What every psychiatrist needs to know about club drugs.

Detecting and monitoring new psychoactive substances

An update on new drugs and “legal highs”

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TICTAC collects legal & illegal drugs (at St. George’s, University of London) to compile a database that is used by both Healthcare and Law & Order professionals.

28,000 products containing 3,000 drugs
AmHiCo  Red Eye Frog  Everyone Does It

Biorerepublik  Salviadee

“Research chemicals” - not for human consumption
The driver for change

new compounds are used as drugs because they fall outside legislation

the law catches up

The consequence is that vulnerable young people are exposed to a succession of compounds that have never been tested for safety
New Psychoactive Substances

Where do the new compounds come from?

China!!

- minor changes to existing compounds
- fundamental pharmaceutical research papers in academic journals e.g.
  - Dr David Nichols, Purdue University
  - Dr John W. Huffman, Clemson University


The risks - remember MPTP!

We might stumble upon another compound like MPTP.

Made accidentally by a chemistry student who was trying to make MPPP – a pethidine like analgesic.

MPTP causes irreversible symptoms of parkinsonism in humans and monkeys.

Kills dopaminergic neurons in the substantia nigra.


New Psychoactive Substances

Early Warning System

EMCDDA Reitox network:
27 EU Member States, Croatia, Turkey and Norway

EMCDDA Lisbon
The UK legal process

- monitor the appearance of new compound
- report to FEWS, ACMD, EMCDDA (EWS)
- constitute a sufficient problem to warrant import ban (OGIL) or Temporary Class Drug Order (TCDO)?
- TCDO (for 1 year)
  - perform rigorous risk assessment by observation of effects on users
  - assess pharmacology
    * literature review
    * mechanistic studies (in vitro, in animals)
    * clinical vigilance
- amend Misuse of Drugs Act or remove from TCDO
- enforce legislation
New Psychoactive Substances

**Designer drugs**

Increasing number of new “designer drugs” reported through Early Warning System’

49 new compounds in 2011
New Psychoactive Substances

Types of substances reported to EMCDDA (1997 – 2010)

- Phenethylamines
- Tryptamines
- Piperazines
- Cannabinoid receptor agonists
- Cathinones
- Others
mCPP is known to induce headache in humans and has been used for testing potential antimigraine medications.
New Psychoactive Substances

**Phenethylamine empathogens & their β keto derivatives**

- **Controlled Class A**
  - MDMA
  - MDEA
  - MBDB

- **Uncontrolled Now Class B**
  - β keto MDMA - Methylone
  - β keto MDEA - Ethylone
  - β keto MBDB - Butylone

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New Psychoactive Substances

Tryptamines

- 5-MeO-DALT
  - N,N-diallyl-5-methoxytryptamine
- 5-10mg psychedelic, stimulant vivid visuals and mental phenomenon similar to LSD
- Not controlled in UK

“A family has warned of the disastrous consequences of legal highs after their son walked in front of a lorry on a motorway after taking a drug bought over the internet. Alex Howse, 26, is believed to have been hallucinating after taking a large dose of 5-MeO-DALT, which was sold as a plant food.”
**α-Methyltryptamine**

*alpha*-methyltryptamine (AMT) is a psychedelic tryptamine. It is not controlled in the UK.

*alpha*-Methyltryptamine was used as an antidepressant at a dose of 5-10 mg. At doses of 20-30 mg it may cause euphoria, empathy, and psychedelic effects that might last for 12 hours. Doses of over 40 mg effects may last for 24 hours or more. The freebase form can be smoked.
Cathinone

Cathinone is responsible for the stimulant effect of Khat (Catha edulis)

![Cathinone molecule]

![Khat leaves]
New Psychoactive Substances

Cathinones

Mephedrone

N-Benzyl-4-methylcathinone

Dimethylcathinone

Ethcathinone

4-Methylethcathinone (4MEC)

Methedrone

4-Fluoromethcathinone

3-Fluoromethcathinone
New Psychoactive Substances

Mephedrone, MeOW, Mcat, 4-MMC, bubbles

4-methylmethcathinone, mephedrone
Controlled Class B

BCS Drug Misuse Declared, 2010 / 2011

<table>
<thead>
<tr>
<th>Substance</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine powder</td>
<td>4.4%</td>
</tr>
<tr>
<td>Mephedrone</td>
<td>4.4%</td>
</tr>
<tr>
<td>Ecstasy</td>
<td>3.8%</td>
</tr>
</tbody>
</table>

27,000 respondents from representatively-sampled households, used in past year

**New Psychoactive Substances**

**Spice**

- Purports to be a herbal mixture
  - Damiana
  - Wild Lettuce
  - Skullcap
  - Motherwort
  - Red Clover
  - Marshmallow
  - Blue Lotus
  - Baybean
  - Pink Lotus
  - Dwarf Skullcap
  - Indian Warrior
  - Lion’s Tail
  - Maconha Brava
  - White Lotus
  - Siberian Motherwort
  - Vanilla & Honey

- Contains cannabinoid receptor agonists

- Synthetic cannabis

“Spice is an exotic incense blend of the highest quality herbs and herbal extracts.

Unwind your mind! The only herbal smoke that actually works! anytime, anyplace... (except when operating heavy machinery)"
New Psychoactive Substances

Black Mamba

“It has caused breathing difficulties, vomiting, sudden rashes and loss of control to parts of the body. It has led to one person being taken to A&E. It causes uncomfortable distortions in reality and hallucinations. It is used as a substitute for cannabis and appears to be at least as habit forming.”


Not controlled in UK

AM-2201

Alexandros Makriyannis
Department of Medicinal Chemistry at Northeastern University
Boston USA

Not controlled in UK

Oleamide

Induces sleep in animals and is being studied as a potential medical treatment for mood and sleep disorders, and cannabinoid-regulated depression.
Pipradrol analogues

Pipradrol
Controlled drug Class C
CNS stimulant

D2PM
diphenyl-2-pyrrolidinyl-methanol
Class B - June 2012
CNS stimulant ??

2-DPMP
desoxypipradrol
Class B - June 2012
CNS stimulant ??

Desoxy D2PM
(S)-(-)-2-(diphenylmethyl)pyrrolidine
Class B - June 2012
CNS stimulant ??
New Psychoactive Substances

Pipradrol analogues - desoxypipradrol

Developed by Ciba (Novartis) in 1950s for narcolepsy and ADHD

Potent and long acting

Case series of five patients demonstrated a prolonged toxidrome characterised by:-

- tachycardia
- tachypnoea
- dystonia
- leucocytosis
- rhabdomyolysis
- agitation
- paranoia
- hallucinations

prolonged psychiatric symptoms are a key feature

Desoxypipradrol is more potent than cocaine on evoked dopamine efflux in the nucleus accumbens. Colin Davidson & John Ramsey, Journal of Psychopharmacology

'Civory wave' toxicity in recreational drug users; integration of clinical and poisons information services to manage legal high poisoning. 
DB Murray, S Potts, C Haxton, G Jackson, EA Sandilands, J Ramsey, M Puchnarewicz, DW Holt, A Johnston, DN Bateman, JW Dear Clinical Toxicology Feb 2012;50(2):108-113

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NBOMe derivatives

<table>
<thead>
<tr>
<th>R</th>
<th>Trivial name</th>
<th>Parent</th>
<th>Anecdotal reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>25D-NBOMe</td>
<td>2C-D</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>25I-NBOMe</td>
<td>2C-I</td>
<td>Active hallucinogen - dose 500 mcg. not active orally and must be taken buccally, sublingually or intranasally.</td>
</tr>
<tr>
<td></td>
<td>N-bomb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cl</td>
<td>2C-C-NBOMe</td>
<td>2C-C</td>
<td>Active hallucinogen - dose of 200-500 mcg insufflated, making it only slightly less potent than LSD.</td>
</tr>
</tbody>
</table>

The NBOMe series are primarily N-o-methoxybenzyl analogs of the 2C-X family of phenethylamines, and are 5-HT2A receptor agonists.
New Psychoactive Substances

How we find new compounds

Club “amnesty” bins
- sealed “postbox” near club entrance
- permission to search is condition of entry to club
- drugs deposited voluntarily or as a result of search
- contraband discovered on premises

Music festivals
- Glastonbury, Creamfields, Big Chill, V Festival

Drugs purchased from websites
- “Herbal highs” and “Research chemicals”
- analysed to identify new active constituents
- systematic repeat purchases to monitor effects of legislation

Police
- non forensic submissions

Border Force
- Seizure of miss-declared imports
New Psychoactive Substances

GHB, precursors & pro-drugs

GHB controlled Class C

GBL controlled but only when intended for human consumption
**GBL in Quickies**

“Party-goers have been squeezing nail varnish pads into their drinks in their ongoing quest for instant hits.

One source told The Sun that the effects of the pads were well known on the clubbing scene.

‘They can make you feel a little bit frisky, a little bit happy,’ they said!

---

**GBL controlled but only when intended for human consumption**

**Nail Varnish remover pads reformulated in response to abuse**

Propylene carbonate
Aminooindanes

- Amphetamine
- 2-Aminoindane
- 5,6-Methylenedioxy-2-aminoindane (MDAI)

- commercially available and cheap (£120/kg)
- CNS stimulant similar to amphetamine
- Customs seizures in Denmark & Sweden in 2007
- Police seizures in UK
- made in China
- available from websites
- “non-neurotoxic” analogue of MDMA
Ketamine

Chronic ketamine use and urinary tract pathology

An emerging problem

Ulcerative cystitis and potential long-term bladder sequelae related to ketamine use are a significant problem confronting urologists.

A 27 year old man with a history of ketamine use presented with acute right loin pain and a history of lower urinary tract symptoms. Discontinuing ketamine relieved symptoms temporarily. Intravenous urography showed distension suggesting bilateral obstruction, not present six months before, and a small contracted bladder. Previous bladder biopsies showed ulcerative cystitis with neutrophilic and eosinophilic infiltration. On further questioning, the patient said that several friends who used ketamine had similar symptoms. These findings suggest ketamine associated cystitis. The clinical course in this newly described condition is unknown, but over six months our patient’s urinary function deteriorated.

BS Dhillon (benjeeve@doctors.net.uk), foundation year 2 doctor, M C Nuttall, specialist registrar, N Coull, specialist registrar, T S O’Brien, consultant, department of urology, Guy’s Hospital, London SE1 9RT

Patient’s consent: Obtained.
New Psychoactive Substances

**Methoxetamine**

User report from Erowid:

“I would strongly advise that anyone experimenting this due to its relationship with ketamine be VERY careful. I'm sure under the right circumstance it could be an ALRIGHT experience, but in my view ketamine is a much more friendly (for myself) drug.”

ACMD recommended (March 2012) that methoxetamine is subject to a Temporary Class Drug Order.
New Psychoactive Substances

**Benzo fury**

Product sold as 6-APB actually contained:

- 5-APB
- Caffeine
- D2PM
- TFMPP, BZP, caffeine
New Psychoactive Substances

Methiopropamine

- Thiophene analogue of methamphetamine
- Not controlled in UK

MPA, Methiopropamine

Methamphetamine for comparison
Methylhexaneamine (DMAA)

- 1,3-dimethylamylamine (hence DMAA)
- geranamine
- often mixed with caffeine
- not controlled in UK, banned in sport
New Psychoactive Substances

Fakes

Actually contains:-

Methiopropamine (MPA)
5/6-APB
Caffeine

“Ecstasy” tablets
No drugs – made from plaster-of-Paris

170 tablets
with sucrose octaacetate
New Psychoactive Substances

The latest crop
June 2012

AMT
Methiopropamine
5/6-APB
5/6-APB
5/6-APB
JWH-081
Controlled - Class B

AM-2201
AM-2201
AM-2201

Ethylphenidate
Ethylphenidate
Ethylphenidate
Methiopropamine
Methiopropamine
Methiopropamine

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New drugs of abuse

But how much is used?

- self report
- questionnaires / website monitoring
- hospital admissions
- deaths
- border force / police activity
- waste water analysis
- pooled urine analysis
New Psychoactive Substances

Drugs in wastewater (sewage)

• results demonstrate significant potential of sewage epidemiology
• complements questionnaire data

Alexander L.N. van Nuijs, Adrian Covaci, Hugo Neels
Toxicological Centre
University of Antwerp
Belgium

MDMA levels peak at weekends

Methadone - no peak at weekends

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Pooled urine analysis

- anonymous
- non attributable
- no ethical issues
- informed consent not required
  - no female samples
### New Psychoactive Substances

**Drugs detected in a single pooled urine collection**  
*Wardour Street, London, March 2012.*

<table>
<thead>
<tr>
<th>Substance</th>
<th>Metabolites</th>
</tr>
</thead>
<tbody>
<tr>
<td>alprazolam</td>
<td>carbamazepine</td>
</tr>
<tr>
<td>amitriptylline</td>
<td>cathine</td>
</tr>
<tr>
<td>amphetamine</td>
<td>EDDP</td>
</tr>
<tr>
<td>benzocaine</td>
<td>chlorpheniramine + metabolites</td>
</tr>
<tr>
<td>benzoyllecgonine</td>
<td>citalopram + metabolites</td>
</tr>
<tr>
<td>betaxolol</td>
<td>clozapine metabolite</td>
</tr>
<tr>
<td>bisoprolol</td>
<td>codeine</td>
</tr>
<tr>
<td>bufotenine</td>
<td>dextromethorphan + hydrochlorothiazide</td>
</tr>
<tr>
<td>caffeine</td>
<td>dextrophan</td>
</tr>
<tr>
<td>capsaicin</td>
<td>cotinine</td>
</tr>
<tr>
<td>betaxolol</td>
<td>codeine</td>
</tr>
<tr>
<td>bisoprolol</td>
<td>citalopram + metabolites</td>
</tr>
<tr>
<td>bufotenine</td>
<td>dextromethorphan + hydrochlorothiazide</td>
</tr>
<tr>
<td>caffeine</td>
<td>dextrophan</td>
</tr>
<tr>
<td>capsaicin</td>
<td>cotinine</td>
</tr>
</tbody>
</table>

**Some examples of detected substances:**
- **alprazolam**
- **carbamazepine**
- **diphenhydramine + metabolites**
- **ketamine + metabolites**
- **methyl methcathinone**
- **paracetamol**
- **THC metabolites**
- **opioids**
- **amphetamine**
- **cetirizine + metabolites**
- **cathine**
- **EDDP**
- **lidocaine + metabolites**
- **methamphetamine**
- **MMMA**
- **methamphetamine metabolites**
- **PMMA**
- **PMMA + metabolites**
- **bufotenine**
- **dextromethorphan + hydrochlorothiazide**
- **hydrochlorothiazide**
- **methamphetamine**
- **nordazepam**
- **PMMA**
- **PMMA + metabolites**
- **methoxyphenamine**
- **oxazepam**
- **tetramisole**
- **ethanol 91mg/100mL**

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New Psychoactive Substances

Clinical vigilance

Case Report

Collapse, reported seizure—and an unexpected pill
David M Wood, Paul I Dargan, Jennifer Button, David W Holt, Hanna Ovsaka, John Ramsey, Allison Jones

with Recreational Úse of 1-(3-Trifluoromethylphenyl) Piperazine (TFMPP) and 1-Benzylpiperazine (BZP)

Cardiovascular Toxicity Associated with Recreational Use of Diphenylprolinol (diphenyl-2-pyrrolidinemethanol [D2PM])
Santam Lidder, N John Ramsey, D

Detection of the pharmaceutical agent glaucine as a recreational drug
Conclusion

- compounds used as drugs never made by pharmaceutical industry
- not possible to perform formal toxicity studies

All we can do is observe the effects on a vulnerable population that experiments on themselves.

- systematically monitor emergence of new compounds
- analyse urine / blood from clinical presentations to unambiguously establish the cause
Our team

- **TICTAC Communications** - St. George’s University of London (SGUL) identifies new and emerging substances

- **The Analytical Unit** at SGUL – provides analytical services for the detection of the new drugs in biological specimens

- **Dr Paul Dargan & Dr David Wood** - clinical toxicologists at Guy’s and St. Thomas’ treat patients with problems attributed to the new compounds and submit samples to the Analytical Unit

- **Dr Roland Archer** – States Analyst Guernsey synthesises reference standards for the identification of new compounds

- **Dr Alex Sinclair** – Kingston University provides NMR services

- **Simon Hudson** - HFL Sport Science identifies new cannabinoid receptor agonists in “Spice” type smoking mixtures using High Res Mass Spec

- **Dr Adam Winstock** – psychiatrist questionnaire based surveys backed by urine analysis

- **Dr Colin Davidson & Dr James Moffatt** – dopamine and vascular risk profiling