Establishing the acute harms associated with NPS: what is available, deficiencies with this data and the role of poisons centres and the Euro-DEN Project

Dr David Wood and Dr Paul Dargan
Guy’s and St Thomas’ NHS Foundation Trust and King’s Health Partners, London UK
Acute Drug Toxicity Data

- Recreational drug / new psychoactive use is common
- Systematic data is available on:
  - Prevalence of drug use
  - Drug seizures
  - Use of treatment agencies for problem drug use
  - Drug-related fatalities

- There is no *systematic* data on acute on recreational drug toxicity
New Psychoactive Substances

- Evidence of availability
- Some data on use, largely at subpopulation level
- Emerging reports of deaths
  - Interpret with caution
- Limited information on acute toxicity

Where can we get the data to make an appropriate risk assessment?
Risk assessment of new psychoactive substances

Operating guidelines

A. Physical, chemical, pharmaceutical and pharmacological information
B. Dependence and abuse potential
C. Prevalence of use
D. Health risks
E. Social risks
F. Involvement of organised crime
Data triangulation of information on new psychoactive substance toxicity

- Numerous sources of information on the acute toxicity of new psychoactive substances
  - No single one provides the complete picture
  - Each has its own limitations

- This technique combines the various sources to minimise the limitations and increase the strength of the combination
  - Requires an understanding of the data sources
Potential sources of information on novel drug use and toxicity

- *In vitro* pharmacological studies
- Animal studies
- User reports and sub-population surveys
- Case reports / series
- Pre-hospital emergency services data
- Emergency Department presentations
- Poisons Information Services
- Data collection through specialist / sentinel centres
What is role of pharmacological studies?

- Often very little known about their pharmacology or potential for toxicity
  - Except some NPS which have been used previously in pharmaceutical industry
- More recent studies allow characterisation of likely pharmacological mechanisms of action
  - ‘Prediction’ of pharmacological activity and potential toxicity
  - Need to interpret with caution
Neurochemical profiles of some novel psychoactive substances

Les Iversen, Simon Gibbons, Ric Treble, Vincent Setola, Xi-Ping Huang, Bryan L. Roth
What about animal studies?

- Generally lag significantly behind other data sources
Internet based discussion forums

- Need to interpret with caution
  - Self-reported by users, no corroboration
  - BUT, can be useful source of initial information
Sub-population user surveys

- MixMag 2010/2011 survey
  - 454 (18%) “medical help” due to drugs
  - 1 in 3 of these needed hospital admission

- Data from most recent episode
  - Collapse 32%
  - Palpitations 30%
  - Chest pain 29%
  - Panic / paranoia 25%
  - Hallucinations 22%

- 20% cathinones, 8% other NPS
Ambulance data sets

– UK: >90% cases brought to hospital by ambulance
– Ambulance datasets not widely available/published
– No standard EU/International coding system
– Pilot studies in UK: coding not sufficient to provide reliable/robust data on recreational drug toxicity
– Data linkage occurs in some areas (e.g. Holland)

Other pre-hospital facilities

– Data not routinely available but can be useful
173 presentations to local “club medic room” over 5 months
- 77% had used the drug before
- 23% had been in a club medic room before
‘Toxins’ depend on location individual seen in:

- Ambulance
  - Opiates
- Outpatients
  - Ethanol
- Inpatients
  - Pharmaceuticals
Currently Available National Data on Recreational Drug Toxicity

- Not routinely collected by EMCDDA Reitox National Focal Points
- Some sub-population hospital/pre-hospital data collected e.g. Spain, UK and Netherlands
- Hospital coding of admissions (discharges):
  - Generally only captures admitted patients (50%)
  - No data on those discharged direct from Emergency Department
  - Based on ICD-10
ICD-10 and Acute Recreational Drug Toxicity

- ICD-10 codes: not available for most recreational drugs
- Yes: heroin, cocaine, LSD
  - But cases often coded by presenting feature e.g. chest pain, coma, convulsion, psychosis
- No: amphetamine, methamphetamine, MDMA, ketamine, GHB ... and definitely not NPS
ICD-10 and Acute Recreational Drug Toxicity

ICD-10 coding: poor identification of recreational drug presentations to a large emergency department

David M Wood, Pamela Conran, Paul I Dargan


Population of acute recreational drug toxicity presentations

n=484

No ICD-10 code associated with presentation
n=339 (70.0%)

One or more ICD-10 code associated with presentation
n=145 (30.0%)

13.2% appropriate ICD-10 code

Primary ICD-10 code “acute recreational drug toxicity”

n=64 (44.1%)

Primary ICD-10 code not “acute recreational drug toxicity”

n=81 (55.9%)
Survey of ICD-10 coding of hospital admissions in the UK due to recreational drug toxicity

A.D. SHAH¹, D.M. WOOD¹,²,³ and P.I. DARGAN¹,²,³

<table>
<thead>
<tr>
<th>Description of hypothetical case</th>
<th>Top 3 primary ICD-10 codes</th>
<th>Number</th>
<th>Percent</th>
<th>Number of different primary codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presentations due to recreational drugs for which there is no specific ICD-10 code</td>
<td>T43.6 Poisoning by psychostimulants with abuse potential</td>
<td>45</td>
<td>68.2</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>T65.8 Toxic effect of other specified substances</td>
<td>7</td>
<td>10.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T50.9 Poisoning by oth &amp; unsp drugs medicaments &amp; biological subs</td>
<td>5</td>
<td>7.6</td>
<td></td>
</tr>
<tr>
<td>Collapse in a sauna due to overdose of GBL</td>
<td>T52.8 Toxic effect of other organic solvents</td>
<td>13</td>
<td>20.3</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>T41.2 Poisoning by other and unspecified general anaesthetics</td>
<td>9</td>
<td>14.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T43.8 Poisoning by other psychotropic drugs, NEC</td>
<td>9</td>
<td>14.1</td>
<td></td>
</tr>
<tr>
<td>Seizure, agitation and tachycardia due to ecstasy</td>
<td>T43.6 Poisoning by psychostimulants with abuse potential</td>
<td>55</td>
<td>82.1</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>T43.8 Poisoning by other psychotropic drugs, NEC</td>
<td>4</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F15.0 Men &amp; behav dis due oth stims inc caffeine: acute intoxication</td>
<td>3</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Agitation after ingesting benzylpiperazine at a party</td>
<td>T43.6 Poisoning by psychostimulants with abuse potential</td>
<td>22</td>
<td>34.4</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>T37.4 Poisoning by anthelmintics</td>
<td>12</td>
<td>18.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T50.9 Poisoning by oth &amp; unsp drugs medicaments &amp; biological subs</td>
<td>11</td>
<td>17.2</td>
<td></td>
</tr>
</tbody>
</table>
Survey of ICD-10 coding of hospital admissions in the UK due to recreational drug toxicity

A.D. SHAH¹, D.M. WOOD¹,²,³ and P.I. DARGAN¹,²,³

<table>
<thead>
<tr>
<th>Hypothetical cases</th>
<th>Primary and secondary ICD-10 codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category</td>
<td>Description</td>
</tr>
<tr>
<td>Recreational drugs with no specific ICD-10 code</td>
<td>Palpitations and severe anxiety after taking mephedrone</td>
</tr>
<tr>
<td></td>
<td>Collapse in sauna due to overdose of GBL</td>
</tr>
<tr>
<td></td>
<td>Seizure, agitation and tachycardia due to ecstasy</td>
</tr>
<tr>
<td></td>
<td>Agitation after ingesting benzylpiperazine at a party</td>
</tr>
<tr>
<td>Other toxicological presentations</td>
<td>Chest pain and tachycardia in regular user of cocaine</td>
</tr>
<tr>
<td></td>
<td>Chest pain and tachycardia after first use of cocaine</td>
</tr>
<tr>
<td></td>
<td>Unconscious due to methadone and heroin overdose</td>
</tr>
<tr>
<td></td>
<td>Body stuffer with suspected opioid toxicity</td>
</tr>
<tr>
<td></td>
<td>Collapse due to alcohol intoxication</td>
</tr>
</tbody>
</table>
Case reports and case series

- Requires clinicians to be alert to the ever-changing recreational drug market
- Need access to specialist analytical facilities to confirm that cases are related to potential novel drug
What is a poisons centre or information service?

Poisons Centre
- Local information support / direct case management
- Additional support / advice to regional / nearby hospitals

Information services
- Nationally co-ordinated network of centres
- May not provide direct patient care
What is a poisons centre or information service?

- 54% of countries have ≥1 poisons centre
  - 274 poisons centres worldwide

- Differences in routes of access
  - Healthcare professional only
  - Public and healthcare professionals
  - May follow-up cases

- Variable access to laboratory services

- Typically obtain information second-hand
  - Data may be collated nationally
UK National Poisons Information Service Data: 2012
March 2009 to February 2010:
- TOXBASE: 2901 cathinones (1664 mephedrone)
- NPIS Calls: 188 cathinone (157 mephedrone)
<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Telephone enquiries</th>
<th>TOXBASE reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitation, aggression</td>
<td>32</td>
<td>9</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>29</td>
<td>7</td>
</tr>
<tr>
<td>Anxiety</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>Confusion, psychosis</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>Chest pain</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>No features</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Palpitations</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Fever, sweating</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Dizziness</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Peripheral vasoconstriction</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Mydriasis</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Skin changes, rash</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Reduced level of consciousness</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Parasthesiae</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Insomnia</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Convulsions</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Loin pain</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Tongue disorder</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Myoclonus/abnormal movements</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Tremor</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>ECG abnormal</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Local effects (mouth/pharynx)</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Dystonic reaction</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal vision</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Liver function tests abnormal</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Raised creatine kinase</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Acidosis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Renal function abnormal</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
- Nov 2010-Nov 2011, mid-West poisons centres
- 1633 calls regarding NPS stimulants
  - 62.2% agitation, 55.5% tachycardia, 32.7% hallucinations
  - 16.5% “Major” effect (potentially life-threatening)
- 58.5% treatment with benzodiazepines
- 8.7% intubated
A 9-State Analysis of Designer Stimulant, “Bath Salt,” Hospital Visits Reported to Poison Control Centers

Brandon J. Warrick, MD; Meredith Hill, DO; Kimberly Hekman, MPH; Rachelle Christensen, PharmD; Robert Goetz, PharmD; Marcel J. Casavant, MD; Michael Wahl, MD; James B. Mowry, PharmD; Henry Spiller, MS; Deborah Anderson, PharmD; Alfred Aleguas, PharmD; David Gummin, MD; Ronald Thomas, PhD; Christopher Nezlek, DO; Susan Smolinske, PharmD

Synthetic Cannabinoid Exposures Reported to Texas Poison Centers

*Journal of Addictive Diseases, 30:351–358, 2011*

Mathias B. Forrester, BS
Kurt Kleinschmidt, MD
Evan Schwarz, MD
Amy Young, MD

- 572 call to the Texas Poisons Centre Network in 2010

<table>
<thead>
<tr>
<th>Month</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>January</td>
<td>5</td>
</tr>
<tr>
<td>February</td>
<td>8</td>
</tr>
<tr>
<td>March</td>
<td>13</td>
</tr>
<tr>
<td>April</td>
<td>23</td>
</tr>
<tr>
<td>May</td>
<td>26</td>
</tr>
<tr>
<td>June</td>
<td>38</td>
</tr>
<tr>
<td>July</td>
<td>56</td>
</tr>
<tr>
<td>August</td>
<td>57</td>
</tr>
<tr>
<td>September</td>
<td>57</td>
</tr>
<tr>
<td>October</td>
<td>59</td>
</tr>
<tr>
<td>November</td>
<td>61</td>
</tr>
<tr>
<td>December</td>
<td>61</td>
</tr>
</tbody>
</table>
Commonly reported symptoms:

- Tachycardia 37.3%
- Agitation 18.5%
- Drowsiness 18.5%
- Vomiting 15.7%
- Hallucinations 10.8%
- Confusion 9.9%
- Dypsnoea 4.7%
‘Ivory wave’ toxicity in recreational drug users; integration of clinical and poisons information services to manage legal high poisoning

DOUGLAS B. MURRAY¹, STEPHEN POTT⁵, CAROLE HAXTON², GILLIAN JACKSON¹, EUAN A. SANDILANDS¹, JOHN RAMSEY³, MALGORZATA PUCHNAREWICZ², DAVID W. HOLT⁴, ATHOLL JOHNSTON⁴, D. NICHOLAS BATEMAN¹, and JAMES W. DEAR¹

Clinical Toxicology (2012), 50, 108–113

Fig. 1. Cumulative number of admissions to RIE ED with self-reported ‘ivory wave’ toxicity.

Table 1. Physiological features and laboratory results in patients presenting following self-reported ‘ivory wave’ ingestion.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Number (%) of patients affected</th>
<th>Mean (+/- SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachycardia (&gt; 100/min)</td>
<td>22 (65)</td>
<td>106.4 (21.2)</td>
<td>57–137</td>
</tr>
<tr>
<td>Tachypnoea (&gt; 16/min)</td>
<td>26 (76)</td>
<td>17.4 (3.0)</td>
<td>12–24</td>
</tr>
<tr>
<td>Raised CK* (&gt; 170 IU/L)</td>
<td>26 (96)</td>
<td>801 (741)</td>
<td>145–2658</td>
</tr>
<tr>
<td>Raised WBC* (&gt; 11 × 10⁹/L)</td>
<td>17 (57)</td>
<td>13.5 (5.8)</td>
<td>5.4–30.2</td>
</tr>
</tbody>
</table>

*In patients with no evidence of preceding seizure or unconsciousness, results available for 27 patients. # White blood cell count, results available for 30 patients.
‘Ivory wave’ toxicity in recreational drug users; integration of clinical and poisons information services to manage legal high poisoning

DOUGLAS B. MURRAY1, STEPHEN POTTS2, CAROLE HAXTON2, GILLIAN JACKSON1, EUAN A. SANDILANDS1, JOHN RAMSEY3, MALGORZATA PUCHNAREWICZ4, DAVID W. HOLT4, ATHOLL JOHNSTON4, D. NICHOLAS BATEMAN1, and JAMES W. DEAR1

Clinical Toxicology (2012), 50, 108–113

**Fig. 3.** Geographical distribution across the United Kingdom of TOXBASE® enquiries for ‘ivory wave’. Data from 3 quarter years is presented. Each point represents an enquiry.
Telephone calls:
- Apr 2010 - Aug 2012
- 47 calls

TOXBASE accesses:
- Jun 2011 – Aug 2012
- 298 accesses
### Table 1  Clinical features reported in telephone enquiries related to suspected methoxetamine exposure

<table>
<thead>
<tr>
<th>Feature group</th>
<th>Reported terms</th>
<th>Number of cases</th>
<th>% of total (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulant</td>
<td>Tachycardia, hypertension, mydriasis, palpitation, increased sweating</td>
<td>17</td>
<td>36 (24 to 50)</td>
</tr>
<tr>
<td>Acute mental health disturbance</td>
<td>Agitation, confusion, euphoria, aggression, hallucination, paranoia, hysteria, manic reaction, psychosis</td>
<td>20</td>
<td>43 (30 to 57)</td>
</tr>
<tr>
<td>Dissociative</td>
<td>Catatonia, dystonia, hypertonia, tetany</td>
<td>5</td>
<td>11 (5 to 23)</td>
</tr>
<tr>
<td>Cerebellar</td>
<td>Nystagmus, tremor</td>
<td>3</td>
<td>6 (2 to 17)</td>
</tr>
<tr>
<td>Reduced consciousness</td>
<td>Reduced conscious level, stupor, somnolence, coma</td>
<td>8</td>
<td>17 (9 to 30)</td>
</tr>
<tr>
<td>Seizures</td>
<td>Seizures</td>
<td>1</td>
<td>2.1 (0 to 11)</td>
</tr>
</tbody>
</table>
Limitations of Poisons Information Services

- Potential useful source of data
- Can be useful in following trends in ‘established’ NPS
- Need to interpret with caution
  - May get multiple calls about one case
  - Requires clinicians to contact poisons services AND to report all used drugs
  - Needs awareness of the NPS by the poisons centre
- Early information often lags behind availability of NPS on the recreational drug market
Specialist / Sentinel Centres and Acute Harm

- Single centre datasets can collect detailed clinical data on prevalence of novel drug use
  - Links with specialist analytical facilities are important
  - Requires interest and finance
  - Can monitor trends in areas with high volume drug use
Five-year trends in self-reported recreational drugs associated with presentation to a UK emergency department with suspected drug-related toxicity

David M. Wood\textsuperscript{a, b}, Shaun L. Greene\textsuperscript{a} and Paul I. Dargan\textsuperscript{a, b}

Usefulness of ED data

- Presentations pre- and post-UK Mephedrone control
  - Frequency of presentations falls after control
  - Reasons unclear

Specialist / Sentinel Centres and Acute Harm

- Single centre datasets can collect detailed clinical data on prevalence of novel drug use
  - Links with specialist analytical facilities are important
  - Requires interest and finance
  - Can monitor trends in areas with high volume drug use

- Single centres can be “linked” to allow comparison
  - Recent EMCDDA funded pilot compared data collection in London and Mallorca
Euro-DEN Project
European-Drug Emergencies Network

- Two year European Commission DPIP Grant
- €464,220
- Overarching objectives
  - Develop a network of sentinel centres across Europe with a specialist interest in the acute recreational drugs and new psychoactive substances (NPS) toxicity to collect data on acute drug toxicity
  - Improve the health and wellbeing of European citizens through improved pre-hospital recognition and assessment of acute drug toxicity
Euro-DEN Project
European-Drug Emergencies Network

- Full scoping exercise on current data collection
- Network of 14 specialist ED centres
  - Clinical interest in drug toxicity
  - Data collection over 1 year using minimum dataset
  - Establish seasonal trends
  - Compare drugs responsible for toxicity across Europe
  - Document patterns of NPS toxicity

Also night-time economy training in drug toxicity
Workstream 1: Systematic collection of data on European Emergency Department Admissions

- **Activity 1**
  - Current European Data on Recreational Drug Emergency Room Presentations
  - Survey of REITOX Focal Points, September 2013
  - Report on current European data, March 2014

- **Activity 2**
  - Development of the minimum dataset
  - Case definition, June 2013
  - Minimum dataset and report, August 2013
Workstream 1: Systematic collection of data on European Emergency Department Admissions

- Activity 3
  - Development of network of sentinel data collection centres
  - Data collection using minimum dataset, October 2013 – September 2014
  - Data collation and analysis by co-ordinator centre
    - Ongoing December 2013 – December 2014
  - Collation of information on difficulties with data collection
Workstream 2: Training /guidelines for staff in recreational settings to respond to drug incidents

- **Activity 1: Development of training package**
  - Development of interactive package for staff working in recreational settings
  - Recognition of acute drug toxicity including NPS
  - Pre-hospital assessment guidelines
  - Using information from WS1 A1 and A3
  - Involves staff working in recreational settings

- **Activity 2: Feasibility study**
  - Delivery of training package in four EU centres
Data triangulation examples

Understanding How Data Triangulation Identifies Acute Toxicity of Novel Psychoactive Drugs

D. M. Wood • P. I. Dargan

Novel Psychoactive Substances: How to Understand the Acute Toxicity Associated With the Use of These Substances

David M. Wood, MD, MRCP (UK), FBPharmacoS and Paul I. Dargan, FRCPE, FACMT

The clinical toxicology of the designer “party pills” benzylpiperazine and trifluoromethylphenylpiperazine

Clinical Toxicology (2011) 49, 131–141
LEO J. SCHEP1, ROBIN J. SLAUGHTER1, J. ALLISTER VALE2, D. MICHAEL G. BEASLEY1, and PAUL GEE3

The pharmacology and toxicology of the synthetic cathinone mephedrone (4-methylmethcathinone)

Paul I. Dargan, a,b Roumen Sedefov, c Ana Gallegos c and David M. Wood a,b,s
Conclusions

- No pan-European data collection systems on the acute harms related to novel substances
- Data triangulation from multiple sources allows patterns of acute toxicity to be determined
- Poisons centres and information services can provide useful information
  - Potential to link international centres to provide more robust data
- Euro-DEN project is novel pan-European co-ordinated approach to collecting Emergency Department data
  - Novel key indicator to report to EMCDDA
Novel Psychoactive Substances
Classification, Pharmacology and Toxicology