Lothian drug trends relative to Scotland drug-related deaths

Scottish Drug Forum Conference
10th October 2018

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Royal Infirmary of Edinburgh
Scotland leads Europe in Drug-Related deaths.

2016 had a 23% increase over 2015. 2017 had an 8% increase over 2016.

There were regional differences in 2016 with:
- Ayrshire +99%
- Forth Valley +61%
- Lanarkshire +55%
- Lothian +28%
- Glasgow/Clyde +16%

2017:
- Tayside +52%
- Fife +47%
- Grampian +25%
- Glasgow/Clyde +9%
- Lothian +8%

Ref: Drug-related deaths Scotland in 2016/2017: National statistics for Scotland
Gabapentinoids (opioid boosters) were implicated in 26% of DRDs in 2016.

Gabapentin increased by 51% in 2016 but decreased in 2017. Pregabalin increased by 69% in 2016 and a further 70% in 2017.

Street benzodiazepines increased from 63 cases in 2015 to 294 in 2016 and 446 in 2017.

Etizolam and Diclazepam were the main findings in 2016. Etizolam and Alprazolam were the main findings in 2017.

Correlates with increased DRD in Ayrshire, Lanarkshire and Glasgow / Clyde in 2016, and the East of Scotland in 2017.
What is killing drug users in Scotland?

- Opiates/methadone are implicated in most DRD, but poly drug use is likely to be a major contributing factor.
- Heroin implicated in 55% of DRD in 2016 falling to 50% in 2017.
- Methadone implicated in 42% of DRD in 2016 increasing to 47% in 2017.
- Gabapentinoids implicated in 26% of DRD in 2016 increasing to 28% in 2017. Switch from gabapentin to more potent pregabalin in 2017.
- Benzodiazepines implicated in 59% of DRD in 2017 with large increase in more potent street benzodiazepines but with regional variations.
- Etizolam and Xanax implicated in 43% of DRD in 2017.
- Trend of increase in cocaine: implicated in 14.2% DRD in 2016 and 18.9% in 2017.
Cost effective: £12 per sample

24 drugs analysed to confirmation standards on every sample:

- Opiates: morphine, codeine, 6MAM, DHC, Oxycodone
- Methadone, buprenorphine, tramadol
- Amphetamine, MDMA, Methamphetamine
- Cocaine + benzoyl eegonine
- Gabapentin + Pregabalin
- Benzos: Diazepam Nordiazepam temazepam oxazepam nitrazepam
- Street benzo: etizolam, diclazepam, delorazepam, alprazolam.

No false positive and more sensitive than immunoassay.
Liquid Chromatography - Tandem Mass Spectrometer Detector
TANDEM MS Detector
Lothian have an established, cost effective Tandem MS method for drugs of abuse

- Lothian service covers both urine and oral fluid.
- 50µL sample  6 min. per sample
- ISO 15189 accredited proven method
- >40,000 urine; >40,000 oral fluid to date
- Electronic ordering and reporting
- Cannabis only available in urine by immunoassay screening
Oral fluid chromatogram analysed on Waters Xevo Tandem MS in 5.2 minutes

Urine also includes EDDP, Norbuprenorphine and 7-amino-clonazepam

Chromatogram of 24 drugs:
- Morphine
- Codeine
- Dihydrocodeine
- Gabapentin
- Pregabalin
- Amphetamine
- Methamphetamine
- MDMA
- Oxycodone
- 6 mono-acetyl morphine
- Oxycodone
- Pregabalin
- Gabapentin
- Codeine
- Dihydrocodeine
- Morphine
- Diclazepam
- Diazepam
- Delorazepam
- Temazepam
- Nordiazepam
- Etizolam
- Alprazolam
- Methadone
- Oxazepam
- Nitrazepam
- Buprenorphine
- Cocaine
- Tramadol
- Benzoyl ecgonine
- MDMA
- Methamphetamine
- Amphetamine
- Oxycodone
- Pregabalin
- Gabapentin
- Codeine
- Dihydrocodeine
- Morphine
Drug identification:
1) Retention times match Internal Standard
2) Peaks are same shape.
3) Ratio of quantifying : qualifying match calibrators.

Calibration curve

- Compound name: Nordiazepam
- Correlation coefficient: $r = 0.999453$, $r^2 = 0.998906$
- Calibration curve: $0.00434045 \times x - 0.0162782$
- Response type: Internal Std (Ref 45), Area $\times (IS\ Conc. / IS\ Area)$
- Curve type: Linear, Origin: Exclude, Weighting: 1/x, Axis trans: None

Calibrators
- 5µg/L
- 10µg/L
- 30µg/L
- 100µg/L
- 300µg/L
- 1000µg/L

Quality Control
- 10µg/L
- 20µg/L
- 50µg/L
- 100µg/L
- 300µg/L
- 400µg/L
<table>
<thead>
<tr>
<th>Drug</th>
<th>DRUID</th>
<th>EWDTs screen</th>
<th>EWDTs confirmation</th>
<th>RIE</th>
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<tr>
<td>Morphine</td>
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<td>Codeine</td>
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<td>6MAM</td>
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<td>MDMA</td>
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<td>Cocaine</td>
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<td>EDDP</td>
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<td>Gabapentin/Pregab</td>
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<td></td>
<td>40</td>
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<tr>
<td>Tramadol</td>
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<td>Buprenorphine</td>
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<td>Norbuprenorphine</td>
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## Drug thresholds and duration of detectability

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<tr>
<th>Drug</th>
<th>Threshold urine µg/L</th>
<th>Threshold Oral fl µg/L</th>
<th>Duration of detectability</th>
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<tbody>
<tr>
<td>Amphetamine MDMA Methamphetamine</td>
<td>300</td>
<td>30</td>
<td>48 hrs urine 24 hrs oral fluid</td>
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<tr>
<td>Diazepam Nordiazepam Other Benzodiazepines</td>
<td>5</td>
<td>1</td>
<td>long-acting 7+ day urine &lt;7 days Oral fluid</td>
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<tr>
<td>Cannabinoids</td>
<td>50</td>
<td>N/A</td>
<td>2-28 days urine – varies with usage</td>
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<tr>
<td>Cocaine metabolite Cocaine</td>
<td>300</td>
<td>10</td>
<td>48-72 hrs urine 1-5 days oral fluid</td>
</tr>
<tr>
<td>Methadone EDDP</td>
<td>300</td>
<td>20</td>
<td>7 days urine &lt;7 days Oral fluid</td>
</tr>
<tr>
<td>Opiates 6-MAM</td>
<td>50</td>
<td>20</td>
<td>48 hrs urine 1-5 days oral fluid</td>
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<tr>
<td>Buprenorphine Norbuprenorphine</td>
<td>N/A</td>
<td>1</td>
<td>&lt;12-48 hrs Oral fluid 4-6 days urine</td>
</tr>
<tr>
<td>Gabapentinoids Tramadol</td>
<td>300</td>
<td>40</td>
<td>48 hrs urine &lt;48 hrs Oral fluid</td>
</tr>
</tbody>
</table>
Heroin (Diacetyl Morphine + Acetyl Codeine)
- metabolised too quickly to detect in urine

6-MonoAcetyl Morphine 327.4

Morphine 285.3

Codeine 299.4

Hydrocodone 299.4

Dihydrocodeine 301.4

Conjugates

Conjugates
Benzodiazepine metabolism

Chlordiazepoxide (librium) $T_1/2$ 6-28 h

Diazepam (valium) $T_1/2$ 20-70 h

Nitrazepam $T_1/2$ 20-30 h
Clonazepam $T_1/2$ 18-50 h
Flunitrazepam $T_1/2$ 10-40 h

Nordiazepam $T_1/2$ 39-96 h

Oxazepam* $T_1/2$ 5-15 h

Temazepam* $T_1/2$ 8-20 h

Conjugation

Urinary Excretion

7-Amino metabolites

Active drug
Drugs implicated in Drug-related deaths in Lothian 2015-2017

- DRD continue to increase
- Heroin peaked in 2016
- Methadone increase
- Cocaine increase
- Benzos increase
- Diazepam increase
- Street benzos increase
Heroin: 48.9% - 32.4% = 34% drop
Cocaine: 15.7%-33.3% = 112% increase
Methadone and buprenorphine in oral fluid % positive

![Bar chart showing methadone and buprenorphine positivity over time from January 2016 to May 2018.](chart.png)
Gabapentin/pregabalin consistently present in 20-25% of all samples – almost always with opioid: 92% of these take methadone or buprenorphine. Pregabalin increasing, gabapentin falling.

A survey of substance misusers in Lothian in 2012: 22% admitted abusing gabapentinoids to potentiate the high obtained from methadone and to increase the level of intoxication.

Ref: Baird CRW, Fox P, Colvin LA. Gabapentinoid abuse in order to potentiate the effects of methadone: a survey among substance misusers. Eur Addict Res; 2014; 20:115-118
Lothian trend in benzodiazepines:
Diazepam; nordiazepam; temazepam; oxazepam and nitrazepam

Lothian trend in street benzos:
March - Sept 2018
Diclazepam 22/10925 = 0.20%
Delorazepam 28/10925 = 0.26%

Glasgow urine samples for amphetamine confirmations:
April – Sept 2018

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Etizolam</th>
<th>Diclazepam</th>
<th>Delorazepam</th>
<th>Alprazolam</th>
<th>Total</th>
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<tr>
<td>Total</td>
<td>146</td>
<td>51</td>
<td>2</td>
<td>8</td>
<td>0</td>
<td>61</td>
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<tr>
<td></td>
<td></td>
<td>34.9%</td>
<td>1.40%</td>
<td>5.50%</td>
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<td>41.80%</td>
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</table>
**Novel “street” Benzodiazepines properties**

**Etizolam** (thienotrizolodiazepine):
- is rapidly absorbed and levels peak in 1-2 hours.
- Half-life is around 3-4 hours with duration of detectability around 48 hrs
- 10 times more potent than diazepam.

**Diclazepam**:
- metabolises to delorazepam and then to lorazepam.
- is a longer acting benzo with a half life 42 hours and duration of detectability 7 days.

**Delorazepam**:
- also an active metabolite of diclazepam, metabolised to lorazepam
- is rapidly absorbed and peak levels within 1-2 hours.
- half life of 80-115 hours and duration of detectability is around 7 days.
- like diclazepam is 10 times more potent than diazepam.

**Alprazolam** (Xanax):
- Rarely prescribed in the UK – almost always due to street Xanax.
- Short-acting: rapidly absorbed and levels peak 1-2 hours the dose.
- Half-life is 6-27 hours and duration of detectability is 2-3 days.
- is around 6 times more potent than diazepam.
Dihydrocodeine / codeine / oxycodone / tramadol in oral fluid % positive
Methamphetamine – 1 positive in 40,000 samples over 3 years
Present in 14 samples (>30µg/L) as contaminant of street amphetamine
### Possible candidates for inclusion in drugs of abuse panel

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<td><strong>Anti-depressants</strong></td>
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<td>Amitriptyline</td>
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<td>Lorazepam</td>
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<td>6</td>
<td>11</td>
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<td><strong>Other drugs</strong></td>
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<td>Fentanyl</td>
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<td>6</td>
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<tr>
<td>Zopiclone</td>
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<td>9</td>
<td>15</td>
<td>9</td>
<td>20</td>
<td>22</td>
<td>29</td>
<td>82%</td>
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</table>
Current service in rest of Scotland

- Other HB offer only urine testing by immunoassay
- Confirmation testing by Gas Chromatography Mass Spectrometry: slow, labour intensive and expensive – not available for benzos
- Oral fluid by commercial company using immunoassay - unconfirmed drug results.
- Identification of gabapentinoids or street benzodiazepines not available
Business case for NHS oral fluid service by tandem MS for Scotland

- Outline business case approved by Diagnostic Steering Group – to proceed to full business case
- National v Regional options
- Reduce costs?
- Improve service
- Need for accurate workload
- Clinical Buy-in?
### Predicted drug workload - Scotland

<table>
<thead>
<tr>
<th>Health Board</th>
<th>Population</th>
<th>Drug users</th>
<th>OF tests predicted</th>
<th>Urine</th>
<th>Total</th>
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<tbody>
<tr>
<td>Scotland</td>
<td>5,348,600</td>
<td>61,500 (100%)</td>
<td>110,000</td>
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<tr>
<td>Grampian</td>
<td>584,220</td>
<td>4,600 (7%)</td>
<td>8,300</td>
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<tr>
<td>Highland</td>
<td>320,730</td>
<td>2,000 (3%)</td>
<td>3,600</td>
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<td>Orkney</td>
<td>21,580</td>
<td>30</td>
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<td>23,220</td>
<td>340</td>
<td>600</td>
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<tr>
<td>Tayside</td>
<td>413,800</td>
<td>4,600 (7%)</td>
<td>8,300</td>
<td>??</td>
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<tr>
<td>Western Isles</td>
<td>27,250</td>
<td>110</td>
<td>200</td>
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<td>200</td>
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<tr>
<td><strong>NORTH</strong></td>
<td><strong>1,390,800 (25%)</strong></td>
<td><strong>11,680 (19%)</strong></td>
<td><strong>21,050 (90/day)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Borders</td>
<td>114,000</td>
<td>710 (1%)</td>
<td>1,300</td>
<td>800</td>
<td>2,100</td>
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<tr>
<td>Fife</td>
<td>367,250</td>
<td>2,900 (5%)</td>
<td>5,200</td>
<td>2,900</td>
<td>8,100</td>
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<tr>
<td>Lothian</td>
<td>858,120</td>
<td>9,800 (16%)</td>
<td><strong>17,500 (1.8 tests/yr/user)</strong></td>
<td>4,500</td>
<td>22,000</td>
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<tr>
<td><strong>EAST</strong></td>
<td><strong>1,339,370 (25%)</strong></td>
<td><strong>13,410 (22%)</strong></td>
<td><strong>24,000 (100/day)</strong></td>
<td><strong>8,200</strong></td>
<td><strong>32,200</strong></td>
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<tr>
<td>Ayrshire &amp; Arran</td>
<td>371,140</td>
<td>4,100 (7%)</td>
<td>7,400</td>
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<tr>
<td>Dumfries &amp; Galloway</td>
<td>148,900</td>
<td>1,300 (2%)</td>
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<td>Forth Valley</td>
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<td>3,100 (5%)</td>
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<td>5,600</td>
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<td>Lanarkshire</td>
<td>653,300</td>
<td>6,900 (11%)</td>
<td>12,400</td>
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<tr>
<td>Glasgow &amp; Clyde</td>
<td>1,142,390</td>
<td>20,900 (34%)</td>
<td>37,600</td>
<td>20,000</td>
<td>57,600</td>
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<tr>
<td><strong>WEST</strong></td>
<td><strong>2,616,390 (49%)</strong></td>
<td><strong>36,300 (59%)</strong></td>
<td><strong>65,300 (270/day)</strong></td>
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