From "Special K" to "Special M: The Evolution of the Recreational Use of Ketamine and Methoxetamine

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Summary

Objective: To review the recreational use of ketamine ('Special K'; KET) and explore

the recent diffusion of its new derivative methoxetamine (‘Special M’; MXE). **Methods:** The literature search on the non-clinical/recreational use of KET and MXE was carried out in a range of medical databases. Considering the limitations of peer-reviewed information, data were integrated with a qualitative assessment of a range of websites, drug fora and other online resources including. **Results:** The recreational use of KET has started since its discovery in 1962. This was due to its rapid onset, short duration of action, and peculiar psychotropic effects (‘K-hole’). The latter effect ranges from confusion to dissociation and depersonalization (near-death experience). However, KET abuse is often associated with physical and psychological side effects of which the worst is urological/bladder toxicity. Recently, MXE has emerged as a legal and ‘bladder friendly’ KET alternative. MXE presents with the same dissociative effect of KET but with slower onset and longer duration of action. However, MXE seems to be associated with worse side effects than KET, ranging from mood disturbances/suicidal attempts to acute cerebellar toxicity. **Conclusions:** After 50 years of its discovery, KET has led to the emergence of MXE. However, this latter derivative does not appear to be a safer alternative to KET itself.

Keywords: Ketamine, methoxetamine, near-death experience, phencyclidine, psychoactive.

Introduction

Ketamine (KET) is a phencyclidine (PCP) derivative that blocks non-competitively the glutamate N-Methyl-D-Aspartate (NMDA) receptor; consequently, it inhibits the excitability of pain neurons to induce its dissociative anaesthetic activity [1-3]. It binds

as well but with a lower affinity to σ and μ opioid receptors [1]. KET also inhibits nitric oxide synthase, hence further contributing to analgesia [1]. Furthermore, it acts as a noradrenergic and serotonergic uptake inhibitor, both neurotransmitters being involved in descending anti-nociceptive pathways [4, 5]. Since KET binds to both σ(1) and σ(2) receptors with μM affinities, this may suggest that σ receptor-mediated neuronal re-modelling may contribute to the antidepressant effects of KET [6]. Regarding MXE, its pharmacology and toxicology have yet to be elucidated. Although no formal studies have demonstrated the mechanism of action of MXE, it is likely to share the mechanism of action of KET through NMDA receptor antagonism and inhibition of dopamine reuptake [7].

KET dissociative activity involves the sensory loss and analgesia as well as amnesia which are not accompanied by actual loss of consciousness [8]. This unique experience could expand to the sense of a near-death experience (NDE) or even body splitting. For instance, Barbara Collier, an anaesthetist commented: 'Ketamine allows some patients to reason that . . . the strange, unexpected intensity and unfamiliar dimension of their experience means they must have died' [9].

KET causes mild stimulation of the cardiovascular (CVD) system without suppression of the respiration and gag reflex; thus, it has a good safety record [10]. It is used in the UK in both Emergency Departments (EDs) and chronic pain clinics for mild anesthesia in surgeries [11]. Furthermore, KET has been used as a therapeutic tool in a range of remaining conditions, including: assisted psychotherapy for people with heroin dependence [12]; alcoholism [13, 14]; resistant depression [15]. Furthermore, it has been reported that low dose KET can also re-create a number of physiologic abnormalities characteristic of schizophrenia [16,17]. However, administration of the

drug in high doses for recreational purposes can cause CVD and respiratory toxicity. This makes its unregulated use outside the controlled environments a concern [18]. KET is an arylcyclohexylamine derivative with a molecular weight of 237.73 g/ mol. Its molecular formula is 2-(2-chlorophenyl)-2-(methylamino)cyclohexanone (Figure 1). KET has three modifications from the PCP main structure [19] (Figure 1). The first modification involves the replacement of the piperidine ring by a methylamine which gives the same potency as PCP but increased tendency to induce nausea. The second modification involves the two chloro to the phenyl ring, which decreases the potency but increases the analgesic effect activity. The third substitution involves the addition of carbonyl group to the cyclohexyl ring which increases the elimination and decreases the duration of action of the anaesthetic activity. KET has one chiral centre at the C-2 carbon and thus has two enantiomers (R and S enantiomers). The S enantiomer has the more potent analgesic properties; whereas, the postsynaptic properties and agitated behavior is more associated with R enantiomer [2, 20].

Regarding pharmacokinetics, KET is extensively metabolized by N-demethylation producing norketamine, a non-competitive NMDA receptor antagonist which might also exhibit enantioselective pharmacological activity, e.g. (S)-norketamine has an 8-fold higher affinity than (R)-norketamine [21]. The pharmacokinetics of KET in analgesic doses after intravenous (IV), intramuscular (IM), and oral administration was investigated in healthy volunteers [22]. Plasma KET concentration-time curves were fitted by a two-compartment open model with a terminal half-life of 186 min. Absorption after IM injection was rapid and the bio-availability was 93%. However, only 17% of an oral dose was absorbed because of extensive first-pass metabolism. This high rate of first pass metabolism may well explain why KET is typically not ingested.

Similarly, MXE is generally taken by nasal insufflation (snorting), sublingual application, and IV and IM injection, with rectal use having been reported as well [7]. The objective of this paper is to comment on both the recreational use of KET along with its side effects and toxicity and one its new derivatives, known as methoxetamine (MXE). The latter seems to be particularly popular compared to others such as N-Ethylnorketamine; methoxyketamine; 3-MeO-PCP; or remaining derivatives, including tenocyclidine (TCP) and tiletamine (for a review of the grey literature) [23,24].

Methods

The literature search on the non-clinical/ recreational use of KET and MXE was carried out in six databases including: Ingenta, PubMed, Sciencedirect, Scopus, Web of Knowledge and Wiley. Considering the limitations of peer-reviewed data in relation to latest trends of abuse and new psychoactive substances [11], such as MXE, results were integrated with a qualitative assessment of a range of websites, drug fora and other online resources including: E-newsgroups, chatrooms, mailing lists, e-newsletters, and bulletin boards. The keywords used in this study included: KET, ketamine, 'Special K', 2-(2-chlorophenyl)2-2(methylamino)cyclohexanone, phencyclidine, PCP, MXE, 'Special M', 2-(3-methoxyphenyl)-2-amino)cyclohexanone, methoxetamine, MXE-Powder, METH-O, 'Special M', psychedelics, near-death experience, NDE, recreational. The search was performed over a period of 10 months (January 2011 - October 2011) in eight languages including: English, Flemish, German, Hungarian, Polish, Italian and Spanish. The inclusion criteria were any studies showing the chemistry, pharmacology, psychedelic and recreational use of KET and/or MXE. Non relevant studies were excluded. To this respect, the initial search retrieved 246 studies

of which 95 were excluded. The authors ended up with 151 studies being monitored on a regular basis and included 108 websites, 41 peer-reviewed data, one newsletter and one monograph (see diagram 1). Data collected were kept confidential in a password-protected online database of the ReDNet (www.rednetproject.eu). Any personal data (that could be identifiable) collected from online fora was kept anonymous. The study was cleared for ethical approval by the School of Pharmacy Ethics Committee, Hatfield, Hertfordshire, UK (15 December 2010, PHAEC/ 10 – 42).

Results

Non-clinical use of KET

KET non-clinical use has increased exponentially since its first discovery as a safer anaesthetic alternative to PCP [1, 20]. It was discovered in 1962 by Calvin Stevens, a consultant for Parke-Davis/ Warner [1, 20]. In 1965 its first use as a recreational drug was recorded [20]. However, the recreational use became well-known from the mid-1990s, when it was more popular than cocaine. This was partly because cocaine purity dropped and it was sold as a cheaper alternative [25]. KET, also known in these contexts as 'Special K' or simply 'K', is widely used as a recreational drug in clubs, raves and squat parties for self-experimental purposes and it has caused problems as such in the EU and internationally. It might be difficult to understand why an anaesthetic could become a popular substance of misuse. A few reasons can be identified [7, 26]. These include its (a) short time-to-effect 30 seconds IV, 5 - 30 minutes intranasally and 20 minutes orally) and duration of action which can last up to three hours, (b) low cost, (c) peculiar psychotropic effects. The latter, known among users as the 'K-hole' [27] range from confusional states, vivid dreams, hallucinations, flashbacks, referential thinking, dissociation and depersonalization to psychotic

experiences. It is known that at sub-anaesthetic doses, KET intake has been anecdotally described to be associated with effects somewhat similar to those reported during a near-death experience (NDE) [8, 28-30]. NDEs usually occur in various situations including: cardiac arrest [31]; hypovolaemic/ septic/ anaphylactic shock; intra-cerebral haemorrhage; cerebral infarction; near-drowning or asphyxia; apnoea; electro-stimulation of the temporal lobe [32] and prolonged isolation/sensory deprivation [33]. Common features of the NDE experience include: (a) the ineffable nature of the experience; (b) a sense of joy (cocaine like rush), peace and love; (c) the detachment from own physical body (out-of-body experiences) [34]; (d) traveling along a region of darkness towards a light at the end; (e) visualization of past experiences, sometimes organized into a life-review [28, 35]; (f) visions and communications with deceased relatives and friends or 'beings of light'; (g) a decision to return to life and (h) altered perception of time, ataxia, among others [35].

Users reporting the near-death experiences felt out of the body or lost their senses and sometimes were feeling as out of the planet. One user, Mr. P, reported the above effects after he injected 100 mg of KET IM while he was listening to a piece of music. He said: "I gradually lost my senses. The music was very distorted. I tested myself by asking basic questions about mathematics, the names of those I love, etc., then suddenly I wasn't interested in this anymore. So I tried to concentrate on 'who I am' and I lost the interest again. Visions become blurred. It wasn't meaningful who I was any more, because I existed anyway. Then I tried the experience of death. I was going down a tunnel. I saw the planet Earth. I could feel the relationship between the human soul, Earth and the planets. I thought I was a doll, you know the matryoshka? I was the matryoshka of the entire system. I understood that earth is inside something else. I felt

its gravity. All this is embraced within a system. I was nothing, but I knew that my place was on Earth" [30].

Another KET user reported: "Two years ago I was with my friends in Valencia. We went to the beach that day and we had some KET. We sat on the sand. The effects started very soon. I felt dizzy and I had to lie down. I closed my eyes. The first thing that I remember is that I felt somehow I was going very fast and that I left my body. It was not frightening. Subsequently, I saw a tunnel and a tiny little light which grew bigger and bigger. I was approaching this light when I heard a voice telling me to go back. So I asked 'Why? I don't want to go back.' I had no reply. A being of light appeared. He wanted to show me something. A big screen also appeared. I saw earth and the planets. I have heard them breathing. I touched the stars and talked to the Sun (God). I cannot remember what he said but it was amazing. I kept thinking that it was wonderful and amazing. And then, suddenly, I was lying back on the beach!"

KET effects and NDEs might bear some level of resemblance at a neurobiological level as well. In fact, both KET and NDEs involve events at glutamate N-methyl-D-aspartate (NMDA) receptors [8,29,36]. However, it is still unclear if reported KET psychoactive effects may appropriately fit into typically described features of an NDE.

Adverse reactions associated with ketamine misuse

Miss L., a 23-year-old who tried KET only once in her life at a disco club, observed: "I felt a bit paranoid, I was going to die. The first effects started very soon. I felt very confused and normal reality just disappeared. I was dizzy and unable to walk. I started bumping against walls. I wanted to go out from the room where I was, but it was very cold. I had no-one close to help me." [30].

The risk of physical harm from accidents, such as blackouts and bad falls, is also very high [18]. There are also reports of people with chronic opiate problems using KET for its anaesthetic and analgesic effects [37, 38].

KET may lead to dependence and tolerance can develop quickly; hence a larger quantity is required in order to achieve the same effects [18]. This can lead users to take it in intense 'binges'. An immediate risk of taking KET in recreational settings is accidents, such as bad falls. The disconnection from the body can be dangerous in almost any situation other than lying down in a safe environment. Other adverse effects can include panic attacks and depression, and when taken in large doses it can exaggerate pre-existing mental health problems [19,30,39]. Stimulant-like weight loss and loss of appetite have also been reported after periods of heavy use. The risks of KET use are increased if it is used with depressant drugs, such as alcohol. It can suppress breathing and heart function in rare cases, although more commonly it stimulates these functions. It is more likely to suppress breathing (i.e. give rise to a period of apnea) if taken as a fast IV [18]. When used with stimulant drugs such as ecstasy (MDMA) or amphetamines, it can also cause high blood pressure [3]. A number of reports suggest that KET can be used as a 'date rape drug' as high doses can cause amnesia for events that happened while under the influence of the drug [27]. Three days after consumption of KET, impairments of working, episodic and semantic memory have been reported [40,41]. One research study has shown that semantic memory impairments associated with recreational KET use are reversible after people stop or substantially reduce its use. However, impairment to episodic and possibly attentional functioning is longer lasting [41-43]. A problem with these studies is that the authors rarely, if ever, provide urine or hair test results to prove that their subjects are not misusing with other drugs at

the time of testing. Cannabis and alcohol are particularly likely culprits as many KET users smoke cannabis and drink alcohol daily [27]. Some users also experience mild forms of schizophrenic-like symptoms and perceptual distortions associated with the use of KET for a short period after they have stopped taking the drug [26]. Initially, following its anaesthetic use, clinicians reported the occurrence of confusional states, vivid dreams and hallucinations as well as flashbacks [44]. The risk of death in has been commented in a few reports [18]. According to a report by the European Monitoring Centre for Drugs and Drug Addiction [37], some 12 persons have died as a result of KET use (seven in the US, and five in Europe) in the previous 10 years. Only three of these deaths were associated with the ingestion of KET on its own [37]. Conversely, Schifano et al [18] focused in KET misuse mortality figures (UK; 1993 – 2006), extracted from various sources and identified 23 victims (typically males, in the age 25 – 44 age group) who self-administered themselves with a miscellany of psychoactive compounds (including KET) and alcohol. KET was detected in four cases on its own and they suggested that KET high safe profile should be questioned.

The bladder toxicity issues associated with KET cannot be disregarded. KET is linked to severe bladder problems including: incontinence, painful bladder, bladder shrinkage and damage to kidney and ureter obstruction which may lead to bladder removal [45-47]. However, the mechanisms of how KET cause bladder toxicity are still somewhat unclear.

MXE

The recent emergence of new synthetic drugs [7, 48], has also involved the 'KET/ PCP-like drugs' market. Since 2010, MXE has been advertised and sold online as a legal alternative to KET [7, 49]. Indeed, MXE can be acquired legally without a veterinary licence which is the minimum requirement for the purchase of KET in various countries, including the US. In the UK, it became the first drug to be banned by the Government under a temporary class drug order in April 2012. MXE chemical formula is 2-(ethylamino)-2-(3-methoxyphenyl)cyclohexan-1-one (Figure 1). Its molecular weight is 283.79 g/ mol. It is available as a white or off-white hygroscopic powder. It differs from PCP by two modifications [7, 50]. The first involves the removal of the piperidine ring and replacement by an ethyl amino group which gives more potency than PCP but increases the tendency to induce nausea. The second modification involves the 3-methoxy substitution on the phenyl ring which increases the μ-opioid receptor affinity, whilst at the same time removing its mood altering effects.

MXE is available online as 'MXE powder' and 'Special M' in the form of white powder. It is labelled as 'Not For Human consumption' in order to circumvent the regulations regarding recreational drugs [7]. MXE primary route of administration is intranasal, oral, sublingual, rectal and IM [51, 52]. In addition, very rare cases of IV administration have been reported and included an unconfirmed fatality following an IV injection of both 80 - 100 mg MXE and 400 mg of 5,6-methylenedioxy-2-aminoindane (MDAI) [51, 52].

MXE desired effects and dosages are influenced mainly by the modalities of intake. The dosages can range from 20 - 100 mg for oral administration and 10 - 50 mg for IM administration. Some users suggest the increase in the dosage gradually without exceeding 50 mg on the first occasion when administered orally [53]. The perceived

effect could be delayed of some 30 - 90 minutes after insufflation [54]. This might be dangerous as it often causes the user to ingest another dose of the substance [51], thinking that the first dose was inadequate. MXE duration of action has been described as being in the range of 5 - 7 hours [53]. However, when taken IM, the effect of MXE is faster than orally (within five minutes) [51] and its duration of action is shorter (about one hour).

MXE desired effects and adverse reactions

As reported by users, MXE effects are similar to KET but with longer delay in onset (90 min) and longer duration (5 - 7 hours) when administered orally [51, 53]. MXE ingestion may be associated with NDE whose common features are: sensory deprivation, derealization and dissociation from the physical body [19, 47, 55].

Its reported desired effects include: euphoria, empathy, 'cosiness', pleasant intensification of sensory experiences especially whilst listening to the music, mild to strong sense of dissociation from the physical body, distortion of the sense of reality, vivid hallucinations, introspection, and brief anti-depressant effects [51, 53, 56, 57]. Users reports described MXE experience as:"music sounds great", "trapped inside a glass chopping board", "not for social situation", "feeling like another inanimate object", "...just seems so absurdly surreal and it makes no sense, but I'm quite happy just to stare at the TV screen, feeling all snugly and warm". Somebody described MXE as a "big Christmas cardigan", whose intake was providing both "spinning sensations" and "naturalistic hallucinations in waves", overall referring to the 'M-hole', as opposed to the KET 'K-hole' [51]. This described the subjective state of dissociation from the body, which may mimic the out-of-the-body experiences or NDE [18, 19]. Most users'

reports concluded that MXE is different from KET mainly because of "longer come up" which might lead to a high risk of re-dose, and its longer lasting effects. In summary, MXE seems to work as a short-acting mood enhancer with powerful (visual) hallucinogenic and dissociative properties. However, it ingestion might be associated with several side effects as dizziness, confusion, time distortion, aphasia, synaesthesia, and psychomotor agitation [53, 57].

MXE withdrawal symptoms may include low mood and/ or depressive thoughts [53], decreased levels of cognitive impairment, insomnia [53], and potential suicidal attempts [51].

MXE is allegedly used in combination with a variety of other drugs in order to enhance or prolong its effects and duration of action. These include LSD, 2CC (4-chloro-2,5-dimethoxyphenethylamine), alpha-MT (alpha-methyltryptamine), MDAI [53]. However, web fora users do not recommend its consumption with alcohol, tetrahydrocannabinol (THC), selective serotonin reuptake inhibitors (SSRIs) or monoamine oxidase inhibitors (MAOIs).

Some KET side effects such as agitation and CVD issues (e.g. increased heart rate and blood pressure) may be associated with MXE ingestion. Others have included painful bladder, ureter obstruction, papillary necrosis and hepatic dysfunction [27,47,58]. Regarding MXE psychopathological disturbances, it may seem appropriate to conclude that they are similar to KET [59].

Although MXE has been named as the 'bladder friendly' alternative to 'Special K', work is still needed to confirm that MXE is bladder friendly [47, 50]. Users, admitted to accident and emergency department after having ingested MXE, have experienced both KET-like dissociative/ catatonic and sympathomimetic effects such as agitation,

tachycardia, hypertension, hallucinations, confusion, stupor, mydriasis and nystagmus [47, 50]. MXE was detected in all the patients' serum. Other patients had acute cerebellar toxicity after nasal insufflations of MXE [61]. The toxicity needed several days to recover and was characterised by: severe ataxia, slurred speech, nystagmus, incoordination and reduced consciousness.

User reports on forums confirm these effects. For instance a chronic user, after 18 months of taking MXE, reported that the drug's effects were dose-dependent in most cases [62]. He specified his favourite route as sublingual compared to oral as the latter gives slower effect. In low doses (20 - 35 mg), MXE seemed more of a social drug as "It gave no hangover, lowered inhibitions enough that I could dance and not care if it was bad, and allowed me to feel inebriated enough that I didn't feel like I was missing out on drinking". However, at higher doses (> 40 mg), the dissociative effects started appearing as the user reported: "I found MXE very confusing, numbed the body and yet was still quite suitable for a rave or part setting where socialization would not be required...I occasionally investigated high doses on my own, but did not find them particularly to my liking. I prefer to be functional as I never have much spare time, so the "M-hole" was not great for me. I only investigated it once. Any time I took doses above 60 mg I found that I would awaken the next morning feeling "fuzz"...It is not necessarily an unpleasant feeling, but I certainly feel impaired and would not be comfortable driving a car while experiencing it. It is very hard sensation to describe, but I feel mentally dulled and my vision feels odd".

Another user have experienced the dissociative effect after about one hour of taking 80 mg MXE sublingually with 15 mg of 1-(2,5-dimethoxy-4-ethylphenyl)-2-aminoethane (2C-E) intranasally [57]. The user reported:"I became unable to follow the movie I was

watching while waiting for the chemicals to take effect...From this point on memory is spotty as my mind had deconstructed the concepts of time, order, and reality. Eyes are closed for the duration of the trip. Visuals were truly breathtaking, impossible to relate to my beloved trip report readers. I had the sensation that my body had descended several feet below the earth. I felt as though my mind had disconnected from the confines of its physical structure, projected astrally and was moving though time space at an incalculable speed...I believe I experienced ego death which was terrifying at first but afterward I felt ecstatic".

Discussion and Conclusions

After 50 years of its discovery, KET or "Special K" has led to the emergence of methoxetamine , or "Special M", and possibly other derivatives such as 3-MeO-PCP, PCE, 3-MeO-PCE, tiletamine and 1-(1-(2-thienyl)-cyclohexyl)morpholine (TCM). Most of these new substances share a number of characteristics that may constitute a public health challenge: (a) they are not approved for human consumption; (b) their intake is possibly associated with a number of unknown side effects/ adverse reactions); (c) very few related pharmacological/toxicological data are available in the peer-reviewed, scientific, literature, with the limited knowledge being mostly restricted to pre-clinical studies; (d) they are rapidly appearing in always more sophisticated forms and remain unregulated for a long period of time; (e) they are most often synthesized in underground laboratories simply modifying the molecular structure of remaining controlled drugs, hence raising further concerns in terms of the presence of contaminating agents; (f) they are largely available online and thus 'just a click' away from our homes and potentially available to everyone [7]. In addition, the current legal

status of most of its derivatives may arguably facilitate the increasing levels of popularity of the drug, and might affect as well the users' perception of risks associated with its consumption. In fact, the idea that legality can equate with safety still remains well grounded amongst some recreational users [18, 19]. This work has presented an overview of the first 50 years of KET's history and provided an original refection on its role in the future. A possible limitation of the present study could be given by the fact that only publicly available websites, fora and similar sources were monitored. Conversely, to improve the coverage of the study not only the web pages but also more private ways of communication (including newsgroups, chatrooms, mailing lists, e-newsletters, and bulletin boards) were here considered.

More studies need to be carried out on the issues here described, especially focussing on the clinical pharmacological and acute/chronic toxicity characteristics of the whole range of the PCP-like drugs.

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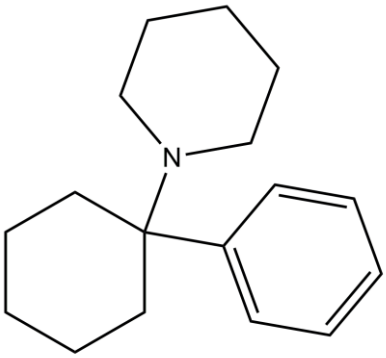
Figures:

Figure 1 Chemical structures of (a) PCP, (b) KET and (c) MXE.

a



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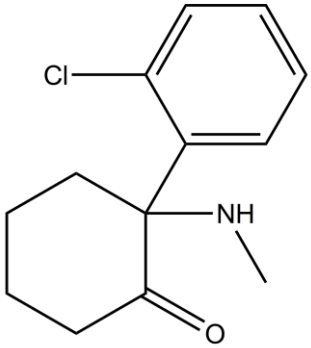

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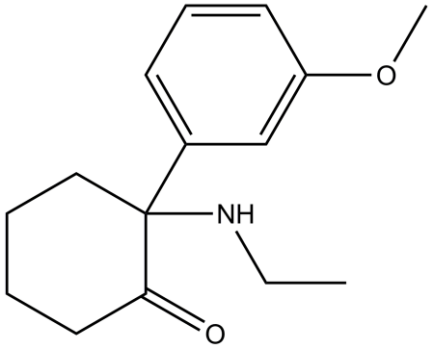

Figure 2 -Diagram: Flow chart illustrating identification of the studies included over the time frame January 2011-October 2011.

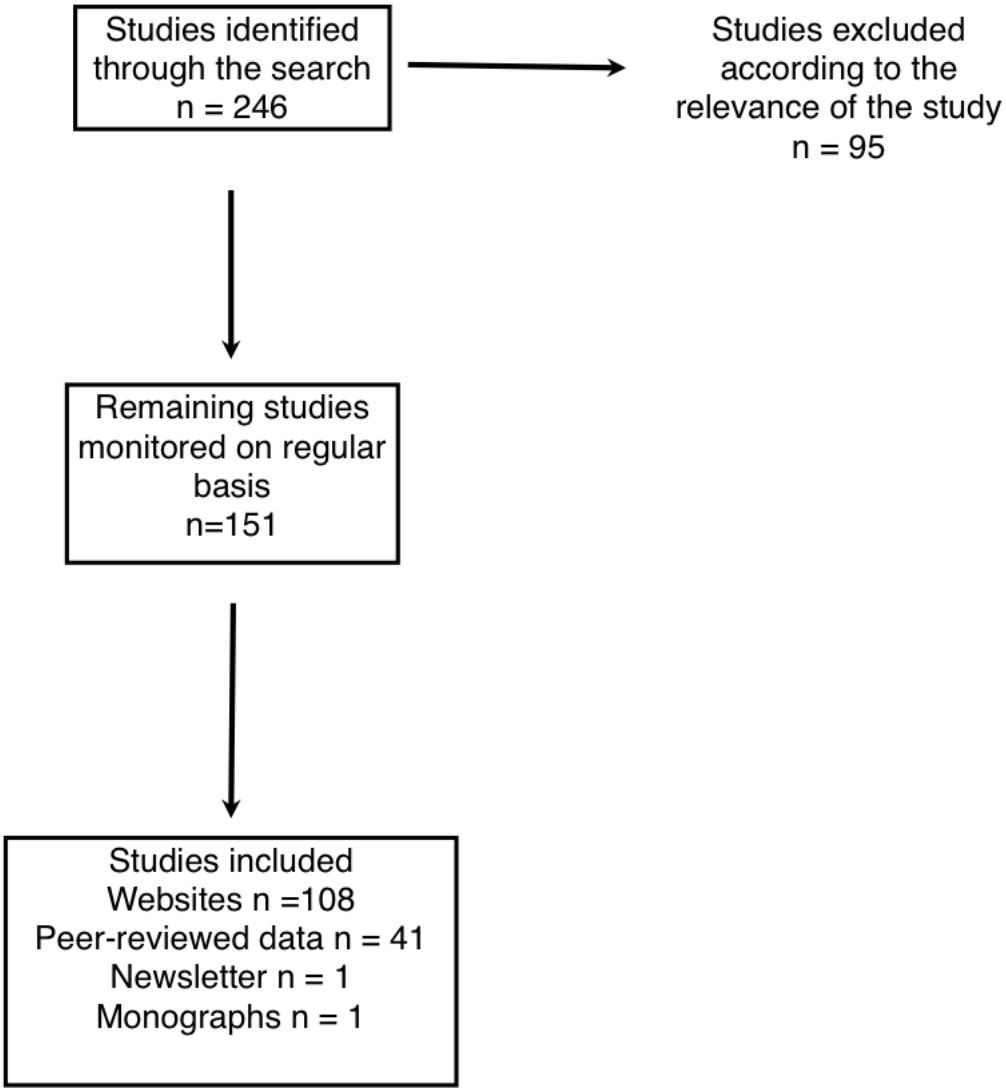

Table 1 - Comparison between KET and MXE chemistry and effects

Criteria	KET	MXE
Chemical Name	2-(2-chlorophenyl)-2-(methylamino)cyclohexanone	2-(3-methoxyphenyl)-2-amino)cyclohexanone
Chemical class	PCP derivative	PCP derivative
Molecular weight	237.73 g/ mol	283.79 g/ mol
Pharmacological class	dissociative anaesthetic	dissociative anaesthetic
Receptors	NMDA, σ and μ	NMDA, σ and μ
Routes of administration	IV, IM, intranasal and oral	intranasal, oral, sublingual, rectal, IM and very rarely IV
Dosage	10 - 250 mg	10 - 100 mg
Onset of action	30 seconds - 30 minutes	30 - 90 minutes
Duration of action	3h 0m 0s	5 - 7 h
Desired effects	depersonalization and out-of-the-body-, including near-death, experiences; stimulation.	euphoria, empathy, cosiness, pleasant sensory experience, dissociation, derealization, vivid hallucinations, introspection, antidepressant, dissociation from body (‘M-hole’).
Risk of re-dose	No	Yes
Tolerance	Yes	Yes
Dependance	Yes	Yes
Known adverse effects	confusion, vivid dreams, hallucination, flashbacks, referential thinking, panic attack, agitation, cardiovascular issues, depression, dissociation, apnoea	confusion, dizziness, time distortion, aphasia, synaesthesia, cardiovascular issues, acute cerebellar toxicity and psychomotor agitation.
Bladder toxicity	Yes	Not confirmed
Cerebellar toxicity	Not reported	Anecdotally reported