Drug abuse and Bladder

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FACTS

• the fastest growing "party drug" among 16-24 year olds – special K, Kit-Kat, Ket, Cat valium, Vitamin K

• boasts an estimated 125,000 users in the UK (More users than crack and heroin combined in UK and Wales)

• internet forums for clubbers the stories were same - people were experiencing strange side effects; incontinence, haematuria and UTIs not responding to treatment.
Ketamine link to bladder failure

Doctors and drug workers in Bristol have established a link between the use of Class C drug ketamine and severe bladder and kidney problems.

A BBC investigation for Inside Out West found a rising number of ketamine users in their teens and 20s were admitted to Southmead Hospital over the past year.

Many had to undergo operations - two even needed their bladders removing.

Doctors at the hospital conducted further research and discovered a similar pattern across the UK.

Ketamine is a short-acting but powerful general anaesthetic which depresses the nervous system and causes a temporary loss of body sensation.

Kidney pains

In the early 1990s the drug started becoming popular on the UK club scene as people bought it in the mistaken belief it was ecstasy.
Ketamine

- BBC – Newsbeat -Thursday, 15 January 2009
- **Warning over rising ketamine use** By Duncan Middleton - Newsbeat reporter, Bristol

**Ketamine** - there are fears it's becoming more popular. Jim Bartlett's (Bristol drugs project) - noticed more ketamine users coming in, asking for help - having problems weeing, they're in lots of pain – “K cramps”.

"We even had one girl who had to have major reconstructive surgery on her bladder after taking ketamine,"

- It is colourless, doesn't smell and is usually smuggled into the UK from India where you can buy it over the counter
Ketamine use 'rises over decade'

The number of people using the drug ketamine increased significantly over the last decade in the UK, while its price fell, a report has said.

The Independent Scientific Committee on Drugs cited surveys that in 2009 found some 68% of UK clubbers had taken the drug, compared with 25% in 2001.

The committee is calling on ministers to offer more help for users and raise awareness of potential health problems.

Ketamine use can cause bladder problems as well as kidney and liver damage.

The committee said that ketamine's classification in the lowest Class C category of controlled substance wrongly suggested it was less dangerous than ecstasy (Class A) or cannabis (Class B).

"Our review of the scientific evidence suggests that this classification of ketamine does not accurately reflect its known and potentially severe harms," the report said.
• **BBC News 20 JULY 2011**

• A review into *Ketamine* by the INDEPENDENT SCIENTIFIC COMMITTEE ON DRUGS -- RECREATIONAL USE of the drug appears to be a growing problem.

• ALTHOUGH not calling for Ketamine to be reclassified, THE COMMITTEE is suggesting - *Ketamine* is **WRONGLY CLASSIFIED** as being less harmful than ECSTASY and CANNABIS.

• *Ketamine* is now the 4th most popular RECREATIONAL DRUG in UK & in extreme cases its use can lead to severe BLADDER DAMAGE
History

• developed by Parke-Davis in 1962

• first given to American soldiers during the Vietnam War

• widely used in humans, also used widely in veterinary medicine or as a battlefield anesthetic in developing nations

• increase in illicit use prompted ketamine's placement in Schedule III of the USA Controlled Substance Act in August 1999.
• In the UK, it became outlawed and labeled a Class C drug on 1 January 2006 (same level as anabolic steroids and cannabis). The maximum penalty for possession is 2 years in prison and 14 for supply and can get an unlimited fine for both.

{Included in WHO list of essential agents used for GA – Halothane, Ketamine, Thiopentone, oxygen and nitrous oxide.}

• can only be used legally by health professionals, for university research purposes, or with a physician's prescription
Ketamine - Pharmacology

- Only agent that induces a state referred to as "dissociative anaesthesia", amnesia, and analgesia
- Pharmacologically, ketamine is classified as an NMDA (N-methyl d-aspartate) receptor antagonist.
- High, fully anesthetic level doses binds to opioid μ receptors type 2 in cultured human neuroblastoma cells
- Ketamine interacts with muscarinic receptors
- Metabolized in the liver
Effects of Ketamine

- **Ketamine is primarily** used for the induction and maintenance of **general anaesthesia**, usually in combination with a sedative.

- Wide range of effect of Ketamine
  - **analgesia** - nerve pain, Palliative care - role in hospice
  - **anaesthesia** - kids, emergency surgery in war zones/ severe trauma (increases Cardiac output/BP), supplementing regional anaesthesia,
  - **hallucinations**, elevated BP
  - **bronchodilation**.

- A **popular anaesthetic** in **veterinary medicine**
- and is used as a **recreational drug** for **hallucinogenic**, and/or **euphoriant** properties.
Ketamine illicit Sale

- The **WHO Expert Committee on Drug Dependence**, in its thirty-third report (2003), recommended research into its recreational use/misuse due to growing concerns about its rising popularity in Europe, Asia, and North America.
- **US Drug Enforcement Agency** - over 80% of ketamine seized in the US is of Mexican origin.
- consignments of **Ecstasy Tablets** known as "**Strawberry**“ and "**Sitting Duck**" contained Ketamine.
- sold in either powdered or liquid form.
- can be **inhaled/snuff, injected**, or taken **orally** crushed crystal has a distinctive bitter taste & the onset of the high is much faster than when ingested or injected intramuscularly (1min- bypasses liver used by heavy users).
Detection

- Urine is often the preferred specimen for routine drug use monitoring
- Detected in blood/ plasma - norketamine, a pharmacologically-active metabolite
- Blood-Therapeutic concentrations - range 0.5-5.0 mg/L
- 1–2 mg/L - arrested for impaired driving and 3–20 mg/L in victims of acute fatal overdosage
Ketamine and Urinary system

- A study in Bristol reported in the BMJ linked urinary tract disease with ketamine use*. Symptoms reported – frequency, haematuria, incontinence and dysuria. These symptoms may be associated with the scarification of the bladder lining, which leads to a shrunken bladder, erythema, and contact bleeding, and can then move to the ureters and damage the kidneys.

- Another small study^ found "marked thickening of the bladder wall, a small capacity, and perivesicular stranding, consistent with severe inflammation. At cystoscopy, all patients had severe ulcerative cystitis. Cessation of ketamine use, with the addition of pentosan polysulfate, appeared to provide some symptomatic relief."


Many long term users report “K cramps” - severe and lasting abdominal pain. The exact cause of these pains are unknown. The Ketamine induced abdominal pain is primarily limited to users of a gram or more of ketamine a day (route of administration does not seem to affect this symptom).
Effect of Ketamine

- **Clinical syndrome** – Overactive bladder syndrome, painful bladder, incontinence, Upper tract obstruction, papillary necrosis and Hepatic damage.


- Patients erroneously treated for recurrent UTI’s/ painful bladder syndrome
Bladder damage – Why?

- Causal link but precise mechanism of Damage – unclear, ? Due to Ketamine/metabolites
  1. Direct toxicity of Ketamine or its metabolites (supported by animal models)
  2. Microvascular damage
  3. Autoimmune reaction triggered by circulating or urinary ketamine
  4. Unrecognised bacteriuria
Ketamine

Histology –
• Absence of urothelium, eosinophilia in blood vessels, lymphocytic infiltration
• specific immune mediated response to Ketamine - mast cells
• Cell Markers – P53 (assoc. with cell death)– high, Ki07 (assoc. with cell growth) v.low, CK20 (assoc with Ca in situ low) – absent but appearance similar to Ca in situ- an important distinguishing feature.
• Cystoscopy — denuded urothelium, that in severe cases sloughs off as intact sheets of cells.

( Wood et al, Recreational : from pleasure to pain. BJUI 2011;107:1881-1884)
CYSTOSCOPIC APPEARANCES OF KETAMINE INDUCED CYSTITIS
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Diagnosis

- Good history esp if recurrent UTI’s of recreational drug abuse
- MSU for C&S
- Cystoscopy and biopsy
- Renal function tests
- CT urogram for extent of disease
Treatment

• Stop ketamine
• Involve drug support agencies and GP
• Work with Chronic pain team as in the initial phase of stopping ketamine – a strategy required for reasonable symptom control
• Bupenorphine patches with cocodamol and amytriptyline at night (Bristol)
Treatment

- Anticholinergics
- Intra-vesical treatment eg Urocyst (chondroitin sulphate) or Cystistat (Hyaluronic acid).
- Bladder augmentation, urinary diversion +/- cystectomy (last resort)
Future

• Awareness and Education of Clinical Staff
• Education and Support for ketamine users - the effects on the urinary tract and where to seek help
• Stopping ketamine does improve symptoms but vicious circle as take Ketamine to relieve pain – close liaison with pain services, psychiatry, social services etc
Stop Taking Ketamine
Think KETAMINE – young patient with bladder pain / cramps, OAB symptoms and Recurrent UTI
Ketamine

Newly evolving problem – issues when/ how to treat... needs Research, patient engagement issue, raising awareness...
Thank you

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