Ketamine (INN)
Update Review Report

Agenda item 6.1

Expert Committee on Drug Dependence
Thirty-seventh Meeting
Geneva, 16-20 November 2015
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Acknowledgements

This report has been drafted under the responsibility of the WHO Secretariat, Essential Medicines and Health Products, Policy Access and Use team. The WHO Secretariat would like to thank the following people for their contribution in producing this critical review report: Prof. Jason White, Australia (updated literature search, review and drafting) and Dr. Stephanie Kershaw, Switzerland (editing).
Summary

Ketamine is an anaesthetic and analgesic drug with a history of medical use dating back to its development in the 1960s. It has a wide range of uses, but is particularly valuable because it does not depress respiration or cardiac function at doses that produce anaesthesia. In situations where respiratory support is unavailable or unreliable, particularly in lower and middle income countries, and during emergencies such as wars and natural disasters, it may be the only viable anaesthetic. It is also extensively used in veterinary medicine for large and small animals and for wildlife.

More recently, extensive research has been carried out on the antidepressant properties of ketamine. It has shown to be effective in the treatment of depression without the delay in onset of action associated with conventional antidepressants. However, the effect is relatively short term and it is not clear whether ketamine itself will be used clinically for this purpose.

Ketamine has also been used non-medically for its hallucinogenic and other effects over a period nearly as long as its medical use. In many countries ketamine use remains at a low level; the highest rates of ketamine use have been recorded in Hong Kong following a rapid increase in the rate of use beginning around the year 2000.

At both its 35th and the 36th meetings, the WHO Expert Committee on Drug Dependence discussed critical reviews of ketamine. During its 36th meeting the Committee considered the updated review report on ketamine and came to the following recommendation: “Although we acknowledge the concerns raised by some countries and UN organizations, ketamine abuse currently does not appear to pose a significant global public health risk to warrant scheduling. Countries with serious abuse problems may decide to introduce or maintain control measures, but should ensure ready access to ketamine for surgery and anaesthesia for human and veterinary care. On this basis, we, the Expert Committee, decided that bringing ketamine under international control is not appropriate”.

The Committee also resolved to monitor the information arising from published literature and other sources relating to ketamine. The present report is an update of this information since the 36th ECDD meeting in 2014. It covers material that has become available since that time and some aspects of the available information that were not covered extensively in the Update Review Report for the 36th ECDD meeting.

The material covered in this report confirms the importance of the medical use of ketamine, particularly for low and middle income countries, and highlights the potential role of ketamine as a prototype for a completely new class of antidepressants. Updated prevalence data indicate that globally ketamine use is widespread, but at relatively low levels in most countries; Hong Kong is a major exception where use has been relatively high for a number of years and China reports significant use. Currently available data do not suggest that ketamine use is increasing globally. Some medical problems associated with the use of ketamine have been better documented recently, but there have been no major developments in this area over the last year. Similarly, there have been no major changes in the assessment of abuse liability or toxicity.
1. Substance identification

A. International Non-proprietary Name (INN)

Ketamine; ketamine hydrochloride.

B. Chemical Abstract Service (CAS) Registry Number

6740-88-1 (free base)
1867-66-9 (current: hydrochloride salt)
81771-21-3; 96448-41-8; 42551-62-2 (previous: hydrochloride salt)

C. Other Names

2-(2-chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride;
2-(o-chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride;
2-(methylamino)-2-(2-chlorophenyl)cyclohexanone hydrochloride;
2-(methylamino)-2-(o-chlorophenyl)cyclohexanone hydrochloride;
cyclohexanone, 2-(2-chlorophenyl)-2-(methylamino) hydrochloride;
cyclohexanone, 2-(o-chlorophenyl)-2-(methylamino) hydrochloride.

D. Trade Names

Some of the trade names used include:
Anaket®, Anasket®, Anesketin®, Brevinase® Brevinaze®, Calypsol®,
Calypsovet®, Chlorketam®, Ereska®, Imalgene®, Inducmina®, Kalipsol®,
Katalar®, Keta®, Keta-Hameln®, Ketaject®, Ketalar®, Ketalin®, Ketalor®,
Ketamav®, Ketamax®, Ketamil®, Ketamin®-ratiopharm, Ketaminol Vet®,
Ketanarkon®, Ketanest®, Ketanest-S®, Ketaset®, Ketasol®, Ketava®, Ketaved®,
Ketavet®, Ketmine HCl®, Ketolar®, Ktmin®, Narkamon®, Narketan®, Pan-
Ketamine®, Ralatek®, S-Ketamin®, Tekam®, Velonarcon® Vetaket®, Vetalar®,
Vetus Ketha-Thesia®.

E. Street Names

A number of street names for ketamine can be found in the literature, like:
“Super K”, “Tac et Tic”, “Vitamin K”.1,2

One should be aware of the fact that street names are not always exclusive for just
one substance. Flatliners is also used for 4-MTA and Liquid E for GHB.

F. Physical properties

White to almost white, crystalline powder.
G. WHO Review History

During both its 35\textsuperscript{th} and 36\textsuperscript{th} meetings, the WHO Expert Committee on Drug Dependence discussed critical reviews of ketamine and determined that it was not appropriate to bring ketamine under international scheduling. The United Nations Commission for Narcotic Drugs at its 10\textsuperscript{th} session, held on 13 March 2015, decided by consensus to postpone the consideration of a proposal concerning the recommendation to place ketamine in Schedule IV of the Convention on Psychotropic Substances (1971) and to request additional information from the World Health Organization and other relevant sources.

2. Chemistry

A. Chemical Name

IUPAC Name: 2-(2-Chlorophenyl)-2-(methylamino)-cyclohexan-1-one
CA Index Name: Not applicable

B. Chemical Structure

Free base:

![Chemical Structure Diagram]

Molecular formula: C\textsubscript{13}H\textsubscript{16}ClNO (free base)  
C\textsubscript{13}H\textsubscript{17}Cl\textsubscript{2}NO (hydrochloride salt)
Molecular weight: 237.73 g/mol (free base)  
274.18 g/mol (hydrochloride salt)
Melting point: 92-93°C (free base)  
262-263°C (hydrochloride salt)

C. Stereoisomers

Ketamine contains a chiral centre at the C-2 carbon of the cyclohexanone ring, so that two enantiomers exist: S-(+)-ketamine and R-(-)-ketamine. The S-enantiomer being the pharmacologically more active stereoisomer. Increasingly, the S-(+)-enantiomer is being used in the commercially available preparations.
D. Synthesis

Ketamine is manufactured by the pharmaceutical industry. The preparation is described by Stevens, Belgian patent 634208 (1963), which corresponds to the U.S. patent 3254124 (1966 to Parke-Davis). The synthesis of the optical isomers is described by Hudyma et al., German patent 2062620 (1971 to Bristol-Myers).³

Ketamine for recreational use may be obtained by diversion of commercial sources, but extensive illicit manufacture has been reported in China.

E. Chemical description

Ketamine (2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone) is an arylcycloalkylamine structurally related to phencyclidine (PCP).

F. Chemical properties

Ketamine hydrochloride is a water-soluble, white crystalline powder and has a pKa of 7.5.³ It is free base, ketamine, has lipid solubility 10 times that of thiopentone. The commercially available pharmaceutical form is an aqueous solution for injection of the racemic mixture of the hydrochloride salt.

G. Chemical identification

Ketamine is metabolized to at least two compounds. The parent compound and both major metabolites are further transformed by hydroxylation and conjugation prior to elimination. About 90% of a dose is excreted in urine in 72 hours, with about 2% of the dose unchanged. There are different methods described in the literature to analyze ketamine in the urine. One of them is an analytical method using solid-phase extraction and positive ion chemical ionisation-gas chromatography-mass spectrometry.⁴

3. Ease of convertibility into controlled substances

Ketamine is not converted into controlled substances.

4. General pharmacology

The pharmacology of ketamine will be described in two parts. The first one will deal with the effects of the substance on various neurotransmitter systems related to both its clinical use and its use as a recreational agent. The second part will deal with the effects on various organ systems sometimes leading to adverse reactions.

A. Pharmacodynamics

Ketamine is a dissociative anaesthetic.⁵ Originally, the dissociation component refers to a functional and electrophysiological dissociation of thalamoneocortical and limbic systems.⁶,⁷ More recently, the nature of the subanaesthetic ketamine experience has led to the use of the term ‘dissociative’ in a more psychological sense referring to a feeling of dissociation of the mind from the body.⁸,⁹
Ketamine binds to the so-called PCP-binding site of the N-methyl-D-aspartate (NMDA)-receptor complex, located within the ion channel, thereby blocking the transmembrane ion flux. This makes ketamine a non-competitive NMDA-receptor antagonist. NMDA-receptors are calcium-gated channel receptors. The endogenous agonists of this receptor are the excitatory amino acids glutamic acid, aspartic acid, and glycine. Activation of the receptor results in opening of the ion channel and the depolarisation of the neurone. The NMDA-receptor is involved in sensory input at the spinal, thalamic, limbic and cortical levels. Ketamine would be expected to block (or interfere with) sensory input to higher centres of the CNS, with the emotional response to these stimuli, and with the process of learning and memory.\(^{10}\)

Awakening from ketamine anaesthesia takes place at plasma concentrations of 0.64-1.12 µg/ml.\(^6\) Psychotropic effects have been described in the presence of plasma concentrations ranging from 50 to 300 ng/ml and with regional brain concentrations higher than 500 ng/ml.\(^{11-13}\)

Several studies indicate that opioid receptors are also involved in the pharmacological effects of ketamine\(^{14}\), and that the analgesic effect of ketamine may largely be attributed to the activation of these central and spinal receptors.\(^{15}\)

The plasma levels at which analgesia is achieved are 0.15 µg/ml following intramuscular administration and 0.04 µg/ml after oral administration. This difference may be explained by a higher norketamine concentration due to first-pass metabolism. This main metabolite apparently contributes to the antinociceptive effect of ketamine.\(^{16}\)

Furthermore, new developments show strong interactions between ketamine and the NMDA system in the brain of animals. In contrast to earlier findings, new results point to NMDA receptors and not sigma-receptors as having a role in the morphine withdrawal response.\(^{17}\) It has also been shown that competitive and non-competitive NMDA receptor antagonists prevent morphine tolerance and decrease the development of physical dependence on this opiate in mice.\(^{18}\) Another study indicates that ketamine has the ability to suppress morphine withdrawal syndrome in experimental settings without motor interference.\(^{19}\) The nucleus accumbens (NAc) is mentioned as the site of action.

Some effects of ketamine may be due to its actions on catecholamine systems, notably an enhancement of dopamine activity.\(^{20-22}\) A series of experiments\(^{23}\) on the effects of ketamine on uptake and efflux of dopamine in the rat NAc led the authors to conclude that ketamine increases NAc dopamine efflux not by the blocking of dopamine uptake, autoreceptors or NMDA receptors, but by mobilisation of the dopamine storage pool to releasable sites. In the rat, it has been shown that repeated ketamine administration diminished the initial five-fold increase in dopamine release in the prefrontal cortex, whereas the increase in extracellular 5-hydroxyindole acetic acid (a serotonin metabolite) levels is enhanced. This suggests that the balance between dopamine and serotonin neurotransmission in the prefrontal cortex is altered after repeated exposure to ketamine.\(^{24}\) The dopaminergic effects may be of relevance for the euphorogenic, dependence-producing and psychotomimetic properties of ketamine.
Other neuropharmacological actions are an agonistic effect on $\alpha$- and $\beta$-adrenergic receptors, an antagonistic effect at muscarinic receptors of the CNS, and an agonistic effect at the $\sigma$-receptor.\(^\text{10}\)

The principal metabolite, norketamine, is pharmacologically active. Its binding affinity to the NMDA-receptor and anaesthetic properties are approximately one third of the parent compound, potentially contributing significantly to the effects of ketamine.\(^\text{16}\)

The commercially available form of ketamine is a racemic mixture of two enantiomers. The S-enantiomer is shown to be the more potent one with an approximately 3-4 fold anaesthetic potency compared to the R-enantiomer. This correlates with the higher binding affinity for the PCP-site of the NMDA-receptor. The psychotomimetic properties of ketamine are mainly caused by the S-enantiomer, although subanaesthetic doses of R-ketamine may induce a state of relaxation.\(^\text{25,26}\)

**Effects on the cardiovascular system**

Ketamine differs from most anaesthetic agents in that it appears to stimulate the cardiovascular system, producing changes in heart rate, cardiac output, and blood pressure.\(^\text{7}\) Possibly, re-uptake inhibition of circulating catecholamines may contribute to this phenomenon. On the other hand, cardiodepressant effects have been noted in critically ill patients. This may be due to chronic catecholamine depletion preventing any sympatomimetic effects of ketamine and unmasking a negative inotropic effect, which is usually overshadowed by sympathetic stimulation.\(^\text{6,20}\) The cardiovascular effects of ketamine usually do not pose a problem, but its use is contraindicated in patients with significant ischaemic heart disease and should be avoided in patients with a history of high blood pressure or cerebrovascular accidents.\(^\text{7}\) In recreational ketamine users presenting to an emergency department, tachycardia was the most common finding upon physical examination.\(^\text{27}\)

**Effects on the respiratory system**

Ketamine is a mild respiratory depressant. It causes a modest shift of the CO\(_2\) dose–response curve to the right, in a dose-related manner, but does not change the slope of the curve. Respiratory drive to CO\(_2\) may be depressed as much as 15 to 22%. This effect is similar to that of opioids, but dissimilar from most sedative hypnotics and anaesthetics, suggesting that opioid receptors may play a role in the respiratory depressant effect. In clinical studies, the effects were observed only at high doses. Some case reports describe respiratory depression after rapid intravenous injection, but also after routine paediatric use of ketamine administered intramuscularly.\(^\text{6,20}\) At recreational doses, respiratory depression is not likely to occur, but cannot wholly be excluded.

Ketamine has a bronchodilatory effect and pharyngeal and laryngeal reflexes are maintained.\(^\text{6}\)

**Other pharmacological effects**

Ketamine increases muscle tone.\(^\text{6}\)

Blood glucose and plasma cortisol and prolactin are increased after ketamine administration.\(^\text{6,28}\)

Ketamine may decrease intraocular pressure.\(^\text{6}\)
B. Routes of administration and dosage

Clinically, the medicine is usually administered by intramuscular or intravenous injection or by infusion. For analgesia, the intrathecal route is used as well. Also, the oral, nasal and rectal routes have been described.\(^6\)

A dose equivalent to 2 mg of ketamine per kg body-weight given intravenously over 60 seconds usually produces surgical anaesthesia within 30 seconds lasting for 5-10 minutes (dose may range from 1 to 4.5 mg/kg); an intramuscular dose equivalent to 10 mg per kg body-weight (range 6.5-13 mg/kg) usually produces surgical anaesthesia within 3 to 4 minutes lasting for 12 to 25 minutes.\(^29\)

Analgesia is obtained by administration of 0.2-0.75 mg/kg intravenously.\(^6\)

Subanaesthetic doses inducing psychotropic effects range from 0.1 to 1.0 mg/kg i.v. In clinical studies, this dose may be divided into a bolus of 0.1-0.2 mg/kg and a maintenance infusion of 0.0025-0.02 mg/kg/min.\(^12,25,26,28,30\)

Intramuscular administration of ketamine in a dose range from 25 to 200 mg has been reported to produce psychotropic effects in humans.\(^31\) It is reported that the bioavailability of nasally administered ketamine in children was approximately 50%, whereas bioavailability of intramuscularly administered ketamine is approximately 93%.\(^32,33\)

C. Pharmacokinetics

The reported volume of distribution varies from 1.5 to 3.2 l/kg. The clearance is in the range of 12-28 ml/(kg.min). The volume of distribution and clearance for S-ketamine are 9 and 14% greater than those for R-ketamine, respectively.\(^26\)

Absorption

Ketamine is rapidly absorbed when administered through the intramuscular (Tmax 5-15 min), nasal (Tmax 20 min) or oral route (as a solution) (Tmax 30 min). Bioavailability is low when ketamine is given orally (17%) or rectally (25%). Extensive first-pass metabolism in liver and intestine is largely responsible for this effect. Bioavailability after nasal administration is approximately 50%.\(^32\)

Distribution

Ketamine has a high lipid solubility and low plasma protein binding (12%), which facilitates rapid transfer across the blood–brain barrier. Initially, it is distributed to highly perfused tissues, including the brain, to achieve levels 4-5 times those in plasma (distribution half-life after i.v. 24 sec.). CNS effects subside following redistribution to less well-perfused tissues (re-distribution half-life, 2.7 min.).

Biotransformation

Biotransformation primarily takes place in the liver. The most important pathway is N-demethylation to norketamine. When administered orally or rectally, initial plasma norketamine concentrations are higher than those of ketamine, but the plasma area under the curve (AUC) for norketamine is similar for all routes of administration. Norketamine has one-third the anaesthetic potency of ketamine and has analgesic properties.
Norketamine may be metabolised through multiple pathways, but the largest part is hydroxylated and subsequently conjugated.

Elimination
The predominant route of elimination is by liver metabolism. The high extraction rate (0.9) makes ketamine clearance susceptible to factors affecting blood flow. The conjugated hydroxy metabolites are mainly excreted renally. Terminal elimination half-life ranges from 100-200 minutes.

Pharmacokinetic interactions
Ketamine, and its primary metabolite, norketamine, are metabolised by enzymes from the cytochrome P450 (CYP) family. In a recent study, it has been shown that ketamine induces the expression of multiple forms of P-450 in rat liver microsomes and increases CCl4-induced liver toxicity and cocaine-mediated acute toxicity. As the combination of cocaine and ketamine is used and known in the party scene (often as CK or Calvin Klein), these findings should lead to further investigations into the possible risks for users of this combination.

5. Toxicology
The clinical safety profile of ketamine is largely based on extensive clinical experience. The preclinical data may therefore be of less importance. However, in contrast to recreational use, long-term clinical use of ketamine is rare. Therefore, some preclinical data may be of greater importance for the recreational substance user than for clinical practice.

Animal

Single-dose toxicity
Single dose acute toxicity shows an LD50 between 140 (intraperitoneally in the neonatal rat) and 616 mg/kg bw orally in the mouse. In adult mice and rats, LD50 values were 224±4 mg/kg and 229±5 mg/kg, respectively (route not indicated).

In squirrel monkeys, doses above 25 mg/kg i.v. caused anaesthesia. At the highest concentration tested (350 mg/kg), 4 out of 5 monkeys died. In humans, the lowest recommended i.v. dose to induce anaesthesia is 1 mg/kg. Applying the same ratio of minimal anaesthetic dose to highest non-lethal dose to humans implies that doses above 11.3 mg/kg i.v. may be lethal in humans. For a person of 60 kg this is equivalent to i.v. doses above 680 mg. This estimate is based on an experiment with a low number of animals and interindividual and interspecies differences may exist. Yet, considering data from case reports of fatal ketamine intoxications in humans, this estimate seems to be a realistic one.

Several studies investigated the local tolerance of ketamine when administered intrathecally. Ketamine, when injected without preservative did not cause neurotoxicity in the spinal cord of swine or rabbits.
Repeated-dose toxicity
There are a small number of studies examining the effect of repeated administration of ketamine on the adrenal glands and pancreas. Mice receiving 30mg/kg of ketamine intraperitoneally were found to have a decrease in the localisation of cells expressing enzymes important in the production of catecholamines in the adrenal glands (tyrosine hydroxylase and dopamine β-hydroxylase). This reduction suggests a significant disruption of catecholamine production. However, normal arrangement of the three adrenal cortical zones and the medulla was observed.

Decreases in the number of large β-islet have also been found, following both ketamine only and ketamine-alcohol treatment. The decreases in these groups (40-70% reduction compared to control mice) would likely result in a decrease in insulin production. However, there was no indication of apoptosis and only a slight increase in a marker for necrosis.

In rats, daily intravenous doses of 2.5, 5 or 10 mg/kg bw for 6 weeks provoked a slight but not significant decrease of food intake and moderate weight gain depression.

In a repeated dose toxicity study in dogs, 3 groups of 4 animals were given daily intramuscular doses of 4, 20 or 40 mg/kg bw during 6 weeks. At all dose levels there was some degree of weight loss and anorexia. Some blood parameters were also elevated and dose-related. Histological changes in the liver were minor.

Acute hyperglycaemia following ketamine administration (100mg/kg) was observed in fasting rats. This hyperglycaemia was not observed in fed rats administered the same amount of ketamine.

Further investigation is required to determine how these effects may translate to long-term ketamine use in humans.

Reproductive function
Rats were injected during the pre-mating period (10 mg/kg bw i.v. on Days 9, 10 and 11 prior to mating). No effect on litter size was observed.

Embryo-foetal and perinatal toxicity
Summarizing the available literature, at doses ten times those used in humans for anaesthesia, histopathological changes in rat foetuses have been observed. These effects are dependent on the period of exposure. Based on these preclinical data, in the absence of sufficient toxicokinetic data in animals, and considering that rodents have a higher metabolic rate and doses administered were in the subanaesthetic range in these animals, it cannot be excluded that ketamine in (sub)anaesthetic doses may adversely affect pregnancy outcome in humans.

Other studies in rats and rabbits point in the same direction but have limited value, since the duration and level of exposure in these studies do not meet current standards of toxicity testing.
A study in female dogs, injected with 25 mg/kg bw intramuscularly six times during one trimester of pregnancy did not show apparent adverse effects on the bitch or the pups.\textsuperscript{35}

No data on human pregnancies exposed to ketamine exist.\textsuperscript{44} There is some clinical evidence during use of ketamine during parturition, where it has been shown that ketamine may depress fetal functions when 2 mg/kg (i.v.) is administered to the mother.

Two studies will be discussed in more detail below as they deserve more attention because of possible serious consequences for users of illicit ketamine, especially in combination with other illicit substances.

Abdel-Rahman and Ismael\textsuperscript{45} studied the teratogenic potency of ketamine hydrochloride in CF-1 mice with and without cocaine. It was shown that ketamine (50 mg/kg/day) potentiated the teratogenic effects of cocaine (20 mg/kg/day), but was not teratogenic on its own. Considering the higher metabolic rate of mice, the authors stated that the doses applied were comparable to those used by dependent humans and should be toxic to first-time users. Another study demonstrated that the combination of cocaine and ketamine is a deleterious one.\textsuperscript{34}

Olney and co-workers\textsuperscript{46} suggested that ketamine has the potential to delete large numbers of neurones from the developing brain by a mechanism involving interference in the action of neurotransmitters [glutamate and gamma-amino butyric acid (GABA) at \textit{N}-methyl-d-aspartate (NMDA)] and GABA\textsubscript{A} receptors during the synaptogenesis period, also known as the brain growth-spurt period. Transient interference (lasting less than or equal to 4 hr) in the activity of these transmitters during the synaptogenesis period (the last trimester of pregnancy and the first several years after birth in humans) causes millions of developing neurones to die by apoptosis.

\textit{Mutagenic and carcinogenic potential}

Taking all the information together, the published data from genotoxicity testing of racemic ketamine are insufficient and do not allow for a reasonable assessment of the genotoxic potential of ketamine. Whereas negative findings were obtained in poorly conducted (compared to current standards) bacterial tests, a positive result was reported from a sister chromatid exchange (SCE) test \textit{in vitro}\textsuperscript{47}. However, the effects observed in the SCE study were only weak (i.e. less than a doubling of control values) and thus the relevance of this finding is questionable. Moreover, unpublished data (submitted to the German Federal Institute for Drugs and Medical Devices as part of an application for a marketing authorization) from genotoxicity testing with the \textit{S}(+) enantiomer of ketamine in a standard battery of validated \textit{in vitro} and \textit{in vivo} tests did not reveal any evidence of a genotoxic potential. Provided that the genotoxicity findings with the \textit{S}(+) enantiomer of ketamine can be extrapolated to the racemate, it can be concluded that ketamine is highly unlikely to possess any relevant genotoxic properties.\textsuperscript{47-48}

\textit{Carcinogenic potential}

No data on the carcinogenic potential of ketamine are available.
Immunotoxicity
As previously mentioned, the combination of cocaine with ketamine is currently popular among young substance misusers. Rofael et al.\textsuperscript{49-50} did a series of investigations in rats in order to elucidate the possible immunological consequences. From the experiments, it can be concluded that cocaine has immunotoxic properties, possibly by neuroendocrine mechanisms. These effects may at least in part be counteracted by ketamine. The immunotoxic effects of cocaine may especially be detrimental in vulnerable groups, like people with HIV or hepatitis-infections.

Neurotoxicity
One issue that has been investigated in animals, but has received little attention in the clinical literature and that may be of importance especially for the recreational user of ketamine, is the neurotoxicity as observed in rats.\textsuperscript{51-52}

When administered subcutaneously, ketamine (40 mg/kg) caused vacuolisation in posterior cingulate and retrosplenial cerebrocortical neurones in the rat. Lower doses ($\leq$20 mg/kg) did not cause such pathological changes. These highly localised neurotoxic effects have been shown for other NMDA-antagonists as well.\textsuperscript{51-54}

After intrathecal administration to rabbits, postmortem investigation of the spinal cord and nerve roots revealed histopathological lesions suggestive of toxic damage in 11 rabbits, from a group of 12 receiving $S$-$(+)$-ketamine. In 5 control animals, no histological changes were observed. Nevertheless, there was no significant difference in neurological status between the two groups after 7 days of intrathecal treatment.\textsuperscript{55}

Also in rhesus monkeys, neuronal cell death has been reported, but this was very much dependent on the stage of development of the animal and the duration of administration. Electron microscopy indicated that ketamine-induced neuronal cell death is most likely to be both apoptotic and necrotic in nature.\textsuperscript{56}

The mechanism for this neurotoxic response is proposed to be based on an NMDA-antagonist-mediated hypofunction of the NMDA-receptor, resulting in a combination of enhancement of excitatory neuronal pathways and inhibition of inhibitory neuronal pathways that lead to and from specific groups of neurones in the cingulate and retrosplenial cerebral cortices. Consistent with this hypothesis, it has been shown that several classes of drugs effectively inhibit the neurotoxic effects of the NMDA antagonists, including a) muscarinic receptor antagonists, b) GABA\textsubscript{A}-receptor agonists and modulators (such as benzodiazepines), c) $\sigma$-receptor antagonists, d) non-NMDA (kainate) glutamate receptor antagonists, e) $\alpha$-adrenergic receptor agonists, f) some typical antipsychotic agents (for instance haloperidol) and g) atypical antipsychotic agents (clozapine, olanzapine).\textsuperscript{10}

Two recent publications give additional insights into the possible mechanisms of the neurotoxicity of ketamine. Wang et al.\textsuperscript{57} show that upregulation of the NMDA receptor subunit NR1 following ketamine administration is, at least, partially responsible for the observed apoptosis. And Liao et al.\textsuperscript{58} describe the induction of the expression of HSP70 by ketamine and also that ketamine injures the neurons of rat hippocampus, and the higher the dose given, the more serious the injury is. Furthermore, ketamine induces a higher level
of HSP70 expression in adult rats than in infant rats. A more pronounced neurotoxic effect in adult rats is also mentioned as a result of the investigations of Beals et al. an effect ketamine shares with nitrous oxide, another NMDA-antagonist also used recreationally.

There may be several reasons why these findings in rats have not led to the abandonment of the clinical use of ketamine. First, ketamine is generally accepted as a safe anaesthetic without long-term adverse effects that is used on an occasional rather than frequent basis. Therefore, the preclinical data are considered of limited clinical relevance. Secondly, benzodiazepines are usually co-administered with ketamine to reduce the occurrence of emergence phenomena (for a description, see below Section 6; Subsection: Clinical experience). Benzodiazepines have been shown in rats to protect against ketamine-induced neurotoxicity.

In contrast, there may be reasons why the findings on the neurotoxicity of ketamine in the rat may be of concern to recreational users of ketamine. First, substance users will not take ketamine in combination with protective agents like benzodiazepines. Moreover, compounds increasing the neurotoxic potency of ketamine might be co-administered. Secondly, recreational use implies repeated exposure, whereas clinical use is mostly incidental. Long-term adverse effects in long-term users of ketamine have been reported, however are scarce. These included persisting impairment of attention and recall and a subtle visual anomaly. A review on internet reports from heavy users of ‘dissociatives’ (i.e. dextromethorphan, ketamine and PCP) is summarised. Effects mentioned after frequent use were “jolts” or “shocks” when moving the eyes, sharply impaired visual tracking, impaired recognition of metaphor, impaired language skills and memory problems. These adverse effects (that fade with time) are related by the author to malfunction of or damage to the cingulate and retrosplenial cortices. To date, there is insufficient evidence to ascertain such a relationship in humans.

In adolescent cynomolgus monkeys, functional magnetic resonance imaging has shown reduced neural activity in the ventral tegmental area, substantia nigra, posterior cingulate cortex, and visual cortex, following repeated exposure to ketamine. In addition, regions implicated in depression and schizophrenia (i.e. mesolimbic and mesocortical systems) were also found to be vulnerable to chronic ketamine use.

While negative effects of ketamine on the brain have been reported, it has also been shown that ketamine can induce synaptogenesis. Synaptogenesis is the formation of new synapses between neurons within the nervous system. This synaptic plasticity appears to be of particular relevance to clinical depression, which is associated with reduced synaptic connectivity in the prefrontal cortex.

Animal studies are beginning to elucidate downstream effects of ketamine that may underlie the beneficial effects in depressed patients. Ketamine antagonism of NMDA receptors is the first step in a cascade of events that includes rapid increases in presynaptic glutamate release, enhanced regional activity in excitatory networks, increases in Brain Derived Neurotrophic Factor (BDNF) and ultimately marked changes in connectivity and synaptic plasticity.

In rodents, microdialysis and electrophysiological studies indicate that low (i.e.
subanaesthetic) doses of ketamine and other NMDA receptor antagonists induce a surge in glutamate within the prefrontal cortex. Interestingly, at anaesthetic doses of ketamine, this increase is not observed.

These results suggest that the synaptogenesis and antidepressant effects of ketamine appear to be limited to subanaesthetic doses.

6. Adverse reactions in humans

Clinical experience
Ketamine is considered to be an anaesthetic with a good safety profile. Its major drawback, limiting its clinical use, is the occurrence of emergence reactions. Emergence phenomena in patients awakening from a ketamine narcosis have been described following early clinical experience, and include hallucinations, vivid dreams, floating sensations and delirium. These symptoms were found to be reduced by concurrent use of benzodiazepines, putting the patient in a low stimulus environment and by providing information on the possible emergence reactions preoperatively. These emergence phenomena appear to occur more frequently in adults (30-50%) than in children (5-15%).

No adverse outcomes were noted in nine healthy children treated in the emergency department who inadvertently received 5 to 100 times the intended dose of ketamine. Toxicity manifested as prolonged sedation in all nine and brief respiratory depression in four of the children. The margin of safety in ketamine overdose may be wide.

Respiratory depression
In two cases, a severe respiratory depression has been described after co-administration of ketamine. In one case, it appeared after premedication with secobarbital in a seven-year-old patient given a subanaesthetic dose of ketamine (approximately 3.3 mg/kg i.m.). In the other case, ethanol was involved with a fatal ending.

Sympathomimetic effects
Serious side effects like hypertension and lung edema have been reported. Such adverse effects appear to be rare and may be related to the combination of ketamine with other substances of abuse. This may be due to the sympathomimetic properties of ketamine. Inhibition of central catecholamine re-uptake and increased levels of circulating catecholamines are believed to cause the cardiovascular stimulant effects.

On the other hand, cardiodepressant effects have been noted in critically ill patients. This may be due to chronic catecholamine depletion preventing any sympathomimetic effects of ketamine and unmasking a negative inotropic effect, which is usually overshadowed by sympathetic stimulation.

Noppers et al. showed that after prolonged and/or repeated infusion of S(+)-ketamine liver injury may occur. In their study, six patients were scheduled to receive 2 continuous intravenous 100-hour S(+)-ketamine infusions (infusion rate 10-20mg/h) separated by 16 days. Three of them developed hepatotoxicity after the start of the second infusion.
Non-medical experience

Fatal intoxications

In the EMCCDA report, a short overview is given of 13 reported deaths in which recreational use of ketamine was involved.

The following conclusions can be drawn from the data as presented in the report:

- Only in 3 out of 13 cases of fatal intoxications was ketamine solely identified. It was administered by injection. Two reports describe mixed drug fatalities. In the other cases ketamine had either a minor role or there was a lack of data for a proper evaluation.

- In contrast to what is known from non-medical use where usually lower dosages are used, the ketamine blood concentrations in the described cases were in the anaesthetic range or above. Where clues about the quantity administered were available, such indicators suggested amounts of approximately 1 g administered i.v. or i.m. in the absence of other substances. Based on a body weight of 60 kg, such a dose is 4-17 times the recommended i.v. dose for anaesthesia or 1.3-2.5 times the recommended i.m. dose for anaesthesia. The i.v. data are in line with preclinical findings. In squirrel monkeys, death occurred when ketamine was administered (i.v.) at a dosage more than ten times the dose producing anaesthesia. The relatively small margin of safety for the acute toxicity applying the i.m. route cannot be explained without any further investigation. From a clinical point of view it is at least not expected.

In the subgroup of multiple substance users, the ketamine concentrations found are lower than those found in the few cases involving ketamine only. This indicates that drug interactions may play a significant role in contributing to these deaths. In this respect, substances with CNS respiratory depressant effects, like ethanol, opioids, barbiturates, and benzodiazepines, or substances with cardiostimulant effects, like cocaine and amphetamines, are indicated as drugs that may increase ketamine toxicity.

Benzodiazepines can have favourable effects in clinical practice as co-administration prevents the occurrence of emergence phenomena (as described above). But when used simultaneously in a recreational setting without proper monitoring of vital functions, they may enhance the respiratory and CNS-depressant effects of ketamine.

In an article by Gill and Stajic all ketamine-positive deaths (87) over a two-year period (1997 to 1999) examined at the New York City Office of Chief Medical Examiner were reviewed. There were 15 non-hospital deaths with 12 due to acute multidrug intoxications. In no instance was a fatal intoxication caused exclusively by ketamine. Opiates, amphetamines and cocaine were the most frequent co-intoxicants. Ethanol was found in only one death. In 2004, two other cases were published in which the use of ketamine was fatal. One case strongly points to ketamine as the sole factor responsible for the fatal ending. In the other case the presence of asthma as a co-morbidity factor cannot be excluded. The WHO Uppsala Monitoring Centre (UMC) reported that out of 1277 reports from adverse effects from world wide PMS-data, over a 2-year period, there were 25 cases of death, (2.0 %) and 1 case of sudden death (0.08%) (unpublished, communication to WHO, 2005)
In a letter to the editor, Schifano et al.\textsuperscript{76} present an overview of all of the ketamine-associated deaths in the UK over the period 1993-2006. Twenty three cases are presented, but in only four cases was ketamine identified postmortem as the sole substance present. Blood levels were not measured and a direct contribution of ketamine to the deaths could not be established.

There are two reports of apparent homicide resulting from assumed ketamine poisoning.\textsuperscript{77,78} Firstly, Tao et al.\textsuperscript{77} reported a case where chronic (over a period of a year) ketamine poisoning was listed as the cause of death. Ketamine was measured in the gastric contents (21μg/ml), blood (3.8μg/ml) and urine (1.2μg/ml). Cardiac muscle fibrosis and connective tissue degeneration in the small arteries were observed. These are pathological features of ketamine poisoning previous reported only in animal studies. Secondly, Licata et al.\textsuperscript{78} reported a case of death by ketamine overdose, with police ruling it a homicide. Ketamine was measured in blood (27.4μg/ml), urine (8.51μg/ml), bile (15.2μg/ml), brain (3.24μg/ml), liver (6.6μg/ml) and kidney (3.38μg/ml). Norketamine was also detected in all samples, but was not quantified.

Peyton et al.\textsuperscript{79} report a single fatality, with death ruled to be caused by an accidental i.v. ketamine intoxication. There was no mention of other drugs that may have contributed to the overdose.

**Non-fatal intoxications**

From the available data on non-fatal intoxications after the use of ketamine by recreational users, the following conclusions can be drawn.\textsuperscript{27,80,81}

The main effects are neurobehavioural:

- anxiety (especially in first-time users),
- agitation\textsuperscript{82}
- changes of perception (e.g. loss of notion of danger, visual disturbances),
- disorientation and impairment of motor function, such as ataxia\textsuperscript{82} and dystonic reaction\textsuperscript{83}

In such a condition, the user will have severely impaired self-control, which poses a risk for injury for him or her self or others (e.g. when participating in traffic).

Common side-effects reported by users were:

- slurred speech,
- dizziness,
- blurred vision,
- palpitations,
- chest pain,
- vomiting, and
- insomnia
The predominant symptom found on physical examination in users who went to an emergency department was tachycardia.\textsuperscript{27} Rhabdomyolysis was noted in several cases.\textsuperscript{27} Other physical side-effects appear to be rare.

Some other effects less often reported were:
- neuropathy of Guillain-Barré type and some physical effects such as general stiffness, increase of body temperature (38 °C),
- hepatic crises,
- myalgia and
- mydriasis.

Urinary tract symptoms are now a well-documented side effect of ketamine.\textsuperscript{84-86}, for an overview see \textsuperscript{87} These are characterised by changes in urinary frequency, urgency, dysuria, haematuria, and cystitis.\textsuperscript{88, 89} These urinary symptoms are more common in long-term users. The symptoms often gradually disappear after ketamine cessation. There is a large volume of reports and studies on urinary symptoms attributed to ketamine use coming from China, consistent with the level of reported ketamine abuse in that country. The earlier cases presented show cystitis and bladder dysfunction, an increase in urinary frequency, urgency, dysuria, urge incontinence and occasionally painful haematuria. Secondary renal damage can occur in severe cases. Chen \textit{et al.} \textsuperscript{90} described the first case of renal infarction after nasal insufflation use of ketamine.

Based on a survey by Winstock \textit{et al.} \textsuperscript{91} one can assume that there is underreporting of the problem. In their survey, 1285 participants reported ketamine use within the last year (33.8%). Of the ketamine users, 340 recent ketamine users (26.6%) reported experiencing urinary symptoms.

Ketamine-induced ulcerative cystitis is a recently identified phenomenon that can have a severe and potentially long-lasting impact on ketamine users.\textsuperscript{89, 92} Zhong \textit{et al.} \textsuperscript{93} describe a case of urinary bladder leiomyosarcoma in a patient with a 5-year history of ketamine abuse. It was suggested that abuse of ketamine played a role in the development of the tumour. However, further investigation is required to elucidate the link. Not only does ketamine impair the urinary tract but it also affects the liver and biliary tract in a negative way. Jaundice and biliary dilatation occur after recreational use of ketamine. Other problems caused by chronic ketamine administration include severe abdominal pain and corneal oedema.\textsuperscript{88, 94}

7. Dependence potential

A. Animal Studies

\textit{Self-administration}

Animal models of dependence are used to test the induction of substance-taking behaviour which might be similar to the recreational use of ketamine. To date there are no animal models that incorporate all the elements of dependence. The observation that animals readily self-administer drugs has led to the argument of face-validity, and psychologically
this is based on the reinforcing properties of a compound. This animal model has also a high predictive validity, although there are some limitations.\textsuperscript{95,96}

Early assessments of the reinforcing properties of ketamine reported that rhesus monkeys shown to self-administer intravenously metamfetamine or cocaine also self-administered ketamine (3.2-1600 microg/kg/inj) under limited access conditions at an intense schedule of reinforcement. An inverted U-shaped dose–response curve was observed. A variation of the fixed ratio so that the animals have to put more effort to obtain their reward, produced an orderly increase in the response rate with a factor of 3.\textsuperscript{97} Increasing the fixed ratio on PCP administration, however, eliminated the responding on PCP.\textsuperscript{98} This suggests a higher intrinsic power of reinforcement for ketamine, which might be more related to the depressant action of the substance than to the psychotomimetic action. In baboons, however, self-administration was obtained at a FR160 schedule both for ketamine and PCP, suggesting that the observed difference between ketamine and PCP might be specific to rhesus monkeys.\textsuperscript{99} No obvious behavioural changes occurred during exposure to doses of 10-32 microg/kg. A ten-fold higher dose of PCP was associated with sedation and ataxia. Food intake was unaffected by the lower doses from data in various species, it appears that substance intake tends to increase slightly with increases in unit dose in each species. However, the increase is of a lesser degree that generally occurs with the self-administration of CNS depressants such as pentobarbital and morphine.\textsuperscript{98}

\textit{Drug discrimination}

Animals are able to give an indication as to how a drug makes them “feel” with the drug-discrimination paradigm, in a behavioural method offering animals a choice and reinforcing them by pelleted food if their choice is correct depending on the treatment (drug or saline or another drug). This drug-discrimination approach is a powerful method to differentiate between subjective feelings (called the stimulus) of drugs, e.g opioids from psychomotor stimulants. It is well-established that the drug–response data in this respect can be handled as pharmacological data showing selectivity and sensitivity.

It is well-recognized that drug-discrimination paradigms can be used also for non-dependence-producing drugs. However, when carefully designed, such studies might be certainly of value in the assessment of common subjective states produced by drugs.\textsuperscript{100}

Drug-discrimination data from a series of stereoisomers of compounds generalising to PCP or ketamine indicate that compounds exhibiting reinforcing properties comparable to PCP share similar stimulus properties of this pharmacological class.\textsuperscript{101,102}

\textit{Tolerance and withdrawal}

A number of studies have demonstrated tolerance to the effects of ketamine.\textsuperscript{20} This type of acute tolerance is related to changes at the site of action rather than any increase in rate of metabolism, as it was shown to be induced after one injection, without changing the plasma concentration.

Continuous IV infusion of PCP and ketamine at maximum tolerated dosages in rats was used to demonstrate whether dependence could be induced by these compounds. The
animals were trained to lever press for their daily food rations under an FR30 schedule of reinforcement. Withdrawal of PCP as well as ketamine markedly reduced response rates, providing evidence of dependence. Readministering the compounds, the rates increased rapidly to control rates, providing evidence of reversal of withdrawal. Cross dependence from ketamine to PCP was described. Observable withdrawal signs have been reported for cynomolgus administered ketamine over 14 days.

B. Human Studies

Acute effects
Studies investigating the pathophysiology of schizophrenia, using ketamine as a model substance, and studies investigating the psychotropic effects of ketamine in their own right, have provided a good characterisation of the psychotomimetic action of ketamine. It appears that ketamine in subanaesthetic doses induces a state of mind that both neurophysiologically and behaviourally resembles that of a schizophrenic psychosis, but that may be experienced by the experimental or recreational substance user as an altered, ‘psychedelic’, state of mind that allows him to travel beyond the boundaries of ordinary existence.

Effects on cognitive functioning (neuropsychological assessment)
Hartvig et al. showed in a double-blind randomised crossover study with five healthy volunteers that short-term memory could be impaired dose-dependently by administration of 0.1 and 0.2 mg/kg (i.v.), as assessed by a word recall test. Ketamine binding in the brain correlated well with the regional distribution of NMDA-receptors.

Ketamine hydrochloride (0.1 or 0.5 mg/kg i.v. during 40 minutes) did not produce a significant effect on the mini-mental state examination (a brief bedside evaluation of cognition) in healthy subjects (n=18), however tests of vigilance, verbal fluency, and the Wisconsin Card sorting test showed a dose-dependent impairment. Delayed word recall was reduced, but immediate and post-distraction recall were spared.

The effects of ketamine (total dose 0.77 mg/kg i.v. during 1 hour) on attention, free recall of categorically related words and recognition memory of categorically related words has been previously assessed. All three cognitive functions showed significant decrements. Memory impairments were not accounted for by the changes in the subjects' attention and did not correlate to psychosis ratings. In further studies, Adler et al. found that ketamine induced thought disorder significantly correlated with decrements in working memory, but did not correlate with ketamine-induced impairments in semantic memory.

In summary, infrequent recreational ketamine use has not been associated with cognitive deficits. In contrast, compared to healthy controls without any history of drug abuse, frequent ketamine users exhibit severe impairments in both short- and long-term memory. Narendran et al. demonstrated that chronic ketamine users exhibit a regionally selective up-regulation of D1 receptor availability in the dorsolateral prefrontal cortex, an effect also seen after chronic dopamine depletion in animal studies. These data suggest that the repeated use of ketamine for recreational purposes affects prefrontal
dopaminergic transmission, a system critically involved in working memory and executive function.

There is insufficient evidence to rule out an association arising from a greater tendency of people with poor cognitive functioning to use ketamine, but the changes in cognition appear to be reversible following cessation of ketamine use.

**Effects on emotional status, behavioural patterns and personality (psychological instruments, rating scales)**

Ketamine profoundly affects perception of body, time, surroundings and reality. A study in ten psychiatrically healthy volunteers was performed were the subjects were administered an escalating dose of ketamine by i.v. infusion with plasma target concentration of 50, 100, 150 and 200 ng/ml. Each step was maintained for twenty minutes and the subjects were asked to rate various aspects of their consciousness on a visual rating scale (VAS). A good correlation between the plasma ketamine concentrations and the VAS ratings was obtained. The following VAS scores were increased by ketamine, compared with a saline control:

- Body: Body or body parts seemed to change their position or shape.
- Surroundings: Surroundings seemed to change size, depth or shape.
- Time: The passing of time was altered.
- Reality: There were feelings of unreality.
- Thoughts: There was difficulty controlling their thoughts.
- Colours: The intensity of colours changed.
- Sound: The intensity of sound changed.
- Voices: Unreal voices or sounds were heard.
- Meaning: Subjects had the idea that events, objects, or other people had particular meaning that was specific for them.
- High: They felt high.
- Drowsy: They felt drowsy.
- Anxious: They felt anxious.

The intensity of the effects was greatest for high, reality, time, surroundings, thought and sound. They were lowest for anxiety and meaning.

This study clearly shows there is a dose–effect relationship between the ketamine dose and the intensity of the ‘psychedelic’ effects. All but one participant spontaneously reported feelings of intoxication and perceptual distortion during the ketamine infusion; one of these persons also reported such symptoms during the placebo infusion. Three participants became moderately dysphoric during the ketamine infusion, but not during the placebo infusion.

Another study asked 18 healthy volunteers to rate on VAS of mood states after administration of 0.1 or 0.5 mg/kg ketamine hydrochloride i.v. for 40 minutes. A biphasic effect on anxiety was observed along with the low dose decreasing anxiety and the high dose increasing anxiety. VAS rating for high was increased dose-dependently.
The psychotomimetic effect of low doses (0.1 and 0.2 mg/kg i.v.) of ketamine in a double-blind randomised crossover study was assessed in five healthy volunteers. All subjects having peak plasma ketamine concentrations of 70 ng/ml or above or estimated peak regional brain ketamine concentrations of 500 ng/ml or above experienced psychotomimetic effects. These consisted of pronounced feelings of unreality, altered body image perception, sensations of impaired recognition of the limbs, detachment from the body, and modulation in hearing, characterised by preoccupation with unimportant sounds. The intensity of the effects showed a dose–response relation with the degree of regional brain binding of ketamine.

An investigation on the differential effects of S- and R-ketamine found that S-ketamine is responsible for the psychotomimetic effects, whereas R-ketamine induced a state of relaxation. Results of a mood rating scale for S-ketamine showed increased scores for ‘deactivation’, ‘introversion’, negative and dysphoric feelings and anxiety. All subjects reported distortion of body-image, loosening of ego-boundaries, and alterations of the sense of time and space, variously associated with emotional changes ranging from euphoria (30%), indifference (30%) or heightened anxiety (40%).

In an open uncontrolled study seven individuals working in health care explored the psychotropic effects of ketamine for its use as a possible adjunct in psychotherapy by intravenous, intramuscular and oral self-administration of various subanaesthetic doses. They recorded that their inner experiences were extremely intense and possessed a subjective quality, which made it difficult to put them in writing. To a certain extent, they varied from one subject to another and even for the same subject from one session to another. Nevertheless, all of the subjects had experienced most of the following phenomena:

- A sensation of light throughout the body;
- novel experiences concerning "body consistency" (e.g., being described as made up of dry wood, foam rubber, or plastic);
- grotesquely distorted shape or unreal size of body parts (e.g., extremely large or small);
- a sensation of floating or hovering in a weightless condition in space;
- radiantly colourful visions (e.g., images of moving from one room to another filled with moving, glowing geometrical patterns and figures);
- complete absence of time sense (i.e., an experience of virtual timelessness or eternity);
- periodic, sudden insight into the riddles of existence or of the self;
- occasionally, an experience of compelling emotional consanguinity, at times extending to sensations of melting together with someone or something in the environment; and
- an experience of leaving the body (i.e., out-of-body experience).

In nearly every instance, subjects retained the sense of a sober, witnessing "I" that could both observe and consider as well as be amazed, overjoyed or perhaps anxious, and that could, to a certain extent, later remember the unusual phenomena.
In the EMCDDA report\(^1\) a more extensive overview of the effects, including the near-dead effect, described by the participants is given.

*Effects on psychopathological status - psychiatric comorbidity (psychological and psychiatric assessment)*

Studies in healthy volunteers given ketamine have shown that ketamine produces a clinical syndrome with aspects that resemble key symptoms of schizophrenia.

Four key positive and three key negative symptoms of schizophrenia were assessed in healthy subjects after administration of 0.1 or 0.5 mg/kg ketamine hydrochloride i.v. during 40 minutes.\(^2\) The positive symptoms were conceptual disorganisation, hallucinatory behaviour, suspiciousness, and unusual thought content. The negative symptoms were blunted affect, emotional withdrawal, and motor retardation. Ketamine produced a dose-dependent increase in scores for both positive and negative symptoms.

Similarly, scores for key symptoms of schizophrenia (conceptual disorganisation and disorganised speech, unusual thought content, emotional withdrawal, psychomotor retardation and blunted affect) were increased by ketamine.\(^3\)

Adler and co-workers\(^{105,106}\) studied the effects of ketamine on thought disorder and compared these effects with thought disorder in patients with schizophrenia. They found similar scores for 19 of 20 items on the Scale for the Assessment of Thought, Language and Communication. Only the score for the item ‘perseveration’ was lower in schizophrenic patients. However, after Bonferroni correction this difference was no longer statistically significant.

A total dose of 0.56 mg/kg ketamine over 125 minutes was infused in healthy volunteers \((n=19)\) to obtain a pseudo steady state plasma ketamine concentration of 134 ng/ml. Reduced processing negativity and P300 amplitude, psychophysiological anomalies, commonly observed in schizophrenic patients, were recorded. However, no drug effect on mismatch negativity, another parameter commonly reduced in schizophrenic subjects, was found.\(^12\)

A negative correlation has been observed between raclopride’s binding potency in the ventral striatum and S-ketamine-induced euphoria- and mania-like symptoms, suggesting a role for elevated striatal dopamine levels in these positive symptoms.\(^21\)

*Effects on cognition, mood and mental functioning*

Short-term exposure to ketamine appears not induce any long-term adverse effects on cognition, mood or personality. Long-term heavy use of ketamine may be associated with persisting deficits in attention and recall. However, such a condition has been documented only once in the literature.

*Clinical studies in volunteers*

In a follow-up interview in a study of healthy volunteers given ketamine hydrochloride \((0.1\) or \(0.5\) mg/kg), no subject had lingering or recurrent physiological or psychological effects, such as nightmares, flashbacks, or perceptual alterations following a test day.\(^28\)
In another study, subjects in the study did not report any long-term side effects of any nature for up to three years following the ketamine sessions.\textsuperscript{31}

Corssen \textit{et al}.\textsuperscript{109} studied 30 volunteers from a prison population that were given either ketamine or thiopentone or served as control. Psychological assessment was performed before, at 1 week, 4 weeks and 6 months after substance administration. They could not establish a difference between the three groups.

\textit{Studies in patients}

Psychological changes were assessed in 221 patients following ketamine anaesthesia and compared with patients receiving other anaesthetics. Psychometric tests were applied repeatedly for more than 1 year.\textsuperscript{10} There were no significant differences between groups in terms of mental performance, hallucinations and behavioural factors.

Seven case reports of prolonged (several weeks to up to 1 year) psychic phenomena after single (or in one case dual) exposure were reviewed by Steen and Michenfelder.\textsuperscript{111} In one patient, serious effects persisted for 5 days, in three others there were only minor disturbances for 3 weeks, in two patients severe congenital brain abnormalities were present, and in one patient complaining of hallucinations and “passing out spells” and feelings of unreality and hesitation, it could not be excluded that these symptoms were linked to a single dose exposure to ketamine 1 year earlier, but this seems unlikely.

A large number of studies in depressed patients treated with ketamine have shown a positive effect on mood. For example, Berman \textit{et al}.\textsuperscript{112} observed a reduction in depressive symptoms on the Hamilton Depression Rating Scale following a subanaesthetic infusion of ketamine. However, the ketamine-induced mood improvement returned to baseline levels 1-2 weeks after the infusion. Ketamine infusion has also reduced depressive scores in the Montgomery-Åsberg Depression Rating Scale (MADRS). Patients receiving ketamine had greater improvement in the MADRS score than those receiving midazolam 24 hours after treatment.

Ketamine has also been shown to reduce suicidal ideation rapidly.\textsuperscript{112,113} In one study, scores on the Scale for Suicide Ideation (SSI) were significantly reduced within 40 minutes of ketamine infusion and remained below baseline for up to 4 hours post-infusion.\textsuperscript{114} In another study, suicidal ideation was found to be significantly reduced for several weeks after ketamine administration.\textsuperscript{115}

While the studies reported alterations in mood, many have reported minimal changes in cognition. For example, Murrough \textit{et al}.\textsuperscript{116} reported that low-dose ketamine was associated with minimal acute neurocognitive effects in patients with treatment-resistant depression 40 minutes after ketamine infusion. Any changes in cognition appear to be transient in nature, with no adverse neurocognitive effects observed 7 days post treatment.\textsuperscript{117}

These clinical studies suggest that ketamine may have dependence potential as a mood elevating drug. However, the mood elevation appears to be confined to patients with pre-existing depression as there has been no evidence of positive mood effects of ketamine in healthy volunteers. However, it is possible that people with depression may self-medicate using ketamine.
Studies in recreational users
Siegel\(^80\) stated that subjects who reported long-term use of ketamine sometimes complained of “flashbacks”, attentional dysfunction and decreased sociability. Positive effects on mood were mentioned as well, which reinforced and maintained substance use. However, standard psychometric tests did not reveal personality changes. The subjects described were mostly polydrug users, those snorting ketamine also using cocaine. Contrary to the PCP group, that was described in the same paper, a tendency to transient psychosis was not noted.

Amongst 20 recreational substance users studied by Dalgaro and Shewan\(^81\), lasting psychological effects were not reported. Eleven of them used ketamine less than 10 times, 8 used it between 10 and 20 times and only one user reported use of approximately 100 occasions. The last subject, who was an experienced poly substance user, reported "a total loss of reality" during a month-long ketamine binge, after which he stopped completely without major difficulties. Subsequently, he reported having very lucid dreams similar in nature to the ketamine-induced state. These dreams lessened in intensity and ceased completely within 7 to 10 days of the final ketamine episode.

A case has been described in which a subject had persisting impaired recall and attention and a subtle visual anomaly after cessation of long-term high-dose ketamine use\(^8\).

Morgan et al\(^118\) looked at the effect of ketamine in recreational users directly after use and 3 days later. On Day 0, ketamine users were impaired on both source memory and item recognition and scored more highly on schizophrenic and dissociative symptom scales compared to poly substance controls. On Day 3 ketamine users only displayed source memory impairments and these positively correlated with the level of schizophrenic-like symptoms on Day 0. No differences on Day 3 in schizophrenic-like or dissociative symptoms were observed. These findings suggest that repeated use of ketamine produces chronic impairments to episodic memory.

In order to find out if these deficits might be reversible upon reduction or cessation of ketamine use or are long-lasting, the group of Morgan et al\(^119\) performed an additional study in which they looked at ketamine users, already tested 3 years earlier. Meanwhile, this group of ketamine users had reduced their frequency of use of ketamine by an average of 88.3%. Performance of ketamine users on tasks tapping semantic memory had improved and this improvement was correlated with their reduction in ketamine use. On the tasks tapping, episodic memory and attentional functioning, ketamine users still showed deficits compared to poly substance controls. Higher levels of schizotypal symptoms and perceptual distortions were exhibited by the ketamine group, although dissociative symptoms were similar to controls. These findings indicate that semantic memory impairments associated with recreational use of ketamine are reversible upon marked reduction of use; however, impairments to episodic memory and possibly attentional functioning appear long-lasting. In addition, schizotypal symptoms and perceptual distortions may persist after cessation of ketamine use.

Only a very limited number of cases (less than 15) of ketamine dependence have been described over the past 20 years.\(^120-125\) Unfortunately, the use of terms is not well-defined
and therefore one cannot be sure that the cases presented here are really dealing with ketamine dependence. There are case reports of healthcare staff becoming dependent as they have easily access to this kind of product.\textsuperscript{126,127} Furthermore, multidrug use or polysubstance is one of the features these people have in common. More recently, Tung \textit{et al.} assessed 80 treatment seeking ketamine users from 3 treatment centres in Hong Kong. All used the drug intranasally and 56\% did so daily; 68\% met criteria for current ketamine dependence.\textsuperscript{128}

\textit{Tolerance}
Tolerance to ketamine develops quickly and can be high. In one case report, the subject relates the history of his ketamine use. During the first 2 years his consumption developed from an occasional 50 mg oral dose to 500 mg four to five times a day. Switching to intramuscular injection, he was injecting 300-750 mg five to six times a day within a month. The tolerance dissipated on stopping the habit, but redeveloped at the same rate (within a month) after restarting intramuscular injections.\textsuperscript{129}

\textit{Abstinence symptoms}
There is no definitive evidence that ketamine causes an abstinence syndrome in humans. The subject described in the case report by Kamaya and Krishna\textsuperscript{129} found stopping the habit extremely difficult, but never experienced a withdrawal syndrome.

Amongst 20 recreational ketamine users described by Dalgarno and Shewan\textsuperscript{81}, 11 reported to never having experienced mental after-effects and 8 said never to have experienced physical after-effects following a ketamine episode. Of those that did have mental after-effects, three reported a general feeling of well-being, two had a desire for physical contact, two felt mildly depressed and "flat", and two said they were "dopey" (feeling like being under the influence of cannabis). Of those that reported physical after-effects, three reported a general feeling of contentment and happiness, four said they felt mildly "hung over" or drained, three reported vomiting, one said he felt physically and positively changed and one felt nauseous.

Jansen\textsuperscript{130} states that an elevated mood after a ketamine binge is common, whereas a cocaine-like swing into depression is rare. He suggests that high levels of norketamine can take days to subside, thereby providing a "deflating cushion". However, for such a theory no evidence is provided. In rats, norketamine-induced anaesthesia and locomotor activity are of shorter duration than when these effects are induced by ketamine. Both ketamine and norketamine are rapidly cleared from blood and brain.\textsuperscript{131} The prolonged elevated mood is consistent with the antidepressant effects of ketamine.


Substance-seeking behaviour and dependence

A distinction may be drawn between experimental \cite{132} and dependent ketamine use. \cite{129,133} In dependent users, use of the substance continues despite increasing apparent effects on their work or on their health. Amongst the 20 users described by Dalgarno and Shewan \cite{81}, seven had used ketamine once or twice and only three had used 15 times or more. One user in this group reported that he had believed the experience was "never going to end" and another experienced extreme dissociation. These two never repeated their first-time use. It appears that the dissociative experience discourages some experimental users. Another reason for limited use mentioned in this study was the scarcity of the substance. On the other side of the spectrum, one user in this study group said he believed he had been dependent on the use of ketamine during his heaviest period of ketamine use.

According to Jansen \cite{130} tolerance to the effects of ketamine develops, and with higher doses the ability to remember the experience is sharply reduced. Where many stop at this point, others carry on with compulsive binges. These result in cocaine-like stimulation, opioid-like calming, cannabis-like imagery (which also disappears), alcohol-like intoxication, and relief from anxiety, depression, and mental craving. \cite{130} Jansen states that repeated users of ketamine may rapidly become dependent. This dependence-promoting nature of ketamine may be prominent for those that carry on with compulsive binges. No sound data on the prevalence of long-term use are available.

8. Abuse potential

A. Animal Studies

In animal models, intracranial self-stimulation (ICSS) can be used to assess and compare the abuse liability of drugs, particularly their ability to enhance activity in ‘brain reward’ centres. Acute administration of most drugs of abuse (i.e. cocaine, amphetamine, and heroin) facilitates ICSS in animal models. Withdrawal from chronic administration of these compounds results in reduced ICSS, consistent with the negative affective state associated with drug withdrawal syndromes in humans.

Hillhouse et al. \cite{134} used ICSS in rats to examine the abuse-related effects of ketamine in comparison to MK-801 (a higher-affinity NMDA receptor antagonist) and cocaine. Following acute administration of ketamine (3.2-10mg/kg), dose and time dependent decreases in ICSS were observed and ketamine failed to produce an abuse-related facilitation of ICSS at any dose. MK-801 was observed to have pronounced ICSS facilitation at an intermediate dose (0.18mg/kg), and cocaine was also found to cause facilitation of ICSS. Ketamine cessation also failed to produce the decreases in ICSS associated with withdrawal of a number of abused drugs. The results from this study suggest that ketamine does not have significant abuse liability arising from enhancement of activity in brain reward centres.

In contrast, ketamine has been shown to significantly increase conditioned place preference (CPP) scores in rats. \cite{135-137} The CPP test is one measure of the reinforcing effects of a drug. Animal self-administration studies have also shown that ketamine has reinforcing effects. \cite{137-138}
B. Human Studies

Jansen\textsuperscript{130} describes several conditions that may drive the use of ketamine. Amongst these is a characteristic of the ketamine experience, which may be described as escape from reality. Few substances offer such a strong experience of entering a different reality, which is not only experienced as different, but also as no less real than reality without the substance. This possibility for escape and discovery may appeal to some individuals, especially those that have discontent with their ordinary existence and are looking for sense and meaning in their life. The ketamine experience offers in this way a psychological reward, which contributes to the development of dependence.

In those involved in taking substances as much and as many as possible, the sensation-seeking factor will certainly be important.\textsuperscript{139} Ketamine, advertised as The Ultimate Psychedelic Journey will appeal to substance users looking for extremes.\textsuperscript{140}

9. Therapeutic applications and extent of therapeutic use and epidemiology of medical use

The clinical uses of ketamine as an anaesthetic and analgesic have been well characterised in reviews.\textsuperscript{10,141,142} Unlike inhalation anaesthetics, ketamine provides analgesia, preserves airway reflexes, offers haemodynamic stability, and maintains respiratory drive. This provides ketamine with a good safety profile and it is therefore a favoured choice for many situations where respiratory support is not available or is unreliable.

The particular importance of ketamine in developing countries has been described in editorials, correspondence, reviews and reports.\textsuperscript{143-145} Low- and middle-income countries rely heavily on ketamine as an anaesthetic, and their dependence is growing with the increasing need for surgical services. In a study by Vo \textit{et al.}\textsuperscript{146} examining the anaesthesia capacity of 22 low and middle income countries, it was found that uninterrupted electricity supply was available in only 59\% of facilities; only 53\% had functioning anaesthesia machines; access to uninterrupted oxygen supply was available in only 45\% of facilities; and 35\% reported no access to oxygen. Almost half of the facilities lacked basic airway-management equipment (e.g. face masks, laryngoscopes, endotracheal tubes). Nurses and clinical assistants made up the majority of the anaesthesia providers. Ketamine is important in these regions as it can be administered i.v. or i.m. and does not require the availability of oxygen, electricity, and anaesthetic equipment or trained anaesthesia providers. As a consequence, in many situations in developing countries, ketamine is the most widely used and safest anaesthetic drug. This is also reflected in the availability of ketamine, where ketamine is seen as ‘always available’ according to 92\% of anaesthetists surveyed in Uganda.\textsuperscript{144}

In addition to these uses, there are two new indications for ketamine that have been investigated and for which results have been published:

(i) Ketamine has been trialled an antidepressant, particularly in patients who are resistant to two or more of the other typical antidepressants (i.e. considered to have treatment-resistant depression) or have bipolar depression.\textsuperscript{147-150} The treatment of these conditions with ketamine is based on evidence suggesting that major depression is associated with
abnormalities in glutamatergic transmission. For example, Murrough et al. conducted a study with 73 patients with treatment-resistant major depressive disorder experiencing. Patients were randomised to receive a single 40 min infusion of ketamine (0.5mg kg\(^{-1}\)) or midazolam (0.045 mg kg\(^{-1}\)). (Midazolam was used as an active control so that participants would not be aware whether or not they had received the active treatment). A higher proportion of patients who received ketamine had a greater than 50% reduction in their baseline symptoms, compared to those who received midazolam (64% vs 28%, respectively).

As a result of the large volume of research in the last few years on the role ketamine could play in the treatment of depressive disorders, it has the potential to be the prototype for a new generation of antidepressants, with a mechanism that appears to be completely independent of current medications. The effect is characterised by a rapid onset of action (within a few hours) and with a duration of 1-2 weeks following a single administration. However, ketamine itself is unlikely to be introduced for widespread clinical use due to the adverse effects experienced during infusion and for a few hours after (i.e. euphoria, dysphoria, anxiety, nausea, and/or dizziness) as well as concerns around abuse potential. There is also insufficient evidence regarding the effects of repeated administration. However, ketamine may be utilised in emergency situations where the risk of suicide is significant.

(ii) Ketamine has been used as an anti-seizure agent, particularly in the treatment of refractory status epilepticus. The basis for this treatment is the role glutamate overflow plays during epileptic seizures and seizure-related brain damage. There is a high treatment potential for ketamine in this condition, as status epilepticus is life threatening. For this purpose, ketamine is likely to be administered on a single occasion rather than repeatedly. However, to date there are only case reports on the effect of ketamine on seizure activity and no randomised control trials.

10. **Listing on the WHO Model List of Essential Medicines**

11. **Marketing authorizations (as a medicinal product)**
   Ketamine is authorized as a medicine at least in 60 countries including the United States of America and the European Union.

12. **Industrial use**
   Not applicable.

13. **Non-medical use, abuse and dependence**
   There are very few studies that have investigated the demographic, social and psychological factors associated with ketamine use in young people. Previous research has suggested that recreational use of ketamine is highest in particular groups, including people attending rave parties, a subset of gay men also taking more sexual risks, but also homeless and runaway youth.
A study examining these factors and relationships was conducted in Hong Kong, a region with a high prevalence of ketamine abuse.\textsuperscript{161} Ketamine and ecstasy first became prevalent in Hong Kong around 2000, and ketamine quickly became the dominant drug used by young people. The study recruited drug users from outreach youth agencies, and involved 6 interviews at 6 month intervals. The sample size of the survey at time point 1 (T1) was 754, and 600, 434, 376, 347, and 288 at time points T2-T6, respectively.

The demographics of the sample were as follows:

- 65.8% of the subjects were male
- 72.7% were below the age of 21 (mean 20.6 yrs).
- 88.8% were unmarried
- 63.2% had received only secondary form 3 or lower level of education, and 31.1% were students
- More than 60% did not have a religion
- 34.7% of the subjects lived in private housing, while the others mostly lived in public housing or rooms/quarters
- At the first interview session, 51.7% of the subjects had used drugs in the last 30 days; of these, 80% had used ketamine

Sociodemographic variables were found not to be good predictors of drug use, but psychosocial variables (i.e. “permissiveness to the use of drugs”, “found goal in life”, “satisfied with life”, “self-esteem”, and “depression.”) were significantly related to drug use in the last 30 days. It was also found that non-students, or students who were often absent from school, were more likely to use drugs than students who regularly attended school. Subjects with higher life satisfaction were found to be less likely to use drugs. Depression and the experience of a traumatic event within the last 6 months were also found to be strong predictors of drug use. These results are consistent with previous research on use of a wide range of illicit drugs other than ketamine. However, the strength of the relationship with depression and experience of a traumatic event are also consistent with evidence of ketamine’s therapeutic potential in treatment of both depression and PTSD.

Ketamine is not routinely included in many national population level surveys on recreational drug use. However, data is available on ketamine usage in China, Hong Kong, the United Kingdom, the United States, Australia, New Zealand, Argentina, and Brazil.

More than 7.6% of registered drug users in China were using ketamine in 2012.\textsuperscript{160-161} In the same year, the drug abuse registry for Hong Kong found that ketamine was the most popular psychotropic substance used, with 29% of drug users reporting its use. Sixty one per cent were less than 21 years old.\textsuperscript{164}

In 2012, the United States reported the annual prevalence rate for ketamine in 12\textsuperscript{th} graders (aged 17–18 years) as 1.5%.\textsuperscript{165}

In the United Kingdom, there has been a decrease in the prevalence of ketamine use in England and Wales among both the adult population as a whole (aged 16-59; 0.6% to
Ketamine use in Australia has remained relatively steady since 2004, with 0.3% of people reporting recent (within the last 12 months) use of ketamine in the most recent (2013) survey.\textsuperscript{167}

The most recent data from New Zealand come from the 2007/2008 New Zealand Alcohol and Drug Use Survey.\textsuperscript{168} Lifetime prevalence of ketamine use in adults was 1.2%.

Ketamine is a drug of abuse in South America, but the reported rates are low. The latest data available for Brazil are from a household survey conducted in 2005, and this revealed a lifetime prevalence of ketamine use of 0.2%.\textsuperscript{163} In Argentina, lifetime prevalence of ketamine use was 0.3% in a national household survey conducted in 2010.\textsuperscript{163}

In addition to data from population surveys, there is also information on ketamine use from wastewater analysis.

In a 2014 study, the levels of 10 illicit drugs were monitored in wastewater in four cities/provinces in China (Beijing, Guangzhou, Shenzhen, and Shanghai; covering ∼11.4 million inhabitants). The use of ketamine among Beijing inhabitants was low (ketamine or norketamine was only detected in one of the sixteen Beijing influent samples). The median influent load of norketamine in Guangzhou and Shenzhen sewage treatment plants amounted to 5.6 and 16.6 mg per 1000 inhabitants per day, higher than both Beijing and Shanghai.\textsuperscript{169}

The level of ketamine was also determined from wastewater in 17 cities in Italy.\textsuperscript{170} Ketamine was detected in wastewater in all except one of the cities investigated. The level of ketamine progressively increased from 2010 to 2013. Ketamine use was also found to be higher in large cities, compared to small and medium cities.

It should be noted that wastewater studies are unable to differentiate medical from non-medical use of ketamine and in the published reports to date there has been no attempt to independently quantify the medical use of ketamine to allow accurate estimation of non-medical use.

14. **Nature and magnitude of public health problems related to misuse, abuse and dependence**

Copeland and Dillon\textsuperscript{171} give an overview of the health and psycho-social consequences of ketamine use. 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. There are a number of potential ketamine effects that may be seen as adverse or harmful, with growing evidence of the symptoms of ketamine dependence among recreational ketamine users. The use of ketamine with other neurotoxic drugs, such as alcohol, should be avoided. Increased rates of high risk sexual and injecting behaviours in association with ketamine use, however,
have been reported by gay men and marginalised youth in the US. The conclusion of the authors is that ketamine does not appear to currently pose a significant public health risk.

A number of countries have brought ketamine under national control, but clear evidence on the extent of public health problems has not been published in recent years. However, there is increasing evidence for the appearance adverse physical effects of the drug, particularly urinary tract problems after the use of ketamine over a prolonged period and or in high doses. Recently also biliary tract problems have been described (see section 6). In addition to the increasing number of publications on physical problems caused by ketamine there is recent evidence of ketamine dependence in recreational users.\(^{128}\)

15. **Licit production, consumption and international trade**

To be completed following the 37th ECDD meeting (16\(^{\text{th}}\)-20\(^{\text{th}}\) November 2015).

16. **Illicit manufacture and traffic and related information**

In the past due to the difficult chemical synthesis of ketamine only diversion from legal sources had been observed. For instance in Mexico a veterinary pharmaceutical laboratory was dismantled that had manufactured large quantities of ketamine and sold them over the Internet to the United States. Or in France where an armed robbery took place in early April 2007 at the site of a company trading in pharmaceutical raw materials. The robbers disappeared with an amount of 1.3 kilograms of ketamine raw material. By using an intermediate company an unknown party attempted to divert 1000 kg of ketamine from India on its way to a company in Kenya.

The 2014 INCB report\(^{172}\) mentions that almost 60% of all ketamine seizures worldwide in 2008-2011 took place in China. Ketamine is illicitly manufactured in China, although India is also an important source of ketamine seized in the region. It is difficult to give an indication of the amount of the clandestine ketamine labs that are dismantled because often more than one illicit drug is manufactured. And it is not always is specified which lab makes what product.

Hydroxylamine hydrochloride, a precursor used in the manufacture of ketamine has been placed under national control in China in 2009.

In the period 2003-2012, a number of clandestine ketamine laboratories were seized in Indonesia and the Philippines.

With most of the illicit ketamine originating from the Asian region it is also one of the most abused drugs in that area. But ketamine also finds its way to the rest of the world due to smuggling and trafficking. In letters to the WHO, the International Narcotics Control Board (INCB) gave a number of examples of misuse and trafficking.

17. **Current international controls and their impact**

Ketamine is currently not under international control by the international drug control conventions. It may be argued that over the years a situation of de facto international control has emerged due to both CND resolutions and the INCB collecting data from
Member States. There are several CND resolutions on ketamine and INCB reports have included data on ketamine for several years.

18. **Current and past national controls**
To be completed following the 37th ECDD meeting (16th-20th November 2015).

19. **Other medical and scientific matters relevant for a recommendation on the scheduling of the substance**
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