Ketamine

Expert peer review on critical review report (1)

35th Expert Committee on Drug Dependence, Hammamet, Tunisia
June 4-8, 2012
1. Comments based on the review report

a. Evidence on dependence and abuse potential
Dependence has been demonstrated in animal models. A limited number of cases of ketamine dependence in humans over the past 20 years have been described, but the terms are not consistently defined so it cannot be concluded that they are in fact dependence cases. Several conditions may drive the use of ketamine, including an escape from reality. Some effects of ketamine may be due to an enhancement of dopamine activity, which may be of relevance for its euphoric, dependence-producing, and psychotomimetic properties and it will appeal to substance users looking for extremes. This possibility for escape and discovery may appeal to some individuals, offering a psychological reward, which contributes to the development of dependence.
The substance is difficult to synthesize and preparations are mainly used in hospitals and veterinary clinics, so illegal production is unlikely and diversion does not take place on a large scale.

b. Consequences to individual and society because of misuse

Individual
Ketamine can produce a depression of the central nervous system, resulting in hallucinations, disturbances in thinking, perceptions and in motor function. Repeated use produces chronic impairments to episodic memory, which are reversible upon reduction of use. Standard psychometric tests did not reveal personality changes. Studies in healthy volunteers given ketamine have shown that ketamine produces a clinical syndrome with aspects that resemble key symptoms of schizophrenia, which may be experienced by the experimental or recreational substance user as an altered, ‘psychedelic’, state of mind.
In dependent users, use of the substance continues despite increasing apparent effects on their work or on their health.

Society
Information on ketamine is not routinely collected in population surveys and morbidity and mortality data collections. Levels of use in the general population, however, appear to be very low with higher levels in groups with access to the substance, such as medical and veterinarian professionals, and party drug users. Besides these more mainstream groups, several smaller groups have been identified in which ketamine is misused including gay men, homeless and runaway youth.
Data from different studies in the USA and UK indicate that deaths due to ketamine abuse were very few and in most cases, they were due to acute multidrug intoxications. The WHO Uppsala Monitoring Centre (UMC) reported, out of 1277 reports from adverse effects from world wide PMS-data, over a 2-year period, 25 cases of death, (2.0 %) and 1 case of sudden death (0.08%).
The conclusion of several authors cited in the critical review is that ketamine does not appear to currently pose a significant public health risk.

c. **Magnitude of the problem in countries (misuse, illicit production, smuggling etc)**
   Due to the difficult synthesis of ketamine only diversion from legal sources has been observed. Levels of use in the general population appear to be very low with higher levels in groups with access to the substance, such as medical and veterinarian professionals, and party drug users.
   Ketamine misuse is reported from a number of countries in Asia, Europe and North America. Almost half of the cases deal with healthcare staff. Multidrug use or polysubstance is common.
   Of the 64 countries responding to the WHO Questionnaire for the ECDD, 16 reported on the use of ketamine in a harmful way and 9 reported on the extent of the harmful use. The extent of the abuse reported ranges from 0.07% (in Thailand) to <2% (in Denmark) of the youth population. 19 countries have tracked illicit activities involving ketamine. The seizures vary from a few grams (9g/year in France) to 6000 kg/year (in China).
   The ketamine critical review report includes a survey on the use of ketamine among several hospitals in 4 countries in Africa (Ethiopia, Nigeria, Tanzania and Benin). Use of ketamine in anesthesia ranged between 15 to 49% of all the procedures in the surveyed hospitals. None of the hospitals reported cases of abuse or misuse.

d. **Need of the substance for medical (including veterinary) practice**
   Ketamine is listed as an anesthetic both in EML 18th ed (2011) and in EMLc 3rd ed (2011) and is authorized as a medicine in at least in 60 countries. Ketamine hydrochloride is used as an analgesic and anaesthetic in human and veterinary medicine. Is one of the most commonly used anaesthetic agents in the developing countries (readily available, easy to use and inexpensive). Several Member States (Sweden, Denmark, Germany, Portugal) indicate that ketamine is indispensable for its indications in veterinary medicine.

Other uses:
- Supplement to other anesthetics
- In obstetrics
- Adjuvant therapy of status asthmatics
- Immobilization
- Sedation
- Persistent hiccups
- Priapism
- Resistant bronchospasm
e. Need of the substance for other purposes (e.g. industrial)
No other uses and not applicable in industrial use.

f. Measures taken by countries to curb misuse
   In 2006, the Commission on Narcotic Drugs (CND), in its resolution 49/6, and in 2007, in its resolution 50/3, called upon Member States to pay attention to the misuse of and trafficking in ketamine, in particular in East, South-East Asia and South America, and to consider adopting a system of precautionary measures for use by their government agencies to facilitate the timely detection of the diversion of ketamine and controlling its use by placing ketamine on the list of substances controlled under their national legislation, where the domestic situation so requires.
   In its Annual Report for 2007, the International Narcotics Control Board (INCB) called on all Governments to implement Commission resolution 50/3 without delay. In its reports for 2008 and 2009 it called for the implementation of both resolutions 49/6 and 50/3.
   In 2008, in addition, the Board "decided to request all Governments to provide it with information on the specific legal or administrative measures adopted pursuant to Commission resolution 49/6, including information on measures to control ketamine".
   In 2009, a total of 48 Governments reported that ketamine had already been placed on the list of substances controlled under national legislation.

g. Impact if this substance is scheduled
   Ketamine is a widely used anesthetic and analgesic, especially in developing countries because it is easy to use and has a wide margin of safety when compared with other anesthetic agents.
   Data from the INCB indicates that the vast majority of patients do not have access to controlled medications. There are many reasons for this, one of which is unduly restrictive laws and regulations in the countries. If ketamine is placed under international control, it can be assumed that its availability and accessibility will fall into the same level of other controlled medications, which would result a huge public crisis.
   Eight countries reported that if ketamine is placed under more strict international control, the availability for medical use would be affected.
   Seven countries reported how a transfer will impact the medical availability.
   Bhutan reported that there would be an impact of scheduling to some extent. The transfer will impact medical availability as a result of stringent import regulation. The impact in China is the control of the substance as a psychotropic substance since 2001. In Greece it will have an impact on the distribution.
   The Netherlands reported that the impact of the transfer would be that the use of ketamine would be less than medical/veterinary acceptable. According to the Republic of Korea the impact of international control, the administrative process in distribution will be more
complicated. Tuvalu reported that control would affect the quantities allocated for each country.

2. Additional information to the critical review report

Ketamine is also being used as an adjuvant analgesic and as an alternative analgesic in patients in palliative care. Studies indicate that ketamine may reduce pain intensity in patients with advanced cancer and mixed pain syndromes.

References


3. Other comments or opinions

Ketamine has several important medical uses and when used appropriately, it is safe, effective and affordable. Millions of patients (humans and animals) currently benefit from the legitimate use of ketamine.

4. Expert reviewer’s recommendation on scheduling with rationale

In September 2002 the WHO ECDD had a pre-review on ketamine. A critical review was performed in 2006. The WHO ECDD concluded that there was no significant public health issues posed by ketamine and that international control was unnecessary. It was suggested that the drug be kept under surveillance.

Based on the evidence presented in the critical review since the critical review in 2006, which indicates that ketamine:

- does not appear to pose a significant public health risk
- illicit manufacture is unlikely to happen
- abuse occurs in limited population groups
- it is widely used in medical and veterinary practice benefiting millions of people and animals around the world,
- placing ketamine under international control would negatively impact its availability and accessibility for legitimate medical and veterinary practice

I do not recommend placing ketamine under international control and suggest keeping the drug under surveillance to detect trends.