

Acute Recreational Drug Toxicity What's New On The Street ... and the Internet ...

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Epidemiology of Recreational Drug Use

- An estimated 175-250 Million people worldwide used a recreational drug in 2007

Drug	% 15-64yr olds	UK position in Europe	"Top" European country
Heroin	0.9%	2 nd	Estonia (1.5%)
Cocaine	2.3%	2 nd	Spain (3%)
Amphetamine	1.0%	1 st	UK
MDMA	1.5%	5 th	Czech Rep (3.5%)

UN World Drug Report 2009, EMCDDA 2007/8

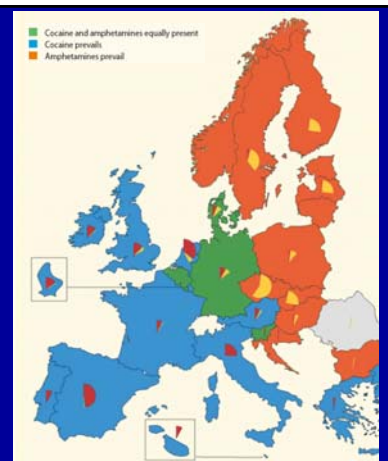
Epidemiology of Recreational Drug Use International Comparison

- Annual adult prevalence rates of drug use

Drug	England and Wales	Spain	Denmark	W Europe overall	USA
Cannabis	7.4%	10.1%	5.5%	7.7%	10.5%
Cocaine	2.3%	3.0%	1.4%	1.4%	2.8%
Amphetamines	1.0%	0.9%	1.2%	0.6%	1.2%

UN World Drug Report 2009/10

Variation in predominant stimulant drug used across Europe



EMCDDA

Drug use is more common amongst those attending nightclubs

Drug	Clubbers life-time prevalence	Clubbers current use	Population current use
Amphetamines	74.2%	24.1%	1.0%
Cocaine	74.9%	41.1%	2.3%
Ecstasy	88.0%	66.6%	1.5%
Ketamine	39.8%	16.6%	1.5%
GHB	17.5%	3.1%	--
Nitrites	68.5%	28.3%	--

The economics of recreational drugs

- Value of the global illicit drug market estimated at:
 - US\$ 12 - 21 Billion at production level
 - US\$ 94 - 136 Billion at wholesale level
 - US\$ 352 - 520 Billion at retail / street level
- In Western Europe / USA ~ 1.5 - 3.0% of GDP

UNODC, EMCDDA

Trends in EU Retail Drug Prices

Table 5: Indexed trends in EU retail prices for major drug types, adjusting for inflation, 2001-06

Drug type	2001	2002	2003	2004	2005	2006
Cannabis resin	100	99	90	70	73	70
Herbal cannabis	100	98	88	80	85	83
Cocaine	100	93	88	83	79	76
Heroin brown	100	90	82	81	91	87
Amphetamines	100	91	93	85	80	89

(European Monitoring Centre for Drugs and Drug Addiction; <http://www.emcdda.europa.eu/stats08/pppfig1>)

Stimulants

MDMA (ecstasy)
Amphetamine
Cocaine
Piperazines
Cathinones

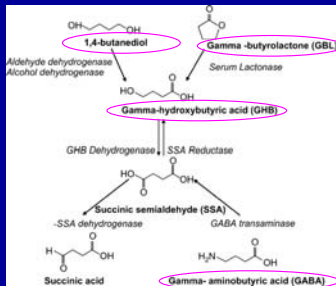
Depressants

GHB / GBL
1,4-butanediol
Heroin
Opium

Hallucinogenics

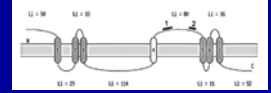
LSD
Ketamine
Glucine
TFMPP

GHB and its Analogues GBL / 1,4BD



- GBL and 1,4BD in many industrial chemicals
- Ingestion of all 3 causes similar clinical features
- London street cost £2 - £12 per 'dose'

GHB - Pharmacology



- GABA agonist
 - *Limited* activity at GABA-A receptors
 - Most effects mediated through GABA-B
- Also
 - Activity at CNS GHB receptors
 - Inhibits dopamine release ... up-regulation of dopamine receptors; important in the psychosis/delirium seen in withdrawal

Carter LP J Clin Pharm Exp Ther 2003, Wong CG Toxicol Rev 2004, Kimmel V J Comp Neurol 2006, Carter LP Pharm and Ther 2009

History of GHB and GBL Use

- 1960s and 1970s
 - General anaesthetic
- 1980s and 1990s
 - Dietary supplement
 - Abused by body builders
 - Treatment of narcolepsy
- 1990s onwards
 - Popular club scene drug
 - Reports of use in DFSA
 - GHB Classified as Class C
 - GBL 'Classified' Class C in Dec 2009

Effects of GHB / GBL / 1,4BD

- Mild-Moderate:
 - ↑relaxation, appreciation for music & dancing, +ve mood change, euphoria
 - nausea, tremor, diarrhoea, agitation
- Severe:
 - Increasing drowsiness coma, convulsions, respiratory depression, bradycardia
 - NB. Vomiting in 15-20%, convulsions in <10%
- Deaths:
 - Pre-hospital: respiratory arrest
 - In-hospital: very rare - aspiration

Management of acute GHB/GBL toxicity

- Hospital assessment
- Supportive care: ABC and monitoring
- Coma normally lasts 1-3 hours
- Complete & often rapid recovery within 2-4 hours
- Airway reflexes generally well maintained
- Need for intubation:
 - Not usually indicated if able to maintain airway *and not vomiting*

GHB/GBL Withdrawal

- Increasingly common
- (Very) frequent use for minimum 2-3 months
- Short duration from last ingested dose to onset of withdrawal symptoms
 - Typically 4-10 hours
- Can occur following admission for acute GHB/GBL toxicity
- Characterised by significant agitation and delirium
- Difficult to manage

Treatment of GHB/GBL withdrawal

- No established recognised treatment protocol
- High-dose benzodiazepines
 - May require 200++mg diazepam in first 24 hours, titrated to symptoms
 - Then reducing course benzodiazepines
 - Usually 7-10 days treatment required
- Barbiturates for resistant withdrawal
 - Up to 50% require ICU admission
- Baclofen may have a potential role in the future

McDonough M. *Drug Alcohol Depend* 2004, Tarabor AF. *Toxicol Rev* 2004, Wood DM. *Clin Tox* 2010

What is a 'Legal High'

- Drug classification systems vary around the world
 - Structure specific ⇔ Generic ⇔ Analogue
- Increasing use of legal substances not covered through these controls
 - Misuse of prescription & 'over the counter' medication
 - Synthetic chemicals
 - Stimulants
 - 'Spice'

What is a 'Legal High'

- The patterns of use of these drugs change rapidly over time
 - 2006-2008: piperazines
 - 2008-2010: 'spice'
 - 2009-2010: cathinones
 - 2010: pipradols, indanes, synthetic cocaines
- Classification lags behind use
 - Dec 2009: piperazines, GBL, 'spice'
 - April 2010: mephedrone / cathinones

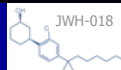
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Spice

- Smokeable herbal mixtures sold under the brand name 'Spice' (often 'K2' in the US)
- Available on the Internet since at least 2006/7



Spice



- Contains synthetic cannabinoid receptor agonists
 - JWH, CP and HU groups
 - JWH-018 found in almost all analysed Spice products
 - varying proportions in different products
 - new active ingredients still being detected
 - 20+ in 2010
 - many remain poorly characterised
- Higher potency than THC
- Effects of the herbal constituents unknown

Vardakou I *Toxicol Lett* 2010; Auwarter V *J Mass Spectrom* 2009

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Stimulant Recreational Drugs

- Many stimulants, legal highs & classical recreational drugs, are structurally similar to phenylethylamine

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Synthesis and Supply

- Currently most synthesis in China and SE Asia
- Supplied as bulk powder but repackaging and tableting in Europe
- Supply to users
 - Street level drug dealers
 - High street head shops
 - Internet

The Internet and Legal Highs

- Many hundred's of sites
- Most English language based but numerous non-English sites
- ~2/3 sites have no restrictions on delivery
 - some have a disclaimer stating the customer has to check legal status in the country of delivery



The Internet and Legal Highs

- Often sold under non-drug product names
 - e.g. mephedrone: 'plant food', 'bath salts'
- Often sold in plastic sealed bags
 - Labelled 'not for human consumption', 'research chemical', 'not tested for hazards or toxicity'
- Generally limited information on content, dose, effects



The Internet and Legal Highs

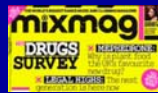
Recent studies from our group & others have shown

- Inconsistency in the products supplied
 - Decline/change in products supplied
 - Substitution of active ingredients in up to 25% of products
- Products advertised as containing legal products may contain classified / illegal active ingredients

Epidemiology of Use

- Data not currently collected in population surveys of recreational drug use
- Small surveys/media interest suggest significant use
 - 20% of 1000+ school/college students in Scotland
- MixMag Survey: 59% had used a 'legal high'

	Use in the last month
Ecstasy	48.4%
Cocaine	47.4%
Mephedrone	33.6%
Ketamine	32.5%
Methylone	7.5%



Dick D *MixMag* 2010; Dargan PI *QJM* 2010

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Legal High Toxicity

- There is limited information on the pharmacology and acute toxicity of these drugs
- Initial data often only available from user reports on Internet discussion forums
- Similar desired and adverse effects to MDMA and cocaine

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Legal High Toxicity

- ED physicians often not aware of novel drugs
- ICD-10 clinical coding
 - poor capture of acute recreational drug toxicity
 - no capacity for coding of novel drugs
- Routine toxicological screening not undertaken
- Lag in National data from poisons centres
 - requires awareness of novel drugs to capture data
- Therefore initial data from case reports & detection in amnesty bin seizures / internet purchases

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Novel Recreational Drug Toxicity

- In the last 3 years we've detected 13 novel drugs in patients presenting with recreational drug toxicity
 - Benzylpiperazine, chlorophenylpiperazine, methyl-BZP, trifluoromethylphenylpiperazine
 - **Mephedrone**, methylone, fluoromethcathinone, MDPV butylone
 - Bromo-dragonFLY
 - Glaucone
 - Diphenyl-2-pyrrolidinemethanol (D2PM)
 - 2,5-dimethoxy-4-chloroamphetamine (DOC)

Wood DM *Lancet* 2007, Dargan PI *EJCP* 2008, Lidder S *J Med Toxicol* 2008, Wood DM *J Med Toxicol* 2008, 2009 & 2010, Wood DM *Clin Tox* 2010, Wood DM *Rev Tox* 2009, Wood DM *Irish Psych* 2009

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Legal High Toxicity

- Patterns of toxicity appear to be similar to that of 'classical' recreational drugs
- Stimulant drugs:
 - Piperazines e.g. 1-benzylpiperazine (BZP)
 - Cathinones e.g. 4-methylmethcathinone (mephedrone)
 - "Fly Drugs" e.g. Bromo-dragonFLY
 - Pipradrols e.g. D2PM
- Hallucinogenic drugs
 - Glucine, TFMP

Dargan Pt. *EJCP* 2008, Lidder S *J Med Toxicol* 2008, Wood DM *J Med Toxicol* 2008, 2009 & 2010
Wood DM *Irish Psych* 2009

Acute Mephedrone Toxicity

- Nasal irritation with nasal insufflation
- 72 self-reported and 7 analytically confirmed acute mephedrone toxicity cases in our unit
 - 57% agitation, 29% chest pain, 14% seizures
 - 70% HR > 100bpm, 18% HR > 140bpm
 - 43% BP_{sys} > 160mmHg
- Dependence potential:
 - Users report significant craving, likened to cocaine
 - Anecdotal reports of dependence from UK and other European drug treatment services

What's Next ???

- Ring and/or chain substitutions of existing phenylethylamines, pyrovalerones, cathinones etc
- New synthetic compounds
 - Indanes, tetralins, synthetic opioid/cocaine derivatives

The challenges

- Difficulties in analytical identification
 - Analytical development, lack of reference materials
- Little or no knowledge of pharmacology, toxicity, safety profile

Conclusions

- Recreational drug use is common
- Toxicity broadly divides up into
 - Depressants
 - Hallucinogens
 - Stimulants
- GHB/GBL withdrawal can be difficult to manage
- Increasing use of a range of novel 'legal highs'
 - Widely available over the Internet
 - Toxicity appears generally similar to 'classical' drugs