AVOIDING DISASTER IN DRUG & ALCOHOL OVERDOSE & WITHDRAWAL

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MEDICALLY ASSISTED WITHDRAWAL

Associated Problems

ALD

NUTRITION

Seizures

Relapse Prevention + Ongoing Care

MEDICATION

DTs

CONFUSION

WKS

‘Frequent Flyers’

SCREENING & ASSESSMENT

ALCOHOL
ALCOHOL USE DISORDERS: DIAGNOSIS AND CLINICAL MANAGEMENT OF ALCOHOL-RELATED PHYSICAL COMPLICATIONS

Clinical Guideline 100

http://pathways.nice.org.uk/pathways/alcohol-use-disorders
Medically Assisted Withdrawal

ALCOHOL
Enkephalin or Dynorphin Inhibitory Neuron

Glutamate Excitatory Input

Dopamine Neuron

ALCOHOL

GABA Inhibitory Feedback

Dopamine Receptors

GABA Neuron

Ventral Tegmental Area (VTA)

Nucleus Accumbens (NAc)

ALCOHOL

Enkephalin Inhibitory Neuron

κ Opioid Receptors

μ Opioid Receptors

Presynaptic Opioid Receptors (μ, δ?)

ALCOHOL

+++
ALCOHOL WITHDRAWAL

- Alcohol interacts with the GABA-BZ receptor
  - ↑ inhibitory activity ➔ ↓ anxiety, sedation, ataxia, slurred speech, respiratory depression
  - ↓ sensitivity of GABA to alcohol underlies tolerance
- In withdrawal, BZ boost GABA function to increase inhibitory function

- Alcohol antagonises glutamate ➔ ↑ NMDA receptors
- Associated with memory impairment
- In withdrawal the ↑ glutamatergic activity contributes to symptoms + seizures and DTs
- Anticonvulsants which ↓ glutamatergic activity can treat alcohol withdrawal
BENZODIAZEPINES

- Advantage = sedative and anti-convulsant
- Long acting - half life of 30 - 60 hours
  - Diazepam (Valium) 5-10mg qds
  - Chlordiazepoxide (Librium) 20 - 30mg qds
- Decrease over a period of 7 to 10 days.
- Severe liver damage:
  - Danger of accumulation and toxicity
  - Use lorazepam or oxazepam (not hydroxylated by liver)
### Table 2-3. Example of dosing regimens for acute alcohol withdrawal.

<table>
<thead>
<tr>
<th>Dosing Regimen</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed dose</td>
<td>20 to 30 mg four times daily</td>
<td>20 to 30 mg three times daily</td>
<td>20 to 30 mg twice daily</td>
<td>20 to 30 mg at bedtime</td>
</tr>
<tr>
<td>Symptom-triggered</td>
<td>20 to 30 mg as needed up to hourly, based on symptoms*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Front-loaded^</td>
<td>100 to 200 mg every 2 to 4 hours until sedation is achieved; then 50 to 100 mg every 4 to 6 hours as needed</td>
<td>50 to 100 mg every 4 to 6 hours as needed</td>
<td>50 to 100 mg every 4 to 6 hours as needed</td>
<td>None</td>
</tr>
</tbody>
</table>

*These symptoms include pulse rate greater than 90 per minute, diastolic blood pressure greater than 90 mm Hg or signs of withdrawal.
<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nausea &amp; vomiting</strong></td>
<td></td>
</tr>
<tr>
<td>Do you feel sick? Have you vomited?</td>
<td></td>
</tr>
<tr>
<td>0 - no nausea and no vomiting</td>
<td></td>
</tr>
<tr>
<td>1 - mild nausea with no vomiting</td>
<td></td>
</tr>
<tr>
<td>2 - intermittent nausea with dry heaves</td>
<td></td>
</tr>
<tr>
<td>3 - constant nausea, frequent dry heaves, and vomiting</td>
<td></td>
</tr>
<tr>
<td><strong>Tremor</strong></td>
<td></td>
</tr>
<tr>
<td>Ask the patient to stand with arms extended and fingers spread apart</td>
<td></td>
</tr>
<tr>
<td>0 - no tremor</td>
<td></td>
</tr>
<tr>
<td>1 - not visible but can be felt fingertip to fingertip</td>
<td></td>
</tr>
<tr>
<td>2 - moderate tremor</td>
<td></td>
</tr>
<tr>
<td>3 - severe, even with arms not extended</td>
<td></td>
</tr>
<tr>
<td><strong>Paroxysmal sweats</strong></td>
<td></td>
</tr>
<tr>
<td>0 - no sweat visible</td>
<td></td>
</tr>
<tr>
<td>1 - barely perceptible sweating with moist palms</td>
<td></td>
</tr>
<tr>
<td>2 - beads of sweat obvious on forehead</td>
<td></td>
</tr>
<tr>
<td>3 - drenching sweats</td>
<td></td>
</tr>
<tr>
<td><strong>Anxiety</strong></td>
<td></td>
</tr>
<tr>
<td>Do you feel nervous or anxious?</td>
<td></td>
</tr>
<tr>
<td>0 - no anxiety, at ease</td>
<td></td>
</tr>
<tr>
<td>1 - mildly anxious</td>
<td></td>
</tr>
<tr>
<td>2 - moderately anxious</td>
<td></td>
</tr>
<tr>
<td>3 - acute panic state as seen in severe delirium</td>
<td></td>
</tr>
<tr>
<td><strong>Agitation</strong></td>
<td></td>
</tr>
<tr>
<td>0 - normal activity</td>
<td></td>
</tr>
<tr>
<td>1 - somewhat more than normal activity</td>
<td></td>
</tr>
<tr>
<td>2 - moderately fidgety and restless</td>
<td></td>
</tr>
<tr>
<td>3 - pacing back and forth or constantly moving about</td>
<td></td>
</tr>
</tbody>
</table>

**Tactile disturbances**

Have you got any itching, pins and needles, burning or numbness?
Do you feel insects crawling on or under your skin?
0 - none
1 - very mild itching, pins & needles, burning or numbness
2 - mild itching, pins & needles, burning or numbness
3 - moderate itching, pins & needles, burning or numbness
4 - moderately severe hallucinations
5 - severe hallucinations
6 - extremely severe hallucinations
7 - continuous hallucinations

**Auditory disturbances**

Are you more aware of sounds around you? Are they harsh? Do they frighten you?
Are you hearing anything that is disturbing to you?
Are you hearing things that you know are not there?
0 - not present
1 - very mild harshness or ability to frighten
2 - mild harshness or ability to frighten
3 - moderate harshness or ability to frighten
4 - moderately severe hallucinations
5 - severe hallucinations
6 - extremely severe hallucinations
7 - continuous hallucinations

**Visual disturbances**

Does the light appear too bright? Is its colour different? Does it hurt your eyes?
Are you seeing anything that is disturbing to you?
Are you seeing things you know are not there?
0 - not present
1 - very mildly sensitive
2 - mildly sensitive
3 - moderate sensitivity
4 - moderately severe hallucinations
5 - severe hallucinations
6 - extremely severe hallucinations
7 - continuous hallucinations

**Headache or Fullness in Head**

Does your head feel different?
Does it feel like there is a band around your head?
Do not rate for dizziness or light-headedness
0 - not present
1 - very mild
2 - mild
3 - moderate
4 - moderately severe
5 - severe
6 - very severe
7 - extremely severe

**Orientation & Clouding of Consciousness**

What day is it?
Where are you?
Who am I?
0 - oriented and can recite months of year backwards
1 - cannot recite months of year backwards or is uncertain about the date
2 - disoriented for date by no more than 2 calendar days
3 - disoriented for date by more than 2 calendar days
4 - disoriented for place and/or person
CIWA-Ar administered within 30 minutes of admission

Score 11 or more

20mg Diazepam

Score 10 or less

No Medication

Repeat CIWA-Ar after 90 minutes

Score 11 or more

20mg Diazepam

Score 10 or less

No Medication

Score 10 or less on 2 consecutive occasions stop medication

Front-Loading Regime
<table>
<thead>
<tr>
<th>Daily Alcohol Consumption</th>
<th>15-25 units</th>
<th>30-49 units</th>
<th>50-60 units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity of Alcohol Dependence</td>
<td>MODERATE: SADQ 15-25</td>
<td>SEVERE: SADQ 30-40</td>
<td>VERY SEVERE: SADQ &gt;40</td>
</tr>
<tr>
<td>Day 1 (start)</td>
<td>15mg qds</td>
<td>25mg qds</td>
<td>30mg qds</td>
</tr>
<tr>
<td>Day 2</td>
<td>10mg qds</td>
<td>20mg qds</td>
<td>25mg qds</td>
</tr>
<tr>
<td>Day 3</td>
<td>10mg tds</td>
<td>15mg qds</td>
<td>20mg qds</td>
</tr>
<tr>
<td>Day 4</td>
<td>5mg tds</td>
<td>10mg qds</td>
<td>15mg qds</td>
</tr>
<tr>
<td>Day 5</td>
<td>5mg bd</td>
<td>10mg tds</td>
<td>10mg qds</td>
</tr>
<tr>
<td>Day 6</td>
<td>5mg nocte</td>
<td>5mg tds</td>
<td>10mg tds</td>
</tr>
<tr>
<td>Day 7</td>
<td>5mg bd</td>
<td>5mg tds</td>
<td>10mg qds</td>
</tr>
<tr>
<td>Day 8</td>
<td>5mg nocte</td>
<td>5mg bd</td>
<td>10mg tds</td>
</tr>
<tr>
<td>Day 9</td>
<td>5mg nocte</td>
<td>5mg tds</td>
<td>10mg qds</td>
</tr>
<tr>
<td>Day 10</td>
<td></td>
<td>5mg bd</td>
<td>10mg tds</td>
</tr>
<tr>
<td>Day 11</td>
<td></td>
<td>5mg nocte</td>
<td>5mg tds</td>
</tr>
<tr>
<td>Day 12</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Medically Assisted Withdrawal

Associated Problems

ALD

NUTRITION

Seizures

Relapse Prevention + Ongoing Care

DTs

CONFUSION

WKS

ALCOHOL
DELIRIUM TREMENS

- **PREVENTION** is the key:
  - prompt recognition of the risk of alcohol withdrawal
  - treatment with benzodiazepines

- Initial management of severely confused or agitated patient requires adequate **sedative** doses of benzodiazepine (IV/IM if necessary)

- Aim is to make the patient calm and sedated but easily roused

- Able to take oral medication:
  - chlordiazepoxide (up to 50mg every 2 hours may be necessary) or lorazepam

- Unable to take oral medication:
  - IV/IM lorazepam 1-2mg at doses of up to 1-2mg every 30 minutes

- For patients with liver failure:
  - IV/IM lorazepam preferred
DELIRIUM TREMENS

- Severe psychotic symptoms:
  - **haloperidol** 1-5mg 2-3 times per day, although adequate treatment with benzodiazepines should be the priority
  - IM **olanzapine** 5-10mg is an alternative
- Close monitoring of fluid balance is important
- Urea and electrolytes (including magnesium) should be regularly checked
Preventing seizures
  - effective treatment of alcohol withdrawal
Treating a seizure
  - usually self-limiting
  - lorazepam may be best alternative
Preventing recurrent seizures
  - lorazepam superior to placebo
  - phenytoin not effective
TALES FROM THE FRONT LINE...

- 56 year old man
- Admitted with abdominal pain and vomiting blood
- Drinking “a few beers at night”
- Prescribed chlordiazepoxide but on second night becomes agitated and aggressive, attacking other patients
- Security attend but cannot manage the situation
- 2 police officers attend at 04:30 - “restrain” patient
- Psych Liaison attend at 08:15 – tells them to get out of his house, shouting and standing up - police gently but firmly return to chair
- D/W acute consultant - haloperidol 7.5mg IM
- Treat under MCA + hospital DOLS procedure enacted
- Haloperidol has good effect → sleeps for 16 hours and DTs are settled when he comes round
It is **SERIOUS** – prompt action needed
Senior nurse/Medical Registrar/Security/ICU
Sufficient nurses to ensure patient isn’t left alone
May need **RESTRAINT** – capacity / MCA / common law
Consistent, reassuring manner + avoid confrontation

**Oral Lorazepam 2mg** – IV/IM if refused or problem persists
Don’t leave unsupervised + Reassess in 15 mins...
Add **haloperidol 5mg IV/IM** + **Lorazepam 2mg IV/IM**
Don’t leave unsupervised + Reassess in 15 mins...
If symptoms don’t resolve add a further dose of **Haloperidol 5mg**
IV / IM

If physical restraint or IV sedation with >1 dose of lorazepam/haloperidol needed → **ICU involvement**
IV midazolam can be used with experience (eg ICU) + facilities to reverse over sedation (flumazenil)
Resus facilities must be available + assess ICU transfer
Review withdrawal drug regimen once control established.
WERNICKE-KORSAKOFF SYNDROME
WERNICKE’S ENCEPHALOPATHY

- Confusional state with apathy, disorientation & disturbed memory, but drowsiness and stupor are uncommon
- Ocular abnormalities: nystagmus, gaze palsies and ophthalmoplegia
- Ataxia affects the trunk and lower extremities

- May develop acutely or evolve over several days
- Degenerative changes in the structures around 3rd ventricle and aqueduct (mammillary bodies)
KORSAKOFF’S PSYCHOSIS

- **Amnesic state** with impairment of both retrograde and anterograde memory
- Relative preservation of other intellectual abilities
- **Confabulation** may be a feature

- Develops after an acute episode of WE, but some develop a combined syndrome from the outset
- Changes in the dorsomedial thalamus.
**Wernicke’s Encephalopathy**
Not everyone equally at risk

**Thiamine**
- Water-soluble, absorbed by upper intestine
- Daily requirement 1-2mg
- (↑ with alcohol misuse)
- Body stores ~30-50mg
- Depleted intracellular thiamine → cell death
- 30-80% alcohol misusers thiamine deficient

**Hard to diagnose?**
Only 10% present with triad
Diagnosis made in life in 20%

**What happens if you don’t treat it?**
Death in 20% and KP in 75% + 25% with KP require institutionalization

**Treatment**

**What is Wernicke’s Encephalopathy?**
A neurological disorder caused by thiamine deficiency, often associated with alcohol misuse.

**Prophylaxis**
for at risk cases?

**Parenteral or oral?**
Oral route gets less effective as alcohol misuse increases

**Other issues:**
- Anaphylaxis
- Compliance
- Hypoglycaemia and glucose administration
- Other vitamins / minerals B2, B6, Mg

**Other alcohol-related brain damage**

**How long for?**

**Biochemical tests**
Indirect methods – ETKA, TPP effect – influenced by factors other than thiamine deficiency
HPLC of erythrocyte TPP levels

**Diet has a crucial role**
- dietary screening questionnaires e.g. Thiamine Deficiency Questionnaire (TDQ)

**No studies tell us which patients are at risk of developing WE**

**Often looks like alcohol intoxication**
Caine operational criteria (1997)
Known or suspected alcohol use disorder

Classical triad of WE signs (acute confusion, ataxia and ophthalmoplegia) only occurs in 10%

High index of suspicion is needed

ONE of the following signs should be sufficient to assign a diagnosis and commence treatment:

- Acute confusion
- Decreased level of consciousness including coma
- Memory disturbance
- Ataxia/unsteadiness
- Ophthalmoplegia
- Nystagmus
- Unexplained hypotension with hypothermia

Risk factors for Wernicke’s Encephalopathy?

- Intercurrent illness
- DTs/treatment for DTs
- Alcohol related seizures/treatment for alcohol related seizures
- IV glucose administration
- Significant weight loss
- Poor diet
- Signs of malnutrition
- Recent diarrhoea or vomiting
- Drinking >20 units/day
- Peripheral neuropathy

WERNICKE’S ENCEPHALOPATHY

Start Pabrinex IVHP

2 amp pairs tds for 2-3 days, then

1 amp pair daily until improvement in clinical condition stops (usually 3-5 days)

Pabrinex not indicated: oral thiamine supplementation if indicated by dietary insufficiency

Start Pabrinex IVHP

1 amp pair daily for 3-5 days

Convert to oral Thiamine 50mg bd for 1 month or until adequate diet is restored
Staff may not consider anything beyond intoxication...

Acute hospital staff do not have the long view...

Capacity may be lost temporarily or more permanently in the case of severe cerebral atrophy or WKS

It is hard to detain patients against their will in general hospital

Patients who are confabulating often fool the professional with answers that sound rational and orientated

Social care staff in the hospital are stretched and do not get to see patients in time before they are discharged/discharge themselves
OPIATES
Social use

Problem use

Dependent use

Detoxification

Relapse prevention

Harm Reduction

Maintenance

Withdrawal from maintenance
METHADONE

- ‘Dole & Nyswander’
  - high doses reduce craving for heroin and block the euphoric effects of injected heroin

- Synthetic opioid ideally suited to maintenance treatment due to 3 properties:
  - As effective orally as parenterally
  - Long-acting (half-life of a single dose is 12-18 hours, but on repeated dosing is 24-48 hours)
  - Relatively non-euphoriant
METHADONE STABILISATION
BUPRENORPHINE

- A mixed agonist-antagonist at opioid receptors:
  - partial agonist at *mu* receptor - low intrinsic activity & high affinity
  - an antagonist at the *kappa* opioid receptor

- Partial agonistic activity (+ low intrinsic activity)
  \[\rightarrow\] less euphoric, less sedating and less likely to cause respiratory depression than full agonists

- High affinity for *mu* receptors
  \[\rightarrow\] prevents other opioids from occupying these receptors & reduces impact of other opioids
Full Agonists: Heroin, morphine, methadone, codeine

Partial Agonists: Buprenorphine

Antagonists: Naltrexone, naloxone

Threshold for respiratory depression

Size of Opiate Agonist Effect

Drug Dose
“On the basis of the evidence, both methadone and buprenorphine in flexible dosing regimens are clinically effective and cost effective, compared to no treatment, for maintenance therapy in the management of opioid dependence”
MEDICALLY ASSISTED WITHDRAWAL

- Short term intervention that aims to:
  - Alleviate withdrawal discomfort
  - Prevent complications of withdrawal
    - Unstable medical / psychiatric problems overdose
    - Social crises
  - Facilitate engagement in post-withdrawal treatments
- Withdrawal is not a ‘cure’ - most patients relapse unless they engage in ongoing treatment
MEDICALLY ASSISTED WITHDRAWAL

- **Symptomatic Medication**
  - **Diazepam** 2-5mg tds - ↓ muscle cramps, anxiety and cravings
  - **Nitrazepam** 5-10mg nocte - helps sleep
  - **Ibuprofen** 400mg tds - ↓ muscular & joint pain
  - **Buscopan** 20mg qds - ↓ gut spasm
  - **Lomotil** 5mg qds - ↓ diarrhoea

- **Methadone reduction**
  - **Out-patient** - slow reduction over a number of weeks
  - Gradual taper at no more than 5% of initial dose/week
  - **In-patient** - 10-day or 21-day reduction
## MEDICALLY ASSISTED WITHDRAWAL

BUPRENORPHINE (from heroin)

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8mg</td>
<td>16mg</td>
<td>12mg</td>
<td>10mg</td>
<td>8mg</td>
</tr>
<tr>
<td><strong>Day 6</strong></td>
<td><strong>Day 7</strong></td>
<td><strong>Day 8</strong></td>
<td><strong>Day 9</strong></td>
<td><strong>Day 10</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6mg</td>
<td>4mg</td>
<td>2mg</td>
<td>0.8mg</td>
<td>0.4mg</td>
</tr>
</tbody>
</table>
MEDICALLY ASSISTED WITHDRAWAL
BUPRENOPHINE

<table>
<thead>
<tr>
<th>Dose of Buprenorphine</th>
<th>Reduction rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 16mg</td>
<td>4mg per week/fortnight</td>
</tr>
<tr>
<td>8 – 16mg</td>
<td>2-4mg per week/fortnight</td>
</tr>
<tr>
<td>&lt; 8mg</td>
<td>2mg per week/fortnight</td>
</tr>
</tbody>
</table>
MEDICALLY ASSISTED WITHDRAWAL

- Lofexidine
  - α-2 adrenergic agonist
- Build up dose of Lofexidine over 3 days to 0.4mg four times per day +/- ‘prn’ medication
- Stop heroin/methadone (blind)
- Maintain Lofexidine for 5-10 days
- + symptomatic medication
- +/- Naloxone challenge & regular Naltrexone
<table>
<thead>
<tr>
<th>Method</th>
<th>Heroin use &amp; retention</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detoxification</td>
<td>5 – 10% long term abstinence</td>
<td>?Increase / no change</td>
</tr>
<tr>
<td>Methadone Maintenance</td>
<td>75% retention @1 yr 50% no heroin use @ 1yr</td>
<td>3 – 4 fold reduction</td>
</tr>
<tr>
<td>Residential rehab</td>
<td>Few remain in Rx unless legal / external pressure</td>
<td>?Increase on discharge</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>10 – 20% retention 6/12 Most ‘drop outs’ relapse</td>
<td>?Increase / no change</td>
</tr>
</tbody>
</table>
QTC INTERVAL PROLONGATION

23% MTD vs 0% BP showed increase QTc (>470 ms)
Randomized trial  MTD vs BP vs levomethadyl

15% MTD vs 0% BP showed increase QTc (>470 ms)
Max mortality from prolonged QTc = 0.06 per 100 pt years
Prevalence study
Social use

Problem use

Dependent use

Detoxification

Maintenance

Relapse prevention

Withdrawal from maintenance

Harm Reduction
Deaths related to drug poisoning in England and Wales, 2014 registrations

• 3,346 drug poisoning deaths registered, the highest since comparable records began in 1993
• Of these, 2,248 (or 67%) were drug misuse deaths involving illegal drugs
• The mortality rate from drug misuse was the highest ever recorded at 39.9 deaths per million population
• Deaths involving heroin and/or morphine increased by almost two-thirds between 2012 and 2014, from 579 to 952 deaths
• People aged 40-49 had the highest mortality rate from drug misuse (88.4 deaths/million population)
Drug use prevalence and drug-related deaths: England & Wales 2011/12 (ONS)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Prevalence in general population (use in last year, age 16-59)</th>
<th>Number of deaths in 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannabis</td>
<td>6.9%</td>
<td>7</td>
</tr>
<tr>
<td>Cocaine</td>
<td>2.2%</td>
<td>112</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>0.8%</td>
<td>62</td>
</tr>
<tr>
<td>Ecstasy</td>
<td>1.4%</td>
<td>13</td>
</tr>
<tr>
<td>Opiates (including heroin &amp; methadone)</td>
<td>0.3%</td>
<td>1,082</td>
</tr>
</tbody>
</table>
Oxygen saturation: case study

Male, age 49
Intravenous diamorphine (6 years)
This dose = 120 mg
Daily dose = 400 mg
Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK General Practice Research Database

Rosie Cornish, statistician,¹ John Macleod, professor in clinical epidemiology and primary care,¹ John Strang, professor in the psychiatry of the addictions,² Peter Vickerman, senior lecturer in mathematical modelling,¹,³ Matt Hickman, professor in public health and epidemiology¹
Risk of death during and after treatment

Cornish et al, *BMJ* 2010; 341: c5475
Meta-analysis of drug-related deaths soon after release from prison

Elizabeth L. C. Merrall¹, Azar Kariminia², Ingrid A. Binswanger³,⁸, Michael S. Hobbs⁴, Michael Farrell⁵, John Marsden⁵, Sharon J. Hutchinson⁶,⁷ & Sheila M. Bird¹,⁷
a) In weeks 1-2 versus weeks 3-12

<table>
<thead>
<tr>
<th>Country</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UK</strong></td>
<td></td>
</tr>
<tr>
<td>Scotland</td>
<td>7.4 (4.6, 12.0)</td>
</tr>
<tr>
<td>England &amp; Wales</td>
<td>7.5 (5.4, 10.5)</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0% (0.0-99.8%), $P = 0.958$)</td>
<td>7.5 (5.7, 9.9)</td>
</tr>
<tr>
<td><strong>Australia</strong></td>
<td></td>
</tr>
<tr>
<td>Western Australia</td>
<td>4.4 (2.0, 9.5)</td>
</tr>
<tr>
<td>New South Wales</td>
<td>4.0 (3.3, 4.8)</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0% (0.0-99.6%), $P = 0.838$)</td>
<td>4.0 (3.4, 4.8)</td>
</tr>
<tr>
<td><strong>USA</strong></td>
<td></td>
</tr>
<tr>
<td>Washington State</td>
<td>8.4 (5.0, 14.2)</td>
</tr>
<tr>
<td>New Mexico State</td>
<td>3.1 (1.3, 7.1)</td>
</tr>
<tr>
<td>Subtotal (I-squared = 74.8% (0.0-94.3%), $P = 0.046$)</td>
<td>8.4 (5.0, 14.2)</td>
</tr>
</tbody>
</table>
## Witnessed Overdose

<table>
<thead>
<tr>
<th></th>
<th>Treatment sample (n=142)</th>
<th>Community sample (n=312)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Witnessing overdoses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever witnessed overdose?</td>
<td>44/48* (92%)</td>
<td>167/ 312 (52%)</td>
</tr>
<tr>
<td>Witnessed O/D in last year?</td>
<td>13/48 (27%)</td>
<td>81/312 (26%)</td>
</tr>
<tr>
<td>last overdose witnessed...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-involved opiates</td>
<td>44/44 (100%)</td>
<td>153/159*(96%)</td>
</tr>
<tr>
<td>-O/D by sexual partner</td>
<td></td>
<td></td>
</tr>
<tr>
<td>close friend</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>casual acq.</td>
<td>32</td>
<td>84</td>
</tr>
<tr>
<td>stranger</td>
<td>1</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>10</td>
</tr>
</tbody>
</table>

* data collected from only 48 cases
* data missing on 8 cases

(Strang, Powis, Best, Vingoe, Griffiths, Taylor, Welch and Gossop, Addiction 1999)
Take-Home Naloxone
Community management of opioid overdose
1. Call 999 and ask for an ambulance

2. Give basic life support – 30 chest compressions and 2 rescue breaths if possible

3. Give 400 micrograms of Naloxone injection into outer thigh or upper arm muscle

4. Give 3 cycles of 30 chest compressions + 2 rescue breaths if possible

5. Repeat steps 3 and 4 until the ambulance arrives or the patient is breathing normally
Overdose training and take-home naloxone for opiate users: prospective cohort study of impact on knowledge and attitudes and subsequent management of overdoses

John Strang, Victoria Manning, Soraya Mayet, David Best, Emily Titherington, Laura Santana, Elizabeth Offor & Claudia Semmler
Training family members to manage heroin overdose and administer naloxone: randomized trial of effects on knowledge and attitudes

Anna V. Williams, John Marsden & John Strang
Addictions Department, Institute of Psychiatry, King’s College London, London, UK

Changes in Knowledge and Attitudes total score: between groups and across time
ONGOING ISSUES

• Route – intramuscular or intranasal?

• Dose – NHS England guidance

• Legal – October 2015 legal change

• ‘Opt-in’ or maybe ‘opt-out’?
OTHER DRUGS
<table>
<thead>
<tr>
<th><strong>STIMULANT DRUGS</strong> [stimulant/euphoric effect]</th>
<th><strong>OPIATES/OPIOIDS</strong> [sedative, pain relief, relaxation]</th>
<th><strong>BENZODIAZEPINES</strong> [anxiolytic, hypnotic, relaxation]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine</td>
<td>Heroin</td>
<td>Valium (Diazepam)</td>
</tr>
<tr>
<td>Methylamphetamine</td>
<td>Opium</td>
<td>Mogadon (Nitrazepam)</td>
</tr>
<tr>
<td>Ecstasy (MDMA)</td>
<td>Codeine</td>
<td>Temazepam</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Dihydrocodeine</td>
<td>Ativan (Lorazepam)</td>
</tr>
<tr>
<td>Crack cocaine</td>
<td>Methadone</td>
<td>Librium (Chlordiazepoxide)</td>
</tr>
<tr>
<td>Mephedrone</td>
<td>Buprenorphine (Subutex)</td>
<td></td>
</tr>
<tr>
<td>Naphyrone (NRG-1)</td>
<td>Tramadol</td>
<td></td>
</tr>
<tr>
<td>Benzylpiperazine (BZP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desoxypipradrol (‘Ivory Wave’)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDAI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dimethocaine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>BENZODIAZEPINES</strong> [anxiolytic, hypnotic, relaxation]</th>
<th><strong>CANNABINOIDS</strong> [relaxation, euphoria]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valium (Diazepam)</td>
<td>Cannabis (Skunk, weed, resin, marijuana)</td>
</tr>
<tr>
<td>Mogadon (Nitrazepam)</td>
<td>Synthetic cannabinoids (‘Spice’)</td>
</tr>
<tr>
<td>Temazepam</td>
<td>Black Mamba</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>LSD-LIKE DRUGS</strong> [hallucinogenic]</th>
<th><strong>PHENCYCLIDINE (PCP) &amp; KETAMINE-LIKE AGENTS</strong> [hallucinatory, altered thinking, mild euphoria, calm detachment]</th>
<th><strong>OTHERS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>LSD (lyseric acid diethylamide)</td>
<td>Phencyclidine</td>
<td>Nitrous oxide</td>
</tr>
<tr>
<td>Psilocin (Magic mushrooms)</td>
<td>Ketamine</td>
<td>Solvents</td>
</tr>
<tr>
<td>Alpha-methyltryptamine (AMT)</td>
<td>Methoxetamine</td>
<td>Alkyl Nitrites (‘Poppers’)</td>
</tr>
<tr>
<td>5-methoxydiallyltryptamine (5-MeO-DALT)</td>
<td>3-methoxy-PCP</td>
<td>GHB/GBL</td>
</tr>
<tr>
<td>Bromo-Dragonfly</td>
<td>4-methoxy-PCP</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 1: Number of new psychoactive substances notified for the first time to the Early Warning System since May 2005, Europe
• Rapidly changing profile
• Harms still poorly understood
• Evidence base limited

http://neptune-clinical-guidance.co.uk/
DEPRESSANTS
- GHB/GBL
- Ketamine and analogues (e.g., methoxetamine)
- Nitrous oxide

STIMULANTS
- Cocaine powder (Acute toxicity only)
- Benzofurans
- Amphetamine-type Substances
- Piperazines; Pipradrols (2-DPMP D2PM)
- Methamphetamine
- MDMA and similar empathogens (e.g., MDEA, PMA, PMMA)
- Synthetic cathinones (e.g., mephedrone)

HALLUCINOGENS
- Agonist at serotonin 5HT2A receptors

SYNTHETIC CANNABINOIDS
- ‘Spice’
- ‘Black mamba’
GAMMA BUTARYL LACTONE (GBL)
GAMMA-HYDROXY BUTYRIC ACID (GHB)

Blue verve, Liquid E, Liquid Ecstasy

Colourless, odourless liquid, mild salty taste

DOSE & ROUTE OF USE:
Usually diluted in a drink
20 - 50mls daily in divided doses
Onset 10-20 mins – effects last up to 4 hrs

Not detected on routine drug screens
GBL detected as GHB in urine samples up to 8-10 hours

GHB structure similar to neurotransmitter gamma–aminobutyric acid (GABA)

Acts on GABA-A & GABA-B receptors - major effect = GABA-B agonist

Alcohol/opiate detox, anti-craving medication, anaesthetic, narcolepsy

DESIRED EFFECTS:
‘Club drug’ – euphoric without hangover

Euphoria
Relaxation - sedation
Increased sociability
Increased libido
Sexual disinhibition

MORTALITY:
Acute toxicity + severe withdrawal syndrome
Deaths in England & Wales


Narrow dosage range
OD usually due to large concentrations over short period, or + other CNS depressants
GAMMA BUTARYL LACTONE (GBL)
GAMMA-HYDROXY BUTYRIC ACID (GHB)

Blue verve, Liquid E, Liquid Ecstasy

Colourless, odourless liquid, mild salty taste

ACUTE HARMs:

- Rapid signs of intoxication and rapid improvement
- A euphoric dose for one person is a sedative dose for another
- Tolerance is not protective of OD

Nausea & vomiting, diarrhoea, drowsiness, headache, ataxia, dizziness, confusion, amnesia, urinary incontinence, tremor, myoclonus, hypotonia, agitation, hypothermia

Coma, convulsions, bradycardia, ECG abnormalities (U waves), hypotension, Cheyne-Stokes respiration, respiratory depression & arrest

Hypernatraemia, hypokalaemia, hyperglycaemia & metabolic acidosis

CLINICAL MANAGEMENT:

- No rapid urine or serum tests
- Similar to alcohol/opiate/BZ intoxication
- Worth trying naloxone

- Symptom-directed supportive care – emphasis on respiratory support
- Protect airway during short period of reduced consciousness (vomiting)
- Intubation not usually necessary
GBL WITHDRAWAL

- Similar to alcohol and benzodiazepine withdrawal
- 1-6 hours last dose – anxiety, insomnia, tremor, episodes tachycardia
- Untreated within 24 hours – confusion, delirium, psychosis, agitation
- Acute symptoms untreated may be prolonged > 2 weeks duration
- Post withdrawal symptoms persistent – anxiety, depression, insomnia x months
## SAMPLE DETOXIFICATION SCHEDULE

<table>
<thead>
<tr>
<th></th>
<th>CHLORDIAZEOPOXIDE</th>
<th></th>
<th>BACLOFEN</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose</td>
<td>Total dose</td>
<td>Dose</td>
<td>Total dose</td>
</tr>
<tr>
<td>Day 1</td>
<td>40mg 2hrly</td>
<td>480mg</td>
<td>20mg 3x/day</td>
<td>60mg</td>
</tr>
<tr>
<td>Day 2</td>
<td>30mg 2hrly</td>
<td>360mg</td>
<td>20mg 5x/day</td>
<td>100mg</td>
</tr>
<tr>
<td>Day 3</td>
<td>40mg 4hrly</td>
<td>240mg</td>
<td>20mg 5x/day</td>
<td>100mg</td>
</tr>
<tr>
<td>Day 4</td>
<td>30mg 4hrly</td>
<td>180mg</td>
<td>20mg 5x/day</td>
<td>100mg</td>
</tr>
<tr>
<td>Day 5</td>
<td>20mg 4hrly</td>
<td>120mg</td>
<td>20mg 3x/day</td>
<td>60mg</td>
</tr>
<tr>
<td>Day 6</td>
<td>10mg 4hrly</td>
<td>60mg</td>
<td>20mg 3x/day</td>
<td>60mg</td>
</tr>
</tbody>
</table>

C/o Dr Siobhan Morris, Royal Edinburgh Hospital
KETAMINE

K, Ket, Special K, Kit-Kat, Super K, Vitamin K


Powder form – typically sold in gram doses

DOSE & ROUTE OF USE:
Used intranasally – doses = ‘bumps’, ‘keying’

Onset 5-10 mins
Effects short-lived (1-4 hours)
Typical recreational dose is 10-25% effective anaesthetic dose

Predominantly sedative... but also dissociative, anaesthetic, psychostimulant and analgesic

Non-competitive antagonist at NMDA glutamate receptors
D2 + 5HT2A actions

Anaesthetic & powerful analgesic

DESIRED EFFECTS:
Associated with clubbing/chill-out – mind-altering
+ no hangover + short duration + cheap

‘Dissociative drug’ – distorts perceptions of sights and sounds
Feelings of detachment from the self/environment – the ‘k-hole’

MORTALITY:
Fatalities rare – only after high IV doses
23 deaths in UK 1993-2006 where ketamine mentioned (4 as sole drug)
KETAMINE

K, Ket, Special K, Kit-Kat, Super K, Vitamin K

Powder form – typically sold in gram doses

ACUTE HARMS:

- Nausea
- Slurred speech & Dizziness
- Collapse
- Impaired consciousness
- Agitation
- High blood pressure
- Tachycardia
- Visual hallucinations
- Abdominal pain
- Lower urinary tract symptoms

Reduced awareness of risk + lack of coordination + temporary paralysis + inability to speak = risk of injuries

CLINICAL MANAGEMENT:

- No easy rapid urine test
- (Young) people with agitation + tachycardia + visual hallucinations or nystagmus

- Symptom-directed supportive care
- Symptoms are rapid and short-lived

CHRONIC USE
Ketamine-induced damage to urinary tract
Direct toxicity
Small, very painful bladder, dysuria, painful haematuria, urge incontinence, nocturia in 20-30% users
**SYNTHETIC CANNABINOIDS**

*Amsterdam Gold, Black Mamba, Spice, Annihilation*

Dried vegetable matter to which drug has been added

---

**DOSE & ROUTE OF USE:**

- Smoked in joints or inhaled through a bong (Ingested/snorted)
- Onset 10 mins
-Effects last 1-8 hours
-Sachets contain 0.5-3g finely ground plant material [wide variation in potency]

---

**INITIALLY SYNTHESISED FOR BIOMEDICAL RESEARCH**

- Large structural heterogeneity – wide range of potency

Bind to **CB1 and CB2 receptors**, but with high affinity and with a stronger effect than cannabis

---

**DESIRED EFFECTS:**

- Similar to cannabis intoxication
  - Relaxation
  - Euphoria
  - Feeling energised
  - Disinhibition
  - Altered consciousness

---

**MORTALITY:**

- **Increasing prevalence** – quasi-legal, readily available, and cheap

A number of deaths reported
- 3 completed suicides following SC intake

---
SYNTHETIC CANNABINOIDs

*Amsterdam Gold, Black Mamba, Spice, Annihilation*

Dried vegetable matter to which drug has been added

**ACUTE EFFECTS:**

- Effects greater in the drug naïve

  **Sympathomimetic effects** – seizures, tachycardia, hypertension, sweating, hyperthermia
  Convulsions
  Paralysis
  **Psychosis**
  Aggression and combativeness
  Bizarre behaviour

**CLINICAL MANAGEMENT:**

- No positive test on routine urine screening for THC metabolites
- Symptoms may be self-limiting and resolve spontaneously
- Symptom-directed supportive care
- **Hydration & monitoring**
- Medication for
  - Agitation or convulsions - BZ
  - Psychosis - antipsyhotics