THE EXPERT ADVISORY COMMITTEE ON DRUGS (EACD) ADVICE TO THE MINISTER ON:

2(2-CHLOROPHENYL)–2-(METHYLAMINO)–CYCLOHEXANONE [KETAMINE]

April 2004

CONTENTS

ADVICE TO THE ASSOCIATE MINISTER OF HEALTH ON KETAMINE

Executive Summary

1. This paper presents evidence on the risk of harm associated with ketamine - a short-acting, hallucinogenic, 'dissociative' anaesthetic. The information presented addresses the criteria which the Expert Advisory Committee on Drugs [EACD] must take account of when considering the appropriate classification of a substance, under section 4B of the Misuse of Drugs Act 1975. Ketamine is currently not a controlled drug under the Misuse of Drugs Act, although it is a prescription medicine under Schedule 1 of the Medicines Regulations 1984. This paper offers arguments in support of classifying ketamine under Part 1 of the Second Schedule of the Misuse of Drugs Act to better reflect the risk of harm associated with the drug. Factors supporting this position include:

   - New Zealand and overseas drug surveys indicate a rise in ketamine use
   - In particular, recreational use of ketamine as a 'party drug' by young people appears to have increased
   - The Customs Service has made two major seizures of ketamine at the border
   - A number of potential ketamine effects may be seen as adverse or harmful (eg. ketamine can induce schizophrenic-like symptoms in healthy adults
   - There is growing evidence of the physical and psychological symptoms of ketamine dependence among recreational ketamine users
   - Consideration is being given internationally to bringing ketamine under control.

2. The paper does not recommend a specific presumption for supply of ketamine.

Recommendations

After considering all of the information put to the Committee and the classification criteria in the Misuse of Drugs Act 1975, the EACD makes the following recommendations to the Minister of Health:

(a) Ketamine should be classified in Part 1 of the Second Schedule of the Misuse of Drugs Act 1975 (ie, B1).

(b) This paper should be made publicly available (eg, posted on the National Drug Policy website www.ndp.govt.nz).

TERMINOLOGY

3. Street names for ketamine include ‘K’, ‘Special K’ and ‘Vitamin K’.

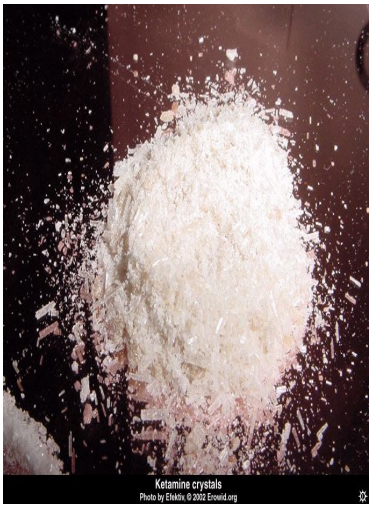
SUBSTANCE IDENTIFICATION

4. Ketamine - 2(2-chlorophenyl)–2-(methylamino)–cyclohexanone – is an arylcycloalkylamine. Functionally, ketamine is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist which interferes with the action of excitatory amino acids including glutamate and aspartate (Anis et al., 1983). It occurs in racemic form and also as an S-enantiomer. Its chemical structure is shown in Figure 1.

FIGURE 1: Chemical structure of ketamine

5. Ketamine is manufactured by the chemical industry for use in pharmaceutical products using the precursors cyclopentyl bromide, *o*-chlorobenzontrile and methylamine. Due to the complicated multi-step synthesis, and the difficulty of obtaining the necessary precursors and numerous solvents and reagents, ketamine sold illicitly for recreational use appears to be mostly obtained by diversion of legitimate supplies of either the bulk drug, or of its pharmaceutical preparations (EMCDDA, 2000).

6. At a street level, ketamine can be sold for recreational use in the form of a vial, gel capsules, or a white powder (ketamine hydrochloride) [see pictures below]. Amounts of ketamine can also be found in pill form. New Zealand testing of all ‘Ecstasy’ seizures between July 1999 and June 2000 found ketamine in a number of the samples (ESR 2000).



Short history of ketamine use

7. Ketamine hydrochloride is marketed as a short-acting, general anaesthetic for human and veterinary use (Parke-Davis 1999-2000). Reports have indicated that ketamine is being used in social rather than medical and scientific settings in many parts of the world (Curran and Morgan 2000; Weiner et al. 2000; New York State Office of Alcoholism & Substance Abuse Services 1997; White and Ryan 1996; Skovmand 1996; Brown 1995; Dotson et al. 1995). The most recent Drug Abuse Warning Network report on trends in drug-related emergency department visits reports a dramatic increase in the number of drug mentions for ketamine from 19 in 1994 to 679 in 2001 (DAWN 2003).

8. Ketamine hydrochloride was first synthesized in 1962. Early clinical studies on ketamine with human volunteers found it to be more effective and shorter acting than PCP, with fewer emergence symptoms and less toxicity (Domino et al. 1965). The drug was first manufactured in the United States in the 1960s as Ketalar. It was described as a 'dissociative anaesthetic' with analgesic and amnesic actions. Use of ketamine as a surgical anaesthetic escalated when it gained popularity on the battlefields of Vietnam (Tori 1996). It was promoted as a dissociative anaesthetic because of its ability to induce a lack of responsive awareness, not only to pain but also to the general environment. It is believed that the drug selectively interrupts association pathways of the brain before producing somesthetic (the consciousness of having a body) sensory blockade (Sparks et al. 1973; Weingarten 1972; Winters 1975).

SIMILARITY TO KNOWN SUBSTANCES

9. Ketamine is structurally related to phencyclidine (PCP) [colloquially known as ‘angel dust’] and cyclohexamine.

CURRENT CLASSIFICATION

10. Ketamine is currently not classified under the Misuse of Drugs Act 1975. It is, however, listed as prescription medicine under Schedule 1 of the Medicines Act 1981.

RATIONALE FOR RECLASSIFICATION

Likelihood or evidence of abuse

New Zealand prevalence data

12. New Zealand drug surveys indicate an increase in ketamine use. Although when compared with other drugs of misuse, overall prevalence rates remain low, the latest national survey undertaken by the former Alcohol and Public Health Research Unit attached to the University of Auckland (Wilkins et al. 2002) found that the number of respondents who had tried using ketamine had more than doubled, and there appears to be a small ongoing user population [see Table 1].

TABLE 1: Use of ketamine, 1998 and 2001

	Ever used		Used Last Year		Current User	
	1998	2001	1998	2001	1998	2001
Ketamine	0.2%	0.7%	0.1%	0.5%	0.0%	0.2%

Source: Wilkins et al. 2002

New Zealand ketamine-related mortality and morbidity

13. Hospital data is unable to provide definitive information about the health-related impact of ketamine. There are some problems associated with the data, including the fact that the data does not differentiate between ketamine-related admissions and those relating to the use of other depressant drugs (combining solvents, tranquillisers and hypno-sedatives). Nevertheless, there were 9271 publicly funded depressant-related hospitalisations between 1996 and 1998, the largest proportion of which were for poisoning by tranquillisers (NZHIS 2001). There was a rise in the total numbers of hospitalisations each year for poisoning by tranquillisers (667 in 1996, 730 in 1997, and 778 in 1998).

14. Although specific figures for ketamine-related deaths are not available, the New Zealand Health Information Service reports that there were 148 deaths between 1990 and 1996 where depressant-related conditions were the underlying cause of death (NZHIS 2001). No ketamine-related deaths were uncovered in a recent study of coronial findings from 1998-2001 (Morgan

2003), but there are rare case reports of unintentional deaths from ketamine overdoses having occurred in New Zealand (Smith 2003). Information about how to deal with ketamine overdose events is also occasionally requested from the National Poisons Centre, with two such requests for advice in the year-to-date (Temple 2003).

New Zealand arrest and interdiction data

15. New Zealand law enforcement data suggests that ketamine may be increasingly available as a drug of misuse, although (because it is not currently a controlled drug) it does not explicitly appear in Police offence records. For example, the New Zealand Customs Service made two significant seizures of ketamine in 2001 (in one case, of four litres of the drug) which appeared destined for use in the dance party scene (Ministry of Health et al. 2001). The Customs Service indicates there have been sporadic seizures of ketamine over the last two years.

Specific effects of ketamine

16. Ketamine has a plasma half life of 2 to 4 hours. It is highly lipid soluble and has a distribution half-life of approximately 7 to 11 minutes. Ketamine is metabolised in the liver within the cytochrome P_{450} system with formation of water soluble conjugates. Some of the metabolites, namely norketamine, have some potency but do not penetrate the central nervous system sufficiently to cause hypnosis. Ketamine is typically administered in doses of 1-2mg/kg intravenously over one to two minutes or 4-5mg/kg intramuscularly. Studies of the pharmacokinetics of ketamine report similar plasma concentration profiles for the same dose administered orally, sublingually, and in suppository preparations with nasal preparations having the highest relative concentration of the non-injecting routes of administration (Yanagihara et al. 2003).

17. As ketamine has analgesic effects it was suggested that it may be partially reversed by naloxone. This has been refuted by Mikkelsen and colleagues (1999) who reported that opioid receptor blockade does not inhibit ketamine-induced analgesic or sedative effects. The synthetic alpha$_{2}$-adrenergic antagonist, atipamezole hydrochloride, is used in veterinarian medicine to reverse the effects of medetomidine and ketamine anaesthetics in a range of animals (eg., Cruz, Loste and Burzaco 1998). There are no reports of its use in humans. At this stage, therefore, there is no agent available to reverse the effects of ketamine in humans.

Pharmacological effects

18. Ketamine has systemic effects on a number of organ systems. The predominant effect of ketamine on the cardiovascular system is thought to be due to decreased catecholamine reuptake, leading to increases in arterial blood pressure and cardiac output, 2-4 minutes after intravenous injection and 10-20 minutes after intramuscular injection. Ketamine may cause an increase in cerebral bloodflow, oxygen consumption and intracranial pressure (Mayberg et al. 1995). Animal studies, however, have demonstrated

a marked neuroprotective effect, mediated by anatagonism of the NMDA channels on central neurones, and may have promise in the future management of cerebro-vascular accidents (Pfenninger and Himmelseher 1997). Upper airway reflexes are usually maintained when ketamine is administered in addition to bronchodilation. Apnoea has been seen with ketamine use but is generally associated with rapid and/or large intravenous doses (Cromhout, 2003). Additional effects are seen in the gastrointestinal tract (increased salivation), the immune system (a significant reduction in leucocyte activation during sepsis) and the eyes (initial rise in intra-ocular pressure, eye movements throughout surgery and preservation of the corneal reflex).

Psychosis

19. The role of the NMDA neurotransmitter system in relation to psychosis is not completely understood. However, pharmacological, post-mortem and clinical studies have implicated the NMDA system in the pathophysiology of schizophrenia (Olney & Farber, 1995). The psychotic states induced by NMDA antagonists such as ketamine have been described as being similar to schizophrenia (Adler et al., 1999, Krystal et al., 1994; Malhotra et al., 1997). The hallucinogenic effect of ketamine arises, at least in part, from its capacity to disrupt thalamo-cortical gating of external and internal information to the cortex. Deficient gating of sensory and cognitive information is thought to result in an overloading inundation of information and subsequent cognitive fragmentation and psychosis (Vollenweider and Geyer 2001). Animal studies have shown that treatment with ketamine leads to an increase in D2 receptor binding in the hippocampus and a decrease in glutamate receptor binding in the frontal cortex with no change in D1 receptor binding. The density of dopamine receptors was increased in the striatum and 5-HT transporters were increased in the striatum, hippocampus and the frontal cortex (Becker et al. 2003).

20. Laboratory studies of subanaesthetic doses of ketamine in humans report that it produces behaviours similar to the positive (e.g. hallucinations and thought disorder) and negative (e.g. detachment, amotivation and blunted affect) symptoms of schizophrenia, elicits alterations in perception, impairs performance on tests of vigilance, verbal fluency and the Wisconsin Card Sorting Test, evoked symptoms similar to dissociative states and preferentially disrupted measures of frontal lobe function such as delayed word recall, sparing immediate recall and postdistraction recall (Krystal et al. 1994). Ketamine also exacerbates the core psychotic symptoms in patients with schizophrenia (Lahti et al. 1995) and is not blocked by other antipsychotic drugs such as haloperidol (Krystal et al. 1999).

21. As a result ketamine is a useful model of schizophrenia and is being used to increase our understanding of the illness and to develop new treatments (Carpenter 1999; Adler et al. 1999; Tsai et al. 1998).

Depression

22. A growing body of preclinical research implicates the NMDA class of glutamate receptors in the pathophysiology of major depression, and the mechanism of action of antidepressant treatments (Skolnick et al. 1996). A small study of those with diagnosed major depression reported robust decreases in depressive symptoms, emerging progressively over three days, following low-dose ketamine infusion (Berman et al. 2000).

Key Psychoactive Effects of ketamine

23. In one of the earliest studies of the recreational use of ketamine, Siegel (1978) reported that the drug was viewed by most of the users in his study as a safe, potent hallucinogen with a short duration of action and an equal balance between positive and negative effects. Self-administration was titrated to achieve the desired amount of dissociative sensations, hallucinations and transcendental experiences. Respondents reported ataxia (inability to co-ordinate muscular movement), slurring of speech, dizziness, mental confusion, blurred vision, anxiety, hyperexcitability and insomnia, amongst other effects.

24. In a later study that examined the subjective effects of ketamine, Hansen and co-researchers (1988) gave seven male volunteers between five and 12 doses of ketamine intermittently over a period of 18 months. They used approximately 10-25% of the anaesthetic dose, believing this to reflect the dose level that occurs during the emergence period. The authors describe a series of phenomena experienced by most of the participants:

- a sensation of light throughout the body;
- novel experiences concerning ‘body consistency’ (e.g. feeling as though they are made from wood or plastic);
- grotesquely distorted shape or size of body parts;
- sensation of being weightless and floating or hovering;
- colourful visions (including geometrical patterns and figures);
- absence of sense of time;
- sudden insights into the nature of the existence or the self;
- strong feelings of association with others in the environment; and
- out-of-body experiences.

25. Subsequent studies of the psychedelic effects of ketamine in healthy volunteers has reported that these effects are dose-related (Bowdle et al. 1998).

26. Anecdotal evidence indicates that many users of other club drugs have hesitated to use it, due either to bad personal experiences or 'horror stories' relayed to them by others. Some users may describe visits to the 'K-hole', a place referring to 'where users are' when under the influence of ketamine (Tori 1996). The K-hole experience appears to vary with the individual, but Stafford (1992) identified six main categories of mental effects produced by ketamine:

- the perception of contact with aliens;
- the perception of entry into information networks;
- access into alternative realities;
- personal and creative problem-solving;
- out-of-body, near-death states; and
- tantra-like enhancement of sexual activity.

27. Ketamine can sometimes reproduce the features of a 'near-death experience' (NDE), including buzzing/ringing/whistling sounds at the beginning, travel through a dark tunnel into light at a high speed, the conviction that one is dead, apparent telepathic communion with God, intense visions and out-of-body experiences (Jansen 20001). A NDE induced by ketamine does not mean that the person is physically near death.

Teratogenic effects

28. Ketamine crosses the placenta easily and concentrations in the foetus are approximately equal to those of the mother (Cromhout 2003). There is accumulating evidence from *in vitro* and *in vivo* experiments that suggests that tonic stimulation of NMDA receptors is vital for the survival of developing nerve cells. The NMDA receptor can be pharmacologically blocked by ketamine among other drugs. While there are no human studies or reports of toxic effects of ketamine in the foetus or neonate, animal studies suggest that the duration of ketamine exposure in seven day old rat pups increases neuronal degeneration of the developing rat brain (Hayashi et al. 2002).

Overall safety profile

29. Ketamine has a wide margin of safety (Green et al. 1999). The predominant adverse reaction is emergence phenomena post anaesthetic where the risk factors are age, female gender, noisy environment during recovery, prior personality disorders and excessive dreaming (Obiaya et al. 1981). The experience of emergence phenomena is not associated with dose (Cromhout 2003). Other side effects include a transient rash predominantly on the face and neck, and nausea and vomiting (Cromhout 2003).

30. In summary, ketamine is a non-competitive NMDA receptor antagonist with a range of hallucinatory and other psychoactive effects. It is best described as a dissociative anaesthetic with analgesic and amnestic properties. Ketamine can induce schizophrenic-like symptoms in healthy adults and schizophrenic patients and may have a role as an anti-depressant. It has a wide margin of safety.

The risks that ketamine poses to public health

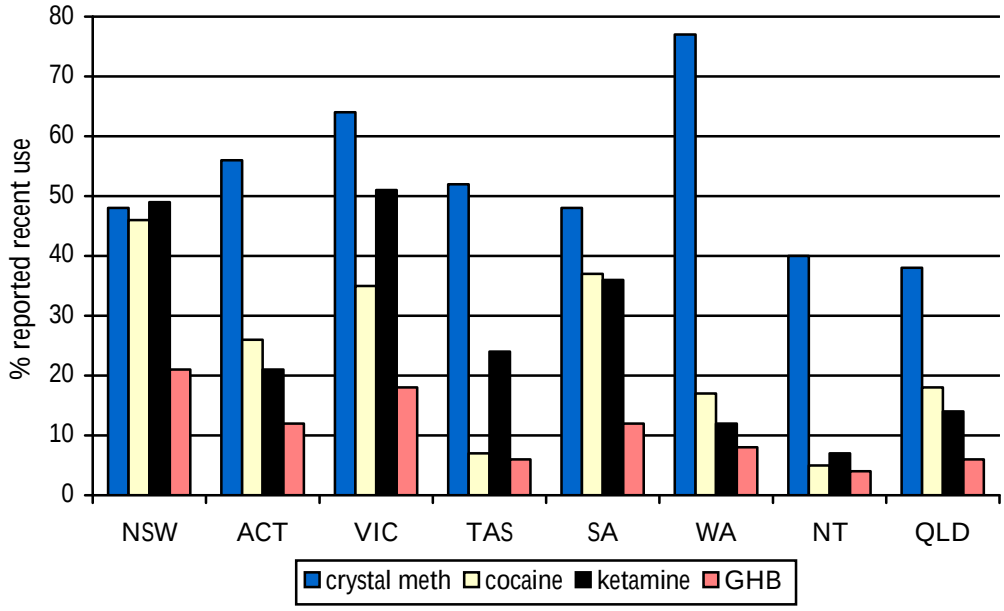
31. In 1980 non-medical, unauthorized experimentation with ketamine was first reported in Australia (Ahmed and Petchovsky 1980). The authors believed that use of the drug was largely confined to medical circles. Since that time, anecdotal evidence indicates that the nature of users has become much

more varied. Jansen (2001) reported that ketamine was being used illicitly as early as 1967-68, with the drug being distributed by those who made it under names such as 'rockmesc'. Several other observers warned about the drug's potential for abuse (Reier 1971; Collier 1972) as ketamine appeared more widely on the illicit drug market in the USA in the early 1970s (Dotson et al. 1995). Street use of ketamine solutions was first noted in 1971 in San Francisco and Los Angeles, while other forms such as powder and tablets were identified in 1974 (Siegel 1978). Some observers (Young et al. 1977) believed that the increased recreational use of ketamine could be attributed to experiences gained among patients in Vietnam and elsewhere during the late 1960s.

32. Clinicians and researchers noted that some non-medical users sought dissociative, hallucinatory experiences (Ashley 1978; Siegel 1978). There are detailed published accounts of such experiences written by users (eg., Turner 1994; Lilly 1978).
33. By the end of the 1970s, the United States Food and Drug Administration (FDA) was becoming concerned about the sale of ketamine on the 'street' (FDA 1979). By the early 1980s a wide range of unauthorised preparations were available in the US including capsules, powder, crystals, tablets and solutions, in addition to the authorised injectable forms (Tori 1996). Solutions sold on the street in the USA have gone by many names such as K, Kay, Jet, Super Acid, 1980 Acid, with powders known as Green, Purple, Mauve, Special LA Coke, Super C, and K (Siegel 1978). Other street names have included Vitamin K and Special K (Tori 1996).

34. Ketamine is not identified in the Australian national household drug surveys, nor the mortality and morbidity data collections. However, in 1994, ketamine was listed in the *Australian Illicit Drug Report* for the first time, with jurisdictions being urged to keep the matter under review during 1995 (ABCI 1995). Very recent surveying conducted as part of the Party Drug Initiative – a national study conducted in the capital city of every Australian state and territory to monitor emerging trends in party drug use - indicates that recreational ketamine use is reported by 20% of respondents in all jurisdictions except Western Australia, the Northern Territory and Queensland [see Figure 1]. Survey respondents reported that ketamine was mainly snorted - although swallowing was commonly reported in Tasmania, Western Australia and the Northern Territory – with prices ranging from AUD$150 per gram in New South Wales to AUD$200 in Victoria and South Australia (Breen et al. 2003).

FIGURE 1: Proportion of PDI respondents reporting recent use of GHB, ketamine, cocaine and crystal methamphetamine, by jurisdiction, 2003



Source: Breen et al. 2003

35. In Australia, ketamine is often marketed in small glass vials with small spoons to measure 'accurate' doses. The spoon is contained in the cap of the bottle, much like a snuff spoon. Other bottles have a self-contained 'measurer' in the cap which when turned over leaves a measured amount, which can then be snorted as ‘bumps’, as very few ketamine users snort the drug in lines (Topp et al. 1998).

36. Ketamine appears to be obtained from the diversion of legitimate supplies (veterinarians and pharmaceutical companies) or is imported from overseas (ABCI 1997; US Drug Enforcement Administration 2003). Ketamine can be bought over the counter in some Asian countries. Reports suggest that some veterinarians are selling ketamine in Sydney and Tasmanian police have reported a case of ketamine being stolen from a veterinary surgery (ABCI 1997).

37. Ketamine sold illicitly is often converted from a liquid form to a powder utilizing a simple evaporation process. The liquid ketamine is dried in a variety of ways (microwave, oven or sun-dried) until a residue remains. This crystal residue is ground into a powder, leaving a fine powdery material similar to cocaine and heroin. In this form it is far more convenient and more marketable than the injectable drug.

38. Evidence from the USA indicates that, up until 1996, ketamine was usually not adulterated with other substances. Of all the ketamine submissions to the USA DEA regional laboratories in that period, there was only one instance of this type of dilution recorded (Tori 1996). However, this situation may well have changed when price and demand rose sufficiently to make such practices profitable.

39. Over the past decade there have been a growing number of reports on the non-medical, unauthorised use of ketamine in the United Kingdom (Dalgarno and Shewan 1996; Riley et al. 2001). Ketamine misuse has also been reported in Sweden (Skovmand 1996) and Australia (White and Ryan 1996; Drugs and Crime Prevention Committee 2003). The International Narcotics Control Board (INCB) *2001 Annual Report* also noted that more young people are misusing ketamine in East and South-East Asia (INCB 2001). In a report to the forty-fifth session of the United Nations Commission on Narcotic Drugs, the Executive Director of the United Nations International Drug Control Programme (UNDCP) also drew attention to worrying evidence of the increasing recreational use of ketamine by young people (United Nations Economic and Social Council 2002).

40. Both popular and research accounts indicate that the recreational use of ketamine has widened in the context of nightclubs, dance parties and 'raves' (Curran and Morgan 2000; Crysell 1998; Kent 1996). This has caused concern as ketamine is an anaesthetic. Dalgarno and Shewan's (1996) study concluded that it was ‘totally inappropriate’ to use ketamine as a 'dance drug'. The reasons for this were factors such as the setting, the rapid onset of the drug and the intensity of the experience as a whole. The respondents believed that using ketamine in a noisy, busy, or crowded environment was potentially dangerous and that use should be confined to a familiar and secure place, such as one's home. All users had been unprepared for the intensity and nature of the effects when they first used the drug.

41. The use of ketamine and other party or club drugs is reportedly associated with an increased incidence of unsafe sex among gay men on the circuit party scene in the United States (Mattison et al. 2001; Ross et al. 2003). This is clearly a public health issue in the spread of blood-borne viruses and other sexually transmitted diseases. A small study of high-risk youth injecting ketamine in New York City also reported that its use was associated with a range of high-risk injection practices, such as group injection with shared paraphernalia (Lankenau and Clatts 2002).

42. Dillon and colleagues (2003) reported a number of ketamine-related problems among their sample of non-medical ketamine users. While only one in five stated that they had ever experienced severe side effects as a result of ketamine use, more than a third (38%) reported having to deal with someone else who had suffered badly following ketamine use. More than half (58%) of those interviewed had experienced the K-hole and this was related to increased exposure to the drug – having used more than twenty times. The most commonly reported problems were employment related (20%). These included vagueness affecting work performance and lower volumes of work productivity. Additional problems reported included relationships (5%), financial (5%), and legal (1%). Twenty two participants reported at least one problem, five reported two problem areas, and one reported three problems areas (Dillon et al. 2003). Ketamine has been sold in the ‘rave’ scene in the United Kingdom as a key component in fake MDMA tablets (Shewan and King 1996). There are also reports of ketamine being

sold as ecstasy in Australia, or used as a cutting agent in other drugs such as cocaine, amphetamines and heroin (ABCI 1997).

43. In conclusion, as levels of ketamine in the general population are very low, the harms reported by recreational users are not excessive, and the mortality rate is low, ketamine does not appear to pose a significant risk to public health at this time. At the individual level, many of those who experiment find the effects aversive and do not persist. The harms that require further investigation are the neurotoxic effects, use in situations where there is a heightened risk of accidental death when the user's cognition is grossly impaired, and the association with unsafe sex and injecting behaviours.

44. Information on ketamine is not routinely collected in Australasian morbidity and mortality data collections. Levels of use in the general population appear to be very low, with higher levels in groups with access to the drug, such as medical and veterinarian professionals. The recreational use of ketamine as a party drug appears to have widened in the context of nightclubs, dance parties and 'raves'. Increased rates of high risk sexual and injecting behaviours in association with ketamine use have also been reported by gay men and marginalised youth in the United States. Ketamine is rarely adultered. Overall, ketamine does not appear to currently pose a significant public health risk at this time.

The therapeutic value of ketamine

45. Ketamine has broad areas of application and is a rapidly acting, relatively safe parenteral analgesic and anaesthetic agent that has been in clinical use for more than three decades. It is the only injectable anaesthetic that induces increases in arterial pressure and heart rate (White et al. 1982). Although the respiratory and pharyngeal reflexes are sometimes momentarily depressed after injection of substantial quantities (Maduska, 1978), they are usually maintained during the period of unconsciousness. The drug is therefore suitable for short anaesthetic and surgical procedures especially in the absence of a trained anaesthetist, although the latest Parke-Davis data sheet stresses that a trained professional should be present, together with resuscitation equipment (Parke-Davis 1999-2000). It is particularly useful in developing countries and remote country areas where a doctor may be working alone.

46. The major concern is the emergence phenomena. Psychic disturbances after ketamine anaesthesia have been reported to occur in about 15% to 40% of adult cases, depending, to some extent, on how these terms are defined (Silvay 1983; Khorramzedeh and Lofty 1976; Hejja and Galloon 1975; Abajian et al. 1973; Hefez and Lanyi 1972; Corssen et al. 1971). Other drugs, such as diazepam, lorazepam and propofol, have been given together with ketamine in an attempt to reduce or abolish these phenomena, with some success. Psychological techniques are also effective in reducing complaints (Sklar et al. 1981). The emergence phenomena have led to less medical use than was originally anticipated, but ketamine is still to be found in many general hospitals in most countries (Green et al. 1998). It is also currently widely used in veterinary medicine.

47. Silvay (1983) suggested a number of clinical uses of ketamine. Ketamine appears to be best used in the young (less than 10 years old) and the old (over 60 years), as these groups have reported fewer emergence reactions (Radford, 1996). Recent studies have confirmed the effectiveness of ketamine in variety of paediatric procedures (Kim et al. 2003; Meyer et al. 2003; Pun et al. 2003) via caudal or intramuscular routes of administration (Koinig et al. 2000).

48. In addition to anaesthesia and sedation, ketamine is used as an analgesic for acute post-operative pain, painful procedures, and more controversially for chronic or neuropathic pain. Analgesic doses of ketamine have been associated with dose-related declines in mood, conscious perception and intellectual performance (Pfenninger et al. 2001). Recent studies also report the successful use of patient controlled analgesia with morphine and ketamine following spinal and hip surgery in adults (Sveticic et al. 2003). An early stage descriptive study of the use of topical ketamine in the management of post-herpetic neuralgia suggests it shows promise in the management of this painful condition (Quan et al. 2003).

49. There is mixed evidence on the effect of ketamine on epilepsy and seizure disorders. Ketamine has been reported as both a pro and anticonvulsant. Recently, ketamine has been recommended for use with electro-convulsive therapy as it has been shown to prolong seizure duration with more rapid post-treatment reorientation (Krystal et al. 2003). A larger body of evidence, however, suggests that it displays anticonvulsant and neuroprotective properties (Sheth and Gidal 1998) but should be used with caution over prolonged periods of time (Ubogu et al. 2003).

50. Studies conducted in the 1950s and 1960s suggested that psychedelic drug-assisted psychotherapy might be an effective treatment for alcohol dependence (Grinspoon and Bakalar 1979). In the 1990s, these findings were used as a partial basis for ketamine-assisted treatment of alcohol dependence. This is known as Ketamine Psychedelic Therapy (KPT) (Krupitsky and Ginenko 1997). The same author reports on the use of ketamine psychotherapy for heroin addiction, where dose was found to be related to treatment outcome at two years (Krupitsky et al. 2002). These are controversial treatments that are yet to be used outside of Russia.

51. In the current environment of growing concern about bioterrorism, the neuroprotective and antieliptic activities of ketamine have led to suggestions that it maybe a useful tool in the management of nerve agent poisoning such as sarin (Mion et al. 2003).

52. In summary, ketamine has broad areas of application, including use in veterinary practice. It is a rapidly acting, relatively safe parenteral analgesic and anaesthetic agent, particularly for children. The experience of psychic disturbance upon awakening from ketamine anaesthesia is problematic. The neurological effects of ketamine are unclear.

The potential for ketamine to cause death

53. There are very few deaths by pure ketamine overdose recorded – that is, not also involving a drug such as alcohol. Of 87 ketamine-linked deaths in New York City, none was purely due to the use of ketamine (Gill and Stajic 2000). Parke-Davis have reported that there are cases of accidental injections with ten times the amount required for surgery, with no obvious, lasting effects (Parke-Davis 1999-2000). The principal physical dangers of most non-medical use are currently believed to arise mainly from the setting, or an interaction between the user and the setting of use (Jansen 1993), as ketamine can leave the user in a confused state. This can, for example, result in burns, falls (sometimes fatal), drowning, death by hypothermia from lying outside in winter, traffic accidents and becoming a crime victim (e.g. 'drug rape'). A recent paper reports the case of an emergency medical technician who died of a combination of asphyxia and intoxication with administered intravenous ketamine in an autoerotic accident (Breitmeier et al. 2002).

54. There are two reports in the literature of deaths by pure ketamine overdose: one is described as 'a homicide for homosexual ends' (Licata et al. 1994); the other describes a middle-aged woman who took the drug daily for seven months (Jansen 2001).

55. There are very few cases of pure ketamine overdose recorded. The majority of ketamine-related deaths are due to the dangerous contexts of its use.

Ketamine-related morbidity

56. There is an extensive list of possible physical effects of ketamine that may be seen as adverse by the user, or that may be directly harmful. Those of principal concern in a non-medical use context are difficulty with walking and balance resulting in falls, numbness, slurred speech, dizziness, visual problems, nausea, headaches, spasms, and twitches. A recent study found that, consistent with animal studies, frequent ketamine use produces long-lasting impairments in episodic memory and aspects of retrieval from semantic memory, even when other drug use is taken into account (Curran and Monaghan 2001).

57. The use of ketamine has been linked with a range of unpleasant mental effects including anxiety, panic attacks, flashbacks, post-traumatic stress disorder, persistent perceptual changes, mania, depression, suicide, insomnia, nightmares, night terrors, an unpleasant feeling of being unreal or that the world is unreal, paranoid delusions, persistent hallucinations, automatic behaviour, fragmentation of the personality and aggression (Jansen 2001).

58. Siegel's study of 23 recreational users noted a high incidence of flashbacks and attentional dysfunction, but exactly what was meant by 'flashbacks' is not defined (Siegel 1978). Large anaesthetic studies do not confirm the finding and generally conclude that ketamine is usually devoid of significant

persistent effects once the drug and its metabolites have cleared the body (Schorn and Whitwam 1980; Modvig and Nielsen 1977). For example, in a study of 1400 patients given ketamine as an anaesthetic for surgical procedures, three had prolonged hallucinations, none lasting beyond three weeks. In no case did hallucinations begin after a period of normality, which is integral to the World Health Organization (1992) definition of flashbacks (Fine and Finestone, 1973).

59. A report showing that ketamine could cause toxic changes in the rat brain (Olney et al. 1989; Olney et al. 1991) caused concern, but to date there are still no published studies which show that these changes occur in the monkey or human brain, and there are metabolic and neurochemical reasons why they are unlikely to do so (Auer 1996).

60. There are a number of potential ketamine effects that may be seen as adverse or harmful. The neurotoxic effects of ketamine are unclear and require further research. The use of ketamine with other neurotoxic drugs, such as alcohol, should be avoided.

The ability of ketamine to cause physical or psychological dependence

61. There is a substantial amount of popular literature describing ketamine as having a marked potential for giving rise to non-physical dependence (eg., Turner 1994; Sputz 1989; Lilly 1978) and case studies in the medical literature are accumulating (Hurt and Ritchie 1994; Soyka et al. 1993; Jansen 1990; Kamaya and Krishna 1987; Ahmed and Petchkovsky 1980). Many of these early reports of ketamine dependence were among those with access to the drug such as anaesthetists and veterinarians (eg., Moore and Bostwick 1999).

62. There is evidence from animal studies to support the view that ketamine can give rise to a dependence syndrome without physical withdrawal phenomena (Beardsley and Balster, 1987). This resembles cocaine dependence without the ‘crash’ after use.

63. A recent Australian study of 100 recreational ketamine users found that around one in five (22%) participants reported physical tolerance to ketamine (Dillon at el. 2003). This is consistent with reports of tolerance to ketamine in multiple anaesthetics (Byer and Gould 1981; Cumming 1976).

64. A paper by Lim (2003) reported on two case histories of inpatient withdrawal from ketamine with observed psychotic symptoms. One case also included reports of a number of previously experienced ketamine withdrawal symptoms such as chills, autonomic arousal, lacrimation, restlessness, nightmare and psychological craving with ketamine being used to relieve the symptoms.

65. There is no research literature on the management of ketamine abuse or dependence. There are some generic descriptions of potentially useful interventions (eg., Jansen 2001; Maxwell 2003) that suggest an abstinence-oriented approach similar to that used for psychostimulants.

66. In summary, there is growing evidence of the physical and psychological symptoms of ketamine dependence among recreational ketamine users. A withdrawal syndrome, including psychotic features, is beginning to be described.

International classification and experience

United Nations drug control conventions

67. Ketamine is not currently listed within the Schedules of the 1961 United Nations Single Convention on Narcotic Drugs or the 1971 United Nations Convention on Psychotropic Substances. The fact that the drug is currently not under international control has been noted as a concern by several bodies, with moves to bring ketamine under tighter control. For example, a meeting of the Scientific Committee of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) was held in April 2000 to undertake a risk assessment of ketamine, including consideration of the possible consequences of its prohibition (EMCDDA 2000).

68. As a first step towards bringing ketamine under control within the United Nations system, a pre-review of ketamine was conducted by the World Health Organization (WHO) Expert Committee on Drug Dependence at its meeting in Geneva on 17-20 September 2002. The Expert Committee noted that the drug has been abused outside of medical advice for almost 30 years, but that ketamine abuse is being increasingly reported as a serious concern in Europe, and a number of countries in Asia and North America. On the basis that there is sufficient information available to justify the scheduling of the substance, the Expert Committee thus resolved to undertake a full critical review of ketamine at a future meeting (WHO Expert Committee on Drug Dependence 2002).

69. While the classification of ketamine in Schedule 1 of the Medicines Regulations therefore does not breach New Zealand's international treaty obligations to control this substance, the EACD may feel that elevating ketamine to the status of a controlled drug under the Misuse of Drugs Act better reflects the potential for harm associated with misuse of the drug.

Other countries' classification of ketamine

70. In the United States, ketamine is a Schedule II substance under the Controlled Substances Act (the same classification as for methamphetamine and cocaine), in recognition of it having a high abuse potential with severe psychic or physical dependence liability. Ketamine is also subject to legal control in several other countries, including Belgium, Estonia, France, Greece, Ireland and Luxembourg.

71. Although not currently under international control, ketamine is classified as a controlled drug in several overseas jurisdictions. The WHO Expert Committee on Drug Dependence has also recently found that there is sufficient information available to justify the scheduling of the substance under the United Nations drug control conventions, and has thus initiated a full critical review of ketamine.

RECOMMENDED PRESUMPTION FOR SUPPLY AND JUSTIFICATION

72. At the present time, there appears to be insufficient information available for the EACD to consider recommending a specific presumption for supply of ketamine.

OTHER RELEVANT INFORMATION

Polydrug use by people who consume ketamine

73. It is also important to note that ketamine users often tend to be polydrug users (see, for instance, Dillon et al. 2003). There is also evidence of an emerging trend where ketamine is being used in conjunction with other drugs: especially MDMA, GHB and other hallucinogenic substances. The health risks associated with ketamine can increase if other drugs are consumed at the same time, or shortly after taking ketamine, because of the uncertain chemical and idiosyncratic reactions that can result from mixing drugs. The use of ketamine with other neurotoxic drugs like alcohol may be a particular cause for concern.

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