Clinical Toxicology: An Update

Dr. Shaun Greene
### Drug Abuse in Australasia

<table>
<thead>
<tr>
<th>Region</th>
<th>Number of drug-related deaths</th>
<th>Mortality rate per million aged 15-64</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>Lower estimate</td>
</tr>
<tr>
<td>Africa</td>
<td>36,435</td>
<td>17,336</td>
</tr>
<tr>
<td>North America</td>
<td>47,813</td>
<td>47,813</td>
</tr>
<tr>
<td>Latin America and the Caribbean</td>
<td>4,756</td>
<td>3,613</td>
</tr>
<tr>
<td>Asia</td>
<td>104,116</td>
<td>16,125</td>
</tr>
<tr>
<td>Western and Central Europe</td>
<td>8,087</td>
<td>8,087</td>
</tr>
<tr>
<td>Eastern and South-Eastern Europe</td>
<td>7,382</td>
<td>7,382</td>
</tr>
<tr>
<td>Oceania</td>
<td>1,957</td>
<td>1,685</td>
</tr>
<tr>
<td>Global</td>
<td>210,546</td>
<td>102,040</td>
</tr>
</tbody>
</table>
NPS: New (Novel) Psychoactive Substances

“...a new psychoactive drug, in pure form or in a preparation that is not scheduled under the Single Convention on Narcotic Drugs of 1961 or the Convention on Psychoactive Substances 1971, but that may pose a threat to public health.....”
Supply: Australian Seizures
Epidemiology

• What’s out there?

• Limited data:
  • Surveys
    • Variable consistency of supply
  • Poison Information Centres
  • Emergency Department presentations

• Little formal analytical data unless death occurs
What makes a good psychoactive?

Noradrenaline

- Stimulant

Dopamine

- Eurphoriant

Serotonin

- Empathogen / entactogen
- Hallucinogen
New Psychoactive Substances: Classes

Noradrenaline

Dopamine

Serotonin

1. Phenethylamines

2. Piperazines

3. Tryptamines
### New Psychoactive Drugs: Classes

<table>
<thead>
<tr>
<th>Class</th>
<th>Chemical Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noradrenaline</td>
<td><img src="image" alt="Noradrenaline" /></td>
</tr>
<tr>
<td>4. Synthetic cannabinoids</td>
<td><img src="image" alt="Cannabinoid" /></td>
</tr>
<tr>
<td>Dopamine</td>
<td><img src="image" alt="Dopamine" /></td>
</tr>
<tr>
<td>5. Other</td>
<td><img src="image" alt="Other" /></td>
</tr>
<tr>
<td>Serotonin</td>
<td><img src="image" alt="Serotonin" /></td>
</tr>
</tbody>
</table>
New Psychoactive Substances

NPS identified in national laboratories 2009-2012
Phenethylamines

- Natural monoamine alkaloid / neuromodulator
- Synthesised in CNS from phenylalanine
- Rapidly metabolised: MAO-A and MAO-B
Phenethylenamines

- Alpha-Methyl Phenylethylamine
- α-carbon methyl group $\downarrow$ MAO degradation and $\uparrow$ CNS penetration
Phenethylamines

- Substitution of the amino group ↑ potency and stimulatory effects via noradrenaline, but often ↓ other effects
Phenethylamines

- MDMA – “ecstasy”
- Substitution at position 4 produces serotonergic or “entactogenic” effects
### Phenethylamine

- **α** methylyated phenethylamines: e.g. amphetamine, methamphetamine
- **β** ketonated amphetamines (highlighted)
- Ring substituted amphetamines
- Benzodifurans: e.g. bromodragonfly (ABDF)
- 2C-B-Fly

### Cathinone

- Ring substituted phenethylamines
- Cathinone
- Substituted cathinones: e.g. methedrine, methcathinone, bupropion, flephedrone, ethcathinone
- Pyrrolidine derivatives: e.g. αPPP, MPPP, MOPPP, Naphyrone
- 2C Series: e.g. 2C, 2C-B, 2C-Fly
- 2C-TFM
- Others: e.g. Mescaline, Tyramine, Dopamine
- N-benzyl derivatives: e.g. 2CBCB-NBOMe
- 2CBFly-NBOMe

### Methylenedioxy-phenethylamines

- Ring substituted methylenedioxyphenethylamines
- MDMA
- MDEA
- MDA
- Amino indans: e.g. MDAI, SIAI, MBDB
- 6APB
- 6APDB
Mephedrone (4-MMC)

- 4-Methylmethcathinone (*meow meow, 4MMC, MCAT, bubbles*)
- Tablets / powder - oral + intranasal most common routes

- Cathinones in vitro inhibit:
  - Dopamine active transporter
  - Serotonin transporter
  - Noradrenaline transporter

  Inhibition of plasma membrane monoamine transporters by beta-ketoamphetamines.
  Cozzoli NV, Sievert MK, Shulgin AT, Jacob P 3rd, Rubbo AE.
  Department of Pharmacology, East Carolina University School of Medicine, Greenville, NC 27858, USA. ncoczzi@brody.med.ecu.edu
Watch how 99.9% pure 4-MMC/Mephedrone (4-Methylmethcathinone) will magically transform your garden right before your very own eyes. Thus leaving you with the most desired garden in your street, for every envious eye to see.

Here at Slyplants we offer the most supreme quality 4-MMC/Mephedrone currently available. We base our goods with all our power so it will definitely meet and surpass every buyer’s highest expectations. We guarantee that after purchasing from Slyplants, you will never look anywhere else again.

Common names used for this chemical:
4-MMC, 4MMC, 4-methylmethcathinone, Mephedrone, Methadone, Methedrone, Methadrone, Mephadrone, M-CAT, MM-CAT & Meow/Miaow Plant Feeder

THE CHEMICALS SOLD BY SLYPLANTS ARE STRICTLY NOT FOR HUMAN INTAKE.

Please do not hesitate to contact us about any queries regarding our products. Many thanks and happy gardening
Mephedrone – The New Ecstasy

- Euphoria
- Stimulant + hallucinogenic
- Elevated mood
- Appreciation of music
- Decreased hostility
- Increased sexual func.
- Improved mental func.
- Empathogen

- Easy to manufacture
- Onset 15-30 minutes, effects last 2-3 hours

*Effects similar to combination of ecstasy, cocaine + amphetamine*
Mephedrone associated with over 125 UK deaths

A harmless high?

Teenager dies of 'net drug' overdose

Published: 15 Dec 08 17:32 CET | Double click on a word to get a translation

An 18-year-old girl has died in Stockholm after overdosing on mephedrone, a drug that until now has been freely available for purchase on the internet.
NPS in Australia

Percentage of regular ecstasy users who used a NPS in 2012

- **Synthetic cannabinoids**
- DMT*
- 2C-B**
- Mephedrone
- Methylone
- MDPV
- Salvia divinorum

* Dimethyltryptamine (DMT) ** 4-bromo-2,5-dimethoxy-phenethylamine (2C-B)
25i-NBOMe

Teen jumps to his death after $1.50 drug hit

June 6, 2013

NBOMe — a very different kettle of fish . . .

David G E Caldicott, Stephen J Bright and Monica J Barratt

New hallucinogenic drug 25B-NBOMe and 25I-NBOMe led to South Australian man's bizarre death
Management

- Benzodiazepines 1\textsuperscript{st}, 2\textsuperscript{nd} and 3\textsuperscript{rd} line

- **Hyperthermia**

- **Seizures**
  - No role for phenytoin
  - Don’t forget the [Na]

- **Hypertension**
  - Beta-blockers are associated with increased mortality....
    ............but not for the reasons previously thought
Management

• Last, but not least:

• **Ketamine uropathy**

  ![BJUI](image)
  "The prevalence and natural history of urinary symptoms among recreational ketamine users"
  Adam R. Winstead, Luke Mitcheson, David A. Gillatt* and Angela M. Cottrell*

• **Cannabis induced hyper-emesis**
  • Try droperidol
Marijuana CAN kill people

ways it can:
- you eat a handful of marijuana and choke to death on it.
- a heavy crate of marijuana falls and crushes you.
- you slip on a baggie of marijuana and break your skull into thousands of pieces.
- a serial killers name is marijuana.

ways it can’t:
- smoking marijuana
Structural Heterogeneity

THC
Structural Homogeneity

Serotonin

JWH-18
CB Receptor Agonism

THC

CB1

CB2

SCRA
Cannabinoid Receptor Agonists
Presentation.......who?

- Young males
- Effects: 1-2 hours
- Adverse effects 70%, only 5% attend ED
  - ethanol, SCRA via bong, young males
    Barratt MJ et al. Drug and Alcohol Review 2013
- SCRA users – 2.5% attended ED past year
  Winstock A et al. Psychopharmacol 2013
Presentation......what?

- **Systematic review – 106 citations > 4000 cases**
- Young male 59-100%
  - Tachycardia 37-77%
  - Agitation 16-41%
  - Nausea 13-94%
- Simple supportive care
  - O2, IV fluid, benzodiazepines
- ED stay < than 8 hours

Tait et al. Clinical Toxicology 2016
<table>
<thead>
<tr>
<th>Clinical features</th>
<th>All patients (n = 510)</th>
<th>Isolated SCRAs use (n = 433)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>General</td>
<td>33</td>
<td>6.5%</td>
</tr>
<tr>
<td>Abnormal sweating</td>
<td>8</td>
<td>1.6%</td>
</tr>
<tr>
<td>Malaise</td>
<td>10</td>
<td>2.0%</td>
</tr>
<tr>
<td>Other</td>
<td>15</td>
<td>2.9%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>64</td>
<td>12.5%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>34</td>
<td>6.7%</td>
</tr>
<tr>
<td>Nausea</td>
<td>16</td>
<td>3.1%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>8</td>
<td>1.6%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>6</td>
<td>1.2%</td>
</tr>
<tr>
<td>Neurological</td>
<td>165</td>
<td>32.4%</td>
</tr>
<tr>
<td>Reduced level of consciousness</td>
<td>87</td>
<td>17.1%</td>
</tr>
<tr>
<td>Mydriasis</td>
<td>24</td>
<td>4.7%</td>
</tr>
<tr>
<td>Headache</td>
<td>16</td>
<td>3.1%</td>
</tr>
<tr>
<td>Seizure</td>
<td>9</td>
<td>1.8%</td>
</tr>
<tr>
<td>Clonus</td>
<td>6</td>
<td>1.2%</td>
</tr>
<tr>
<td>Cardiorespiratory</td>
<td>210</td>
<td>41.2%</td>
</tr>
<tr>
<td>Tachycardia (&gt;100)</td>
<td>81</td>
<td>15.9%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>28</td>
<td>5.5%</td>
</tr>
<tr>
<td>Chest pain</td>
<td>20</td>
<td>3.9%</td>
</tr>
<tr>
<td>Hypotension (SBP &lt;80)</td>
<td>16</td>
<td>3.1%</td>
</tr>
<tr>
<td>Palpitations</td>
<td>14</td>
<td>2.7%</td>
</tr>
<tr>
<td>Bradycardia (&lt;60)</td>
<td>9</td>
<td>1.8%</td>
</tr>
<tr>
<td>Hypertension (SBP &gt;160)</td>
<td>9</td>
<td>1.8%</td>
</tr>
<tr>
<td>Abnormal ECG</td>
<td>9</td>
<td>1.8%</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>6</td>
<td>1.2%</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>121</td>
<td>23.7%</td>
</tr>
<tr>
<td>Agitation/Aggression</td>
<td>50</td>
<td>9.8%</td>
</tr>
<tr>
<td>Confusion</td>
<td>23</td>
<td>4.5%</td>
</tr>
<tr>
<td>Hallucination</td>
<td>22</td>
<td>4.3%</td>
</tr>
<tr>
<td>Paranoid Ideation/Psychosis</td>
<td>6</td>
<td>1.2%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>6</td>
<td>1.2%</td>
</tr>
<tr>
<td>Speech disorder</td>
<td>6</td>
<td>1.2%</td>
</tr>
<tr>
<td>Lab Findings</td>
<td>24</td>
<td>4.7%</td>
</tr>
<tr>
<td>Acidosis/Acidosis Lactic</td>
<td>14</td>
<td>2.7%</td>
</tr>
<tr>
<td>Elevated creatinine</td>
<td>10</td>
<td>2.0%</td>
</tr>
</tbody>
</table>
SCRA Toxicity

- Literature: > 4000 cases, > 50 deaths
- Agitated, tachycardic young male......
- N+V, diaphoresis, seizures, mydriasis, muscle twitching, shortness of breath, injected conjunctivae, HT, paranoia
- AMI, shock, acute kidney injury, ischemic stroke
- Pulmonary infiltrates
- QT prolongation, hypokalaemia, leucocytosis
- Death

- Young person with AKI or unexpected critical illness?
- Ask about SCRA use
Risk of emergency medical treatment following consumption of Cannabis or synthetic cannabinoids in a large global sample

*Winstock A¹, Lynskey M², Borschmann R², Waldron J³.*

*Article in* Journal of Psychopharmacology 29(6) · March 2015

- *Drug use survey: 22000 respondents*
- *Risk of ED attendance 30 x SCRA compared to cannabis exposure*
Some Reading........

A systematic review of adverse events arising from the use of synthetic cannabinoids and their associated treatment

Robert J. Tait, David Caldicott, David Mountain, Simon L. Hill & Simon Lenton

Epidemiology and clinical features of toxicity following recreational use of synthetic cannabinoid receptor agonists: a report from the United Kingdom national poisons information service


Patterns of synthetic cannabinoid use in Australia

MONICA J. BARRATT¹, VINCE CAKIC² & SIMON LENTON³
Prescription Opioid Analgesics
Victoria 2013

Prescription drug deaths overtake state road toll

Prescription drugs

Road toll
Death Rate in Victoria as Percentage of 2005 Value: 
*Neoplastic, CVS and RTA Deaths*

- Neoplasms
- CVS
- RTA
Death Rate in Victoria as Percentage of 2005 Value:

*Deliberate Self-Poisoning Deaths*

![Graph showing the number of road and unintentional pharmaceutical poisoning deaths from 2005 to 2014.](image-url)
Single Drug Overdose Deaths in Victoria

- Heroin
- Alcohol
- Methadone
- Oxycodone
- Paracetamol
- Amitriptyline
- Methamphetamine
- All benzodiazepines
- Codeine
- Codeine
- Quetiapine
- Citalopram

% of total deaths
Multi-Drug Overdose Deaths in Victoria

- Heroin
- Alcohol
- Methadone
- Oxycodone
- Paracetamol
- Amitriptyline
- Methamphetamine
- All benzodiazepines
- Codeine
- Quetiapine
- Citalopram

% of total deaths
Selected Causes of Death: Victoria 2014

Average years of life lost

- All
- CVS
- Neoplasms
- RTA
- Unintentional OD
Prescription Opioid Deaths Australia: 2008-2014

<table>
<thead>
<tr>
<th>Year</th>
<th>Metro</th>
<th>Rural</th>
<th>Australia</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>275</td>
<td>131</td>
<td>406</td>
</tr>
<tr>
<td>2009</td>
<td>302</td>
<td>148</td>
<td>450</td>
</tr>
<tr>
<td>2010</td>
<td>297</td>
<td>176</td>
<td>473</td>
</tr>
<tr>
<td>2011</td>
<td>286</td>
<td>181</td>
<td>467</td>
</tr>
<tr>
<td>2012</td>
<td>321</td>
<td>249</td>
<td>570</td>
</tr>
<tr>
<td>2013</td>
<td>331</td>
<td>245</td>
<td>576</td>
</tr>
<tr>
<td>2014</td>
<td>436</td>
<td>326</td>
<td>762</td>
</tr>
</tbody>
</table>
Who is at risk for prescription opioid harm, including death?

- Men aged 25-54 years
- Economically disadvantaged
- Rural populations
- Psychiatric illness
- A past history of substance abuse

Rintoul et al. 2010
It’s Not Just Death

- Opioid related hospital admissions
- Calls to community support services
- IV drug abuse of prescription opioids

All have increased significantly past 15 years
Opioid Prescribing – Australia

No. of prescriptions (thousands)

Oxycodone
Opioid Prescribing – Australia

- Oxycodone

No. of prescriptions (thousands)

No. of deaths

- 1992
- 1994
- 1996
- 1998
- 2000
- 2002
- 2004
- 2006

- 0
- 20
- 40
- 60
- 80
- 100
- 120

- 0
- 20
- 40
- 60
- 80
- 100
- 120

- 1992
- 1994
- 1996
- 1998
- 2000
- 2002
- 2004
- 2006
Diversion

- 110 million oxycodone tablets prescribed annually
  - 2/3 of these are not used as prescribed
  - 90% of injected prescription opioids are obtained via diversion
my doctor... is a drug dealer
Oxycodone Prescribing: Austin ED

30 prescriptions per day
Opioids are good for pain.....

- Little evidence for long-term use in non-cancer pain

![Graph showing comparison between Opioids and Placebo]

60% of patients experience adverse effects
There is no clear evidence of an advantage in using opioid-based analgesics over non-opioid analgesics in the treatment of non-cancer pain.
A Comprehensive Review of Opioid-Induced Hyperalgesia

Marion Lee, MD\textsuperscript{1}, Sanford Silverman, MD\textsuperscript{2}, Hans Hansen, MD\textsuperscript{3}, Vikram Patel, MD\textsuperscript{4}, and Laxmaiah Manchikanti, MD\textsuperscript{5}
Achieving a Balance

Treating pain

Minimising harm
• Patients
• Others
No Easy Solution

- **Prevention**
- **Treatment**
- **National initiatives**
- **Evidence based guidelines**
- **Public education**
- **Education**
  - Prescribers / medical students
  - Patients
- **Rationalise prescribing and Rx**
  - Patient selection
  - Treatment plans / contracts
  - Alternative pain Rx strategies
- **Reducing diversion**
  - Data sharing / prescription tracking
  - Pharmaceutical / prescribing regulation
  - Law enforcement
  - Safe drug disposal
- **National initiatives**
  - Evidence based guidelines
  - Public education

- Access to pain specialists
- Access to addiction specialists
- Multi-disciplinary approach
- Opioid substitution programs
- Improved Rx of overdoses
- Availability of naloxone

- Rationalise prescribing and Rx

- Reducing diversion

- Education

- Treatment

- Prevention

- No Easy Solution
Supply reduction:

Real time prescription monitoring
Prescriber education
PBS quantities
Limiting hospital discharge amounts
Registration with one doctor
Alternative therapy availability / access
Harm reduction:

Needle and Syringe Programs

Community naloxone provision / OTC naloxone

Pain specialists and programs

Regular prescriber CPD

Prescribing thresholds to trigger Rx escalation

Changing formulations – gel capsules / Targin®

Community education regarding dangers
Will opioids potentially cause harm?

- Substance misuse disorder
- Psychiatric illness: depression
- Sedative drug use
- OSA, respiratory disease
Does my patient understand opioid treatment?

- Only one part of the solution
- Rx is short term
- Adverse effects
- Addiction possible
- Store safely
Does my patient have a follow-up plan?

- LMO review
- Notify LMO
- Provide instructions:
  - Verbal and written
A recommended approach:

- Are opioids good for this pain?
- Will opioids potentially cause harm?
- Does my patient understand opioid treatment?
- Does my patient have a follow-up plan?
How to manage adult pain

Emergency & Pharmacy Departments

This booklet will explain how to manage your pain. It contains information about the most common medications.

Who can help me manage my pain when I go home?

- See your local doctor if you cannot manage your pain or need more supplies of your medications.
- If symptoms persist, seek medical advice.
- If you have any medication related questions, contact Austin Pharmacy Department: 03 9488 5291

Can I become addicted to my pain medications?

- You cannot become addicted to paracetamol or anti-inflammatory medications.
- Addiction to the opioid medications is rare when used for short term management of pain. If you have been taking opioid medications for more than 2 weeks, you will need to stop them gradually. Ask your doctor or pharmacist for advice.

Safe storage and disposal of medication

- Keep your medication where children cannot reach it. A locked cupboard at least one and a half metres above the ground is a good place to store medicines.
- If your doctor tells you to stop taking any of these medications or the tablets have passed their expiry date, ask your pharmacist what to do with any that is left over.

Produced by Emergency & Pharmacy Departments, Austin Health February 2009
Reviewed November 2013 Date of next review: November 2016

This leaflet will be available in Fast Track and Staff base 1 and 2.
Thank you for your attention.....

Questions?