WFSA Presentation to the Expert Committee on Drug Dependence (ECDD)

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Presentation Overview

• Why is Ketamine an essential drug with acute medical value?

• Academic and legislative recognition of ketamine’s importance

• What would be the impact of scheduling ketamine?

• Conclusions & Recommendations
“Drugs that are considered to have little or no therapeutic value” – UN CND definition of Schedule 1 drugs
Why is Ketamine an ‘essential’ drug with enormous medical value?
Ketamine is the primary component of safe anaesthesia in LMICs

Ketamine is the ONLY anaesthetic that can be safely used without safety equipment:

- Uninterrupted electricity in only 59%
- Functioning anaesthesia machines in 53%
- No access to oxygen in 35%
- No access to basic airway management equipment in 21-45%

Ketamine is the ONLY anaesthetic that can be safely used without a skilled anaesthesia provider present:

- Nurses and clinical assistants: majority of the anaesthesia providers.
- Limited skill + Lack of safety ➔ greater risk of complications with general anaesthesia vs local/regional

T. T. Dong, J. Mellin-Olsen and A. W. Gelb 2015
Comparison between ketamine use and basic anaesthetic infrastructure and equipment in 22 LMICs

Anaesthesia & ressource facilities in 22 LMICs

Ketamine is essential part of the armamentarium for many medical and surgical therapies

Ketamine is effective in treatment-resistant bipolar depression

Fond G. Et al. Psychopharmacology (Berl). 2014 Sep;231(18):3663-76

Ketamine is essential to prevent or treat opioid tolerance

Subramaniam K et al Anesth Analg. 2004 Aug;99(2):482-95

Disaster and conflict zones

- little access to complex equipment to provide other forms of anaesthesia and analgesia
- anaesthetic of choice in ICRC practice for major surgery – ICRC War Surgery Volume 1
What does this mean in practice?

Surgery can be performed with anaesthesia in low resource hospitals.

Pain can be managed in order to treat burn victims and other injuries in conflict areas.

Post-operative pain can be managed, reducing recovery time.
5 billion people do not have access to safe and affordable surgery and anaesthesia when they need it.

This number would be even higher without access to ketamine.
Academic and legislative recognition of ketamine's importance
## Essential Medicines

### WHO Model List

<table>
<thead>
<tr>
<th>1. ANAESTHETICS</th>
<th>18th edition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 General anaesthetics and oxygen</td>
<td></td>
</tr>
<tr>
<td>1.1.1 Inhalational medicines</td>
<td></td>
</tr>
<tr>
<td>halothane</td>
<td>Inhalation.</td>
</tr>
<tr>
<td>isoflurane</td>
<td>Inhalation.</td>
</tr>
<tr>
<td>nitrous oxide</td>
<td>Inhalation.</td>
</tr>
<tr>
<td>oxygen</td>
<td>Inhalation (medicinal gas).</td>
</tr>
<tr>
<td>1.1.2 Injectable medicines</td>
<td></td>
</tr>
<tr>
<td>ketamine</td>
<td>Injection: 50 mg (as hydrochloride) / ml in 10-ml vial.</td>
</tr>
<tr>
<td>propofol*</td>
<td>Injection: 10 mg / ml; 20 mg / ml.</td>
</tr>
<tr>
<td>* Thiopental may be used as an alternative depending on local availability and cost.</td>
<td></td>
</tr>
<tr>
<td>1.2 Local anaesthetics</td>
<td></td>
</tr>
<tr>
<td>lidocaine</td>
<td>Injection: 1% / 2% (hydrochloride) in vial. Injection for spinal anaesthesia: 0.5% (hydrochloride) in 4-ml ampoule to be mixed with 7.5% glucose solution.</td>
</tr>
<tr>
<td>bupivacaine</td>
<td>Injection: 0.25% / 0.5% (hydrochloride) in vial. Injection for spinal anaesthesia: 0.5% (hydrochloride) in 4-ml ampoule to be mixed with 7.5% glucose solution.</td>
</tr>
<tr>
<td>lidocaine + epinephrine (adrenaline)</td>
<td>Dental cartridge: 2% (hydrochloride) + epinephrine 1:80,000. Injection: 1% / 2% (hydrochloride or sulfate) + epinephrine 1:200,000 in vial.</td>
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<tr>
<td>Complementary List</td>
<td></td>
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<tr>
<td>ephedrine</td>
<td>Injection: 30 mg (hydrochloride) / ml in 1-ml ampoule. (For use in spinal anaesthesia during delivery, to prevent hypotension).</td>
</tr>
</tbody>
</table>
Ketamine is also on the WFSA list at ALL levels of health care facility (health centre, district hospital, referral hospital).
Ketamine: A Growing Surgical Health Need 2015

BJA

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 1975. Unlike intravenous anesthetics, ketamine produces analgesia, preserves airway reflexes, offers hemodynamic stability, and maintains respiratory drive, which gives ketamine an excellent safety profile. It is therefore a favored choice for trauma triage, use in mass and natural disasters, and for many other patients with compromised hemodynamic stability. However, side-effects, such as agitation, hallucinations, and panic attacks, have limited its clinical use as an anesthetic in affluent countries. Lately, ketamine has found new use in clinical medicine in addition to eased 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, neuroanesthetists and pain specialists have now looked to ketamine to treat chronic pain syndromes.1 Activation of N-methyl-D-aspartate (NMDA) receptors plays a role in central sensitization, wind-up phenomena, and opioid tolerance. The NMDA receptor is an excitatory glutamate receptor present at spinal and supraspinal sites. In chronic pain syndrome type I, providing pain relief with analgesics outlining the treatment period by 50 days. 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.7 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 “flurax” treatment with ketamine may have relatively long-term benefit in both cancer and non-cancer pain.8 For example, in patients taking large amounts of opioids for intractable 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 500 patients with major depressive disorder (MDD) demonstrated that only 30% of patients achieved remission after a 12 week trial of tricyclics.9 This has
What would be the impact of scheduling ketamine?
Limited and no access to ketamine for medical purposes!

Parties to the Convention are obliged to prohibit any medical use of a Schedule I substance except by "persons directly under control of the government,"

In practice:

- It will be possible but difficult for state run medical centres to access ketamine
- Other medical centres (which are the majority of medical centres in some countries) will have no or very restricted access to ketamine
- It will be more difficult to import ketamine and supply will dry up
- Millions more patients will not have access to safe anaesthesia and surgical care
Impact case study - morphine

“Past experiences with morphine indicate that restrictions on medications do limit their availability for medical purposes despite WHO designation as an essential medication” – Gelb & Mellin-Olsen, BJA 2015

• In 2002, 78% of the worldwide morphine consumption went to six countries, namely Australia, Canada, France, Germany, UK, and USA
• Only 6% went to the other countries, which represent 80% of the world's population.

India Example (Following the the Narcotic Drugs and Psychotropic Substances Act)

• Procedures to acquire opioids dizzyingly complex: up to six licenses are required for every consignment of morphine
• Many hospitals simply not stocking morphine
• WHO shows medicinal use of morphine dropped 97% after the law was enacted
Conclusions & Recommendations

• Very good evidence of the reliance upon Ketamine as a safe anaesthetic drug, particularly in LMICs.

• Past experience indicates that further restriction on essential drugs can and does limit availability for medical purposes.

• Any decision to further restrict Ketamine is premature at the very least, and - more alarmingly - a potential risk to large numbers of patients around the world.

Therefore:

• Any legislation regarding Ketamine must consider the effects before it is enacted.

• Such recommendation must be based on valuable trials that provide evidence to consider access and availability for medicinal purposes.