. Accessed from www.dea.gov/drug-information/drug-scheduling.

ensures international obligations for states to implement regulatory processes that meet or exceed requirements established by the treaties that regulate these substances.

Once a drug is reclassified as a Schedule I drug, the impact could result in onerous regulations, limited financial resources, lack of training/awareness of professionals, fear of prosecution/sanctions following possession of the drug, fear of drug diversion, cultural attitudes toward the drug, problems in sourcing the drug, trade control measures, and fear of addiction among member nations.[79] Prioritizing restrictive control to the detriment of ensuring adequate availability of and access to some of the controlled medicines may be perceived as a human right violation.[77] The burden of diseases preventable by surgery may worsen due to over-restricted controls.

Fifteen out of the 46 essential medicines of potential relevance to safe and quality perioperative care are currently scheduled under international drug control.[80] Resultantly, high-quality anesthesia and analgesic medicines are often not available where needed. A closer review of the fight against cannabis and cocaine misuse has revealed that restrictive legislations tend to encourage the proliferation of adulterated drugs, amplify drug trafficking, medicrime, and drug misuse.[81,82]

The ketamine petition sent in 2015 as China's fourth petition on ketamine since 2006 to lobby the United Nations to change the status quo regarding ketamine failed; this decision doesn't mean China won't continue to push, more so that China wields more international influence amidst competing political and economic interests in the global scene.[6,28] Although it is a common practice in international politics to trade off support for a certain policy for political capital on other policies that may seem like a right idea, it is reasonable that high income countries may tread softly if another ketamine petition emerges.

## Discussion

Findings in this review reveal that ketamine has played successful roles in clinical practice. Additionally, the study revealed there are important adverse effects associated with its long-term use. Although ketamine misuse is a global concern, this scoping review argued that this may be geographically clustered around East and Southeast Asia.

Between 2014 and 2019, the regional crackdown in East and Southeast Asia following the failure of the last ketamine petition seems to be working.[70,71] The measures employed are "border clearing" operations, drug prevention education, better service and care to drug users, cracking down on the entire drug crime chains, comprehensive management of drug precursors chemicals and equipment, holistic monitoring and early warning of drug situation, and implementation of drug control responsibilities at all levels.[73]

Dismantling drug gangs rather than concentrating on drug seizures, encouraging abstinence, efficient use of new media and drug-related diplomacy to curb cross border drug trafficking may add more value to the efforts, so far.[83] Nonetheless, whatever measure is undertaken should not prevent the legal use of ketamine. Restricted drugs relevant in the practice of safe anesthesia should be reviewed to address the absence of high-quality anesthesia drugs, deplorable low availability of analgesics, and to ensure availability, accessibility, and affordability where needed, while strengthening the prescription process.[80,84] The growth of substandard and falsified medicines in LMICs should be addressed, too.

Factors such as lack of trainers, lack of medical students' interest in and exposure to anesthesia, need for more higher institutions for postgraduate training in anesthesia, low allocation to anesthesia from the list of available specialist prospects by the health ministry, and low remunerations to anesthesiologists identified in Mozambique are common to LMICs and should be addressed.[85] In the short term, nurses may be mobilized to act as AP in low-level hospitals and primary health care centers; this has been partly successful in some climes albeit not a replacement for trained physicians.[86] Strengthening physician commitment and capacity to oversee patient care and equipment maintenance are important to improve patient safety where tools are put in place.[87] There should be strong political will to address shortfalls in health budget allocations, out-of-pocket health care spending, and poorly motivated health care workers. Additionally, the National Surgical, Obstetrics and Anaesthesia Plans (NSOAPs) as advocated by the World Health Assembly for achieving the sustainable development goals on health should be encouraged in LMICs to upscale the state of preparedness for essential surgery without the routine use of ketamine.[88] The NSOAPs was a success in Ethiopia, the first country in Africa to adopt the strategy; this report of success is encouraging and may be replicated if introduced elsewhere.[88]

Safe anesthesia should be recognized as a compendium to safe surgery while encouraging better funding, practice, and pricing of anesthesia subspecialty to improve local capacities and capabilities.

### *Limitations*

The search was restricted to 2 electronic databases, which included academic literature, excluding books. Additional issues might have

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been discussed outside the academic sources used in this scoping review; however, if contemplated, the scale of such a broad search was beyond the resources available for the review. Additionally, the qualitative nature of this scoping review's analysis means that the author's professional and personal orientations influenced the selection and screening of articles, identification, and classification of themes and subthemes. Also, incomplete retrieval of some of the articles reviewed led to the exclusion of such studies, despite importance. These limitations mean that caution is required in generalizing any of the reported findings.

## Conclusion

The global health consequences of a ketamine ban are far more potent to argue against the reclassification of ketamine. It is important to continue to remind legislators, politicians, law enforcement, prosecutors, and other non-clinical actors of the role of ketamine in clinical practice while encouraging LMICs to prepare if a ketamine petition becomes successful in the future. Focused studies and reviews with an emphasis on how LMICs should reduce overreliance on ketamine may be required, and these should be supported with quality outcome data from epidemiological and observational studies for proper planning, auditing of interventions, and to promote its rational use of ketamine.

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