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Editorial

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Ketamine: a growing global health-care need

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Ketamine was first synthesized in 1962, patented in Belgium in 1963, and approved for human use by the US Food and Drug Administration in 1970. Unlike inhalation anaesthetics, ketamine provides analgesia, preserves airway reflexes, offers haemodynamic stability, and maintains respiratory drive, which gives ketamine an excellent safety profile. It is therefore a favoured choice for trauma triage, use in man-made and natural disasters, and for many other patients with compromized haemodynamic stability. However, side-effects, such as agitation, hallucinations, and panic attacks, have limited its clinical use as an anaesthetic in affluent countries. Lately, ketamine has found new uses in clinical medicine in addition to renewed threats to its availability.

Ketamine has long had a place in the management of acute pain via intraoperative low-dose infusion, especially in opioid-tolerant patients, and has likewise been used after surgery with minimal psychomimetic effects.[1] With a growing number of patients diagnosed with chronic pain and only 30–40% of patients achieving adequate to good pain relief, anaesthetists and pain specialists have now looked to ketamine to treat chronic pain syndromes.[2] Activation of *N*-methyl-D-aspartate (NMDA) receptors plays a role in central sensitization, wind-up phenomenon, and opioid tolerance. The NMDA receptor is an excitatory glutamate receptor present at spinal and supraspinal sites. In chronic pain states, chronic nociceptive stimulation causes activation and upregulation of NMDA receptors, resulting in amplified pain signalling to the brain. There is now evidence that NMDA antagonists, such as ketamine, reduce the excessive signalling of nociceptive input to the brain. In chronic non-cancer pain, ketamine has been shown to alleviate neuropathic pain in a number of conditions, including chemotherapy-induced neuropathy, chronic neuropathic pain, complex regional pain syndrome, fibromyalgia, painful limb ischaemia, and traumatic peripheral nerve injury. A ketamine infusion was shown to be effective in a randomized trial of 60 patients with complex regional pain syndrome type I in providing pain relief with analgesia outlasting the treatment period by 50 days.[3] In cancer pain, however, a review of the literature found only two studies of sufficient quality, with most of the support for its efficacy coming from case reports or uncontrolled studies in patients with refractory neuropathic pain.[4] At this time, there is insufficient evidence to assess the benefits of ketamine as an adjuvant to opioids for the relief of cancer pain. There is some evidence that short-term 'burst' treatment with ketamine may have relatively long-term benefit in both cancer and non-cancer pain.[4] For example, in patients taking large amounts of opioids for ischaemic limb pain, intercurrent ketamine infusions lead to reduced requirements for opioids in the week after. In cancer patients, ketamine infusions have reduced requirements for opioids by 70%. Further investigations are needed to determine the precise role of ketamine in management of chronic pain, especially for cancer pain.

Recently, ketamine has also gained interest among psychiatrists as a treatment for severe clinical depression. Most antidepressant medications modulate the monoamine neurotransmitter system, usually requiring 4–12 weeks for therapeutic effect, if at all. A large study of more than 3600 outpatients with major depressive disorder (MDD) demonstrated that only 36% of patients achieved remission after a 12 week trial of citalopram.[5] This has led researchers to examine new targets, including the NMDA receptor. Ketamine has been observed to exhibit antidepressant activity within several hours of a single subanaesthetic i.v. infusion. In the largest trial to date, 73 patients with treatment-resistant MDD experiencing a major depressive episode were randomly assigned to receive a single 40 min infusion of ketamine (0.5 mg kg^{-1}) or midazolam (0.045 mg kg^{-1}).[6] More patients who received ketamine compared with those who received midazolam (64 *vs* 28%) had a greater than 50% reduction in their baseline symptoms. Ketamine is even as effective as electroconvulsive therapy (ECT). Electroconvulsive therapy is used as a rapid treatment for bipolar depression or

mania and major depression in patients resistant to antidepressant therapy or those needing rapid treatment response, such as pregnant patients or patients with persistent suicidal intent. It has a faster onset than conventional antidepressants. Typically, five to seven ECT treatments throughout ~2 weeks are required for significant reduction in symptom severity. One study randomized 18 patients with MDD to receive repeated therapies of either ketamine infusions or ECT and found that ketamine improved symptoms more rapidly than ECT, with the most improvement after the first ketamine infusion.[7] Another prospective observational study found that ketamine led to a moderately large reduction of depressive symptoms in 17 patients who had previously not responded to ECT.[8] In addition, ketamine may be useful in the treatment of acutely suicidal patients, who need rapid and effective intervention. A randomized trial again compared ketamine with midazolam in 57 patients with treatment-resistant MDD and found that ketamine eliminated suicidal ideation at 24 h in more patients compared with midazolam (53 *vs* 24%).[9] Additional reports have suggested that reductions of suicidal ideation from ketamine treatment can be maintained for up to 10 days.[10] The long-term benefits and consequences of ketamine treatments are still under investigation, but it is a promising option for rapid treatment of patients who have failed conventional therapies of antidepressant oral medications and ECT.

While ketamine has found new clinical uses in high-income countries, ketamine has been absolutely vital in global health. Low- and middle-income countries (LMICs) rely heavily on ketamine as an anaesthetic, and their dependence is growing with the increasing need for surgical services. The global burden of disease preventable by surgery is on the increase and is expected to surpass those of human immunodeficiency virus, tuberculosis, and malaria by 2026.[11] The World Bank recently published the third edition of *Disease Control Priorities*, which re-evaluated the cost-effectiveness of surgical care in resource-constrained settings.[12] Based on substantial need, cost-effectiveness, and feasibility, the report identified 44 essential surgical procedures that could avert 1.5 million deaths a year in LMICs. Improving access to surgical procedures can be accomplished only in conjunction with availability of appropriate anaesthesia services. Health care in LMICs lacks the infrastructure, anaesthesia equipment, and trained anaesthesia personnel to handle the growing need. In a recent survey of anaesthetic care in 22 LMICs, uninterrupted electricity was available in only 59% of facilities, while 53% had functioning anaesthesia machines (Fig. 1).[11] Uninterrupted access to oxygen was available in only 46% of facilities, while 35% reported no access to oxygen. Basic airway-management equipment, such as face masks, laryngoscopes, and endotracheal tubes, were lacking in 21–45% of facilities. Nurses and clinical assistants made up the majority of the anaesthesia providers. The limited skill of the anaesthesia providers and lack of safety equipment in LMICs contribute to the overall greater risk of complications with general anaesthesia compared with local and regional techniques. Ketamine can be administered i.v. or i.m. and does not require the availability of oxygen, electricity, and anaesthetic equipment or trained anaesthesia providers, all of which remain severely limited in LMICs. Thus, ketamine is the most widely used and safest anaesthetic drug, as reflected by being 'always available' according to 92% of anaesthetists surveyed in Uganda.[13]

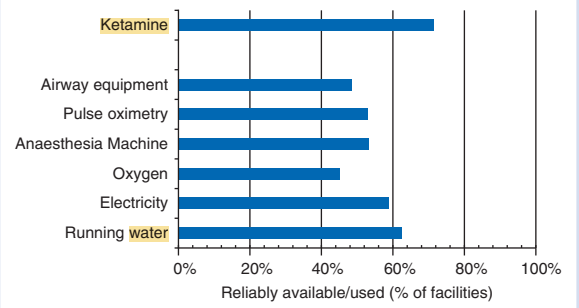

Fig 1 Use of ketamine as an anaesthetic compared with basic anaesthetic infrastructure and equipment at facilities in 22 low- and middle-income countries. Current ketamine use exceeds availability of other anaesthetic options. Redrawn from data by Vo and colleagues.[11]

The side-effects that limited the use of ketamine as an anaesthetic make the substance appealing to recreational drug users. Ketamine is considered a dissociative anaesthetic, which alters sensory perceptions. Ketamine intoxication may involve vivid dreams, 'out-of-body' experiences, and emotions of euphoria or fear. Ketamine is frequently abused with other illicit drugs, such as amphetamines, 3,4-methylenedioxy-methamphetamine, and cocaine. Non-medical uses of ketamine became increasingly popular in the 1990s at dance clubs, which prompted the placement of ketamine as a Schedule III non-narcotic drug on the US Controlled Substance list in 1999. Schedule III drugs are described as 'hav[ing] a potential for abuse . . . and abuse may lead to moderate or low physical dependence or high psychological dependence'.[14] Other Schedule III non-narcotics include anabolic steroids and appetite suppressants.

Illicit ketamine use is gaining popularity worldwide, particularly in China and other parts of Asia. China, the source of much of the world's illicitly consumed ketamine, has felt increasing pressure from countries in its region to limit its use. Recently, China failed to persuade the World Health Oraganization (WHO) Expert Committee on Drug Dependence (ECDD) that ketamine should be reclassified as a Schedule I drug. Such scheduling would designate ketamine as having no or minimal medical use. The ECDD has critically evaluated peer review reports and data regarding ketamine three times, in 2006, 2012, and again in 2014, concluding that despite the limited harmful effects of non-medical use, ketamine abuse does not pose a 'significant global public-health risk' to warrant scheduling.[15] The ECDD has recommended that China maintain domestic control measures instead of enacting international regulations. The ECDD cites the status of ketamine on the WHO list of Essential Medicines for essential surgery and the grave impact on global health of limiting the access of LMICs to this medication. This year, China tried to persuade the United Nations Commission on Narcotic Drugs (CND) to schedule ketamine despite lacking a recommendation by the WHO, which conflicts with the terms of the 1971 Convention that the CND can consider scheduling a substance only if the WHO has recommended the substance be placed in a schedule. In response to intensive lobbying from multiple organizations concerned about the health-care implications, including the World Federation of Societies of Anaesthesiologists and national anaesthesiology societies, China agreed to defer this year's application to have ketamine designated a Schedule I drug but will undoubtedly, and for predominantly political reasons, look to schedule ketamine in the future.

Past experiences with morphine indicate that restrictions on medications do limit their availability for medical purposes despite WHO designation as an essential medication. For example, morphine is controlled under the United Nations CND, which obliges 184 countries to control the legal and illegal uses of narcotic

drugs. The regulatory impediments have resulted in tens of millions of people worldwide, by WHO estimates, experiencing pain associated with late-stage cancer, acquired immune deficiency syndrome, and other painful conditions.[16] In 2002, 78% of the worldwide morphine consumption went to six countries, namely Australia, Canada, France, Germany, the UK, and the USA, while a mere 6% went to the other countries, which represent 80% of the world's population.[17]

Ketamine is undergoing a resurgence of interest for its potential uses for perioperative pain, for chronic pain, and in psychiatry for severe depression. Pharmaceutical companies have noted this, and clinical trials of an S(+)-ketamine nasal spray are already underway, probably with other formulations to follow.[18] Restrictions on ketamine will limit the investigation of these potential treatment options. Any future decisions imposing restrictions on ketamine also need to consider the larger impact on the global burden of surgical diseases where ketamine is a vital component of patient care. Such a restriction should be considered only after a global commitment and successful implementation of improved anaesthetic services making ketamine redundant. As stated by the Global Commission on Drug Policy, it is time to 'begin the transformation of the global drug prohibition regime. Replace drug policies and strategies driven by ideology and political convenience with fiscally responsible policies and strategies grounded in science, health, security and human rights – and adopt appropriate criteria for their evaluation.'[19]

Declaration of interest

J.M.-O. is a Board Member of the European Society of Anaesthesiology, European Board of Anaesthesiology, and World Federation of Societies of Anaesthesiology; A.W.G. is Chair of the Safety & Quality of Practice Committee of the World Federation of Societies of Anaesthesiology, and Editorial Board member of *Candian Journal of Anesthesia* and *Journal of Neurosurgical Anesthesiology*.

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