Drug related mortality prevention – role of opioid substitution/agonist treatment

Matthew Hickman
Acknowledgements

- Louisa Degenhardt, Sarah Larney, Jack Stone, John Marsden, John Macleod
  - Michael Farrell, Garry Stillwell, Hayley Jones, Colin Steer, Kate Tilling, Aaron Lim, John Marsden, Tim Millar, John Strang, Maggie Telfer, Peter Vickerman,


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- NIHR School of Public Health Research

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Interaction & Complex Needs

- Trends
- OST duration
- Buprenorphine vs Methadone
- Prison OAT
- Benzos
- Comorbidity
Opioid overdose deaths increasing in the UK (rate per million)

2018: 2208 opioid related deaths
>50% of all fatal drug poisonings
~39 deaths per million

Source: Office for National Statistics
...in British Columbia, Canada (rate per 100,000)

~300 deaths per million, 2018
All-cause crude mortality rate: 1.7 (0.3-9.0) per 100py

10* (3-30) higher than gen population
Drug-related deaths: highest cause-specific mortality 0.5 per 100 py (0.1 to 2.0 100 py)
Poisoning 32%
NCD 24%
Infectious diseases 20%
Trauma 18%
Unknown 7%
Larney et al, in press JAMA Psych
## Overdose mortality any time in vs. out of methadone and buprenorphine

### Methadone

<table>
<thead>
<tr>
<th>Study</th>
<th>In treatment</th>
<th>Out of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gearing et al 1974</td>
<td>33/14,474</td>
<td>21/1,170</td>
</tr>
<tr>
<td>Cushman 1977</td>
<td>4/1,655</td>
<td>7/297</td>
</tr>
<tr>
<td>Grönbäck et al 1990</td>
<td>7/1,085</td>
<td>27/740</td>
</tr>
<tr>
<td>Caplehorn et al 1996</td>
<td>4/1,792</td>
<td>19/2004</td>
</tr>
<tr>
<td>Buster et al 2002</td>
<td>42/18,747</td>
<td>26/10,983</td>
</tr>
<tr>
<td>Scherbaum et al 2002</td>
<td>6/1,114</td>
<td>13/172</td>
</tr>
<tr>
<td>Davoli et al 2007</td>
<td>7/5,751</td>
<td>9/998</td>
</tr>
<tr>
<td>Clausen et al 2008</td>
<td>24/6,450</td>
<td>28/1303</td>
</tr>
<tr>
<td>Peles et al 2010</td>
<td>5/3,985</td>
<td>13/727</td>
</tr>
<tr>
<td>Kimber et al 2015</td>
<td>169/91,792</td>
<td>216/45,265</td>
</tr>
<tr>
<td>Cousins et al 2016</td>
<td>54/22,648</td>
<td>24/6,247</td>
</tr>
</tbody>
</table>

### Overall

**Buprenorphine**

<table>
<thead>
<tr>
<th>Study</th>
<th>In treatment</th>
<th>Out of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kimber et al 2015</td>
<td>31/21,936</td>
<td>143/31,239</td>
</tr>
</tbody>
</table>

### Overdose mortality rate/1000 person years (95% CI)

<table>
<thead>
<tr>
<th>Study</th>
<th>In treatment</th>
<th>Out of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kimber et al 2015</td>
<td>1.4 (1.0 to 2.0)</td>
<td>4.6 (3.9 to 5.4)</td>
</tr>
</tbody>
</table>

**Sordo et al, 2017 BMJ**
Mortality risk of opioid substitution therapy with methadone versus buprenorphine: a retrospective cohort study

Jo Kimber, Sarah Larmey, Matthew Hickman, Deborah Randall, Louisa Degenhardt

Summary

Background Opioid dependence increases risk of premature mortality. Opioid substitution therapy with methadone or buprenorphine reduces mortality risk, especially for drug-related overdose. Clinical guidelines recommend

The impact of buprenorphine and methadone on mortality: a primary care cohort study in the United Kingdom

Matthew Hickman, Colin Steer, Kate Tilling, Aaron G. Lim, John Marsden, Tim Millar, John Strang, Maggie Telfer, Peter Vickerman & John Macleod

BMJ

Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK General Practice Research Database

Rosie Cornish, statistician; John Madeley, professor in clinical epidemiology and primary care; John Strang, professor in the psychiatry of the addictions; Peter Vickerman, senior lecturer in mathematical modelling; Matt Hickman, professor in public health and epidemiology
Adjusted risk of death, compared with not being on treatment, during and after opiate substitution treatment.

Cornish R et al. BMJ 2010;341:bmj.c5475
### Differences in mortality risk during and after OST

<table>
<thead>
<tr>
<th>Period</th>
<th>Deaths</th>
<th>Person Years</th>
<th>MR</th>
<th>IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>On 1-4 wks OST</td>
<td>8</td>
<td>897</td>
<td>0.9</td>
<td>3.03 (1.37 to 6.66)</td>
</tr>
<tr>
<td>On rest OST</td>
<td>27</td>
<td>9165</td>
<td>0.3</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Off OST 1-4 wks</td>
<td>18</td>
<td>1044</td>
<td>1.7</td>
<td>5.85 (3.22 to 10.63)</td>
</tr>
<tr>
<td>Off OST rest</td>
<td>34</td>
<td>5257</td>
<td>0.7</td>
<td>2.20 (1.32 to 3.64)</td>
</tr>
</tbody>
</table>

Hickman et al, Addiction 2017; 112:1408-1418
Evidence of Confounding

- **Buprenorphine**
  - varies by region, calendar period, practice size
  - ↑ women, older, co-morbid patients
  - ↓ co-prescribed benzodiazepines, reported history of self-harm, overdose, alcohol problems, imprisonment, and homelessness

- **Drug Related Poisoning**
  - Associated with gender, co-morbidity, co-prescribed benzodiazepines, self-harm, overdose, alcohol problems, imprisonment, and homelessness
The figure shows the risk of mortality for buprenorphine relative to methadone for the four treatment periods unadjusted and adjusted, propensity score based weighted analyses (IPW), adjustment for interactions of OST with age or comorbidity. Incident rate ratios are shown on a log scale with 95% CIs.
### Interaction OST Modality with Co-morbidity

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>DRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>1</td>
<td>1.27 (0.78 to 2.07)</td>
</tr>
<tr>
<td>2+</td>
<td>2.69 (1.41 to 5.16)</td>
</tr>
<tr>
<td>0 Meth</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>0 Bup</td>
<td>0.97 (0.52 to 1.78)</td>
</tr>
<tr>
<td>1 Meth</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>1 Bup</td>
<td>0.37 (0.11 to 1.23)</td>
</tr>
<tr>
<td>2+ Meth</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>2+ Bup</td>
<td>0.19 (0.04 to 0.90)</td>
</tr>
</tbody>
</table>
• Highly skewed distribution
• Buprenorphine shorter than methadone
• Especially UK
• Mean (median)
  • 319 days (92) for methadone
  • 165 days (42) for buprenorphine
Probability that opiate substitution treatment (OST) reduces overall mortality for different durations of treatment.

Cornish R et al. BMJ 2010;341:bmj.c5475
DRP Weighted Mortality Risk & probability that DRP deaths would reduce in the population for patients on Methadone/Buprenorphine vs no OST (and assuming 50% or all patients switch from buprenorphine to methadone after 4 weeks) vs no OST

Hickman et al, Addiction 2017; 112:1408-1418
Elevated Risk of Death post prison release

Figure 2. Excess mortality among former heroin users following release from prison (as reported in [10]).


Merrall EL. *Addiction* 2010; 105(9): 1545-54
### Drug Related Poisoning Post-Prison: OST vs leaving drug free

<table>
<thead>
<tr>
<th></th>
<th>Exposed to OST at release</th>
<th>Not exposed to OST at release</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PY at risk (n deaths)</td>
<td>Rate per 100 PY (95% CI)</td>
</tr>
<tr>
<td>0 – 4 weeks</td>
<td>643 (3)</td>
<td>0.47 (0.15-1.45)</td>
</tr>
<tr>
<td>4 weeks – 4 months</td>
<td>1,966 (13)</td>
<td>0.66 (0.38-1.14)</td>
</tr>
<tr>
<td>4 months – 1 year</td>
<td>4,654 (31)</td>
<td>0.66 (0.47-0.94)</td>
</tr>
</tbody>
</table>

**Fully Adjusted** (age, injecting, problem alcohol, crack, benzodiazepine use & community drug treatment)

0.15 (0.04-0.54)

Does OST have an impact on mortality in custody?

- Opioid dependent people may be at particular risk
  - Drug withdrawal as a trigger for suicide; overdose in custody
- ~16,700 people imprisoned for ~31,000 person years

- First 4 weeks of incarceration
  - Each day spent in OST 93% reduction in hazard of unnatural death (adj.HR 0.07; 95%CI: 0.01, 0.53)

- Total time during incarceration
  - Each day spent in OST 87% reduction in hazard of unnatural death (adj.HR 0.13; 95%CI: 0.05, 0.35)

Relative Reduction in Deaths among PWID over 2020-2040

Degenhardt et al., Lancet 2019
Stone et al... under review
Does benzodiazepine co-prescription (prescribed during OAT or 12 months post treatment) increase mortality risk even if benzos also increase OAT & is there a stronger interaction (risk of death) if benzos prescribed concurrently (at same time as OAT)
UK Study Data

- Clinical Practice Research Datalink (CPRD)
  - ~ 674 UK practices, > 11 million patients (7% UK population)
  - 606 GP practices had 1 OST patient
  - 352/395 practices in England linked to ONS data

- OAT >20mg methadone >4mg buprenorphine
  - 12,118 patients & 7,016 with ONS cause of death
  - 29,549 OAT episodes

- Ten benzodiazepine (3 z-drug 2 gabapentinoids)
  - 365,582 benzo prescriptions (75,926 z-drugs 23,451 gabap)
  - 42% benzo co-prescription, 29% benzo concurrent prescription
OAT patients prescribed benzodiazepines associated with prolonged retention

*Adjusted for sex, age, year, comorbidity, region, OAT type, concurrent prescription of, z-drugs and gabapentinoids

<table>
<thead>
<tr>
<th>Concurrent Prescription</th>
<th>Episodes</th>
<th>Median</th>
<th>Mean adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>OAT None</td>
<td>17111</td>
<td>62</td>
<td>244 (236-252)</td>
</tr>
<tr>
<td>Benzos</td>
<td>7961 (32%)</td>
<td>147</td>
<td>416 (404-429)</td>
</tr>
</tbody>
</table>

Macleod et al., Plos Med in press
Co-prescription of benzodiazepines increases risk of DRP/OD

<table>
<thead>
<tr>
<th>Co-prescription</th>
<th>Deaths</th>
<th>PY</th>
<th>MR</th>
<th>HR (95% CI)</th>
<th>Unadj</th>
<th>HR (95% CI)</th>
<th>Adj*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug related poisoning (DRP)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepine Off</td>
<td>74</td>
<td>16270</td>
<td>0.45</td>
<td>1 (ref)</td>
<td>&lt;0.0001</td>
<td>1 (ref)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>On</td>
<td>39</td>
<td>3679</td>
<td>1.06</td>
<td>2.35 (1.6 to 3.5)</td>
<td>2.96 (1.9 to 4.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepine Off</td>
<td>74</td>
<td>16270</td>
<td>0.45</td>
<td>1 (ref)</td>
<td>&lt;0.0001</td>
<td>1 (ref)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Normal Dose</td>
<td>25</td>
<td>2889</td>
<td>0.87</td>
<td>1.93 (1.2 to 3.0)</td>
<td>2.51 (1.6 to 4.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Dose</td>
<td>14</td>
<td>790</td>
<td>1.77</td>
<td>3.83 (2.1 to 6.8)</td>
<td>4.57 (2.5 to 8.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>linear effect of dose</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.95 (1.5 to 2.5)</td>
<td>&lt;0.0001</td>
<td>2.22 (1.7 to 2.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>All Cause Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepine Off</td>
<td>513</td>
<td>28766</td>
<td>1.78</td>
<td>1 (ref)</td>
<td>0.717 (ref)</td>
<td>0.105</td>
<td></td>
</tr>
<tr>
<td>On</td>
<td>144</td>
<td>7361</td>
<td>1.96</td>
<td>1.03 (0.86 to 1.25)</td>
<td>1.17 (0.97 to 1.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*PY – person years follow-up; MR mortality rate (deaths/100 person-years). HR Hazard ratio; *Adjusted for sex, year, comorbidity, region, OAT type, OAT treatment period, z-drug and gabapentinoid exposure.

Macleod et al., Plos Med in press
### Test of whether benzo prescription greater OD risk on or off OAT

<table>
<thead>
<tr>
<th>OAT</th>
<th>Co-Rx</th>
<th>Period</th>
<th>Benzo</th>
<th>Deaths</th>
<th>PY</th>
<th>MR</th>
<th>HR (95% CI)</th>
<th>p</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unadjusted</td>
<td></td>
<td>Adjusted</td>
<td></td>
</tr>
<tr>
<td>OAT on</td>
<td>Off</td>
<td>Off</td>
<td>24</td>
<td>10091</td>
<td>0.24</td>
<td>1</td>
<td>1 (ref)</td>
<td>0.8958</td>
<td>1 (ref)</td>
<td>0.997</td>
</tr>
<tr>
<td></td>
<td>On</td>
<td>On</td>
<td>20</td>
<td>2914</td>
<td>0.69</td>
<td>2.87</td>
<td>2.87 (1.58 to 5.20)</td>
<td>0.0005</td>
<td>2.92 (1.60 to 5.33)</td>
<td>0.0005</td>
</tr>
<tr>
<td>OAT off</td>
<td>Off</td>
<td>Off</td>
<td>50</td>
<td>6179</td>
<td>0.81</td>
<td>1</td>
<td>1 (ref)</td>
<td></td>
<td>1 (ref)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>On</td>
<td>On</td>
<td>19</td>
<td>764</td>
<td>2.49</td>
<td>3.02</td>
<td>3.02 (1.78 to 5.15)</td>
<td>&lt;0.0001</td>
<td>2.92 (1.70 to 5.02)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

*HR Hazard ratio; PY person years at risk; MR mortality rate (deaths/100 person-years)*

*Adjusted for sex, year, comorbidity, region, OAT type, OAT treatment period, z-drug and gabapentinoid exposure. Interaction p value shown in bold.*

Macleod et al., Plos Med in press
Is concurrent exposure to benzodiazepines beneficial – allowing for prolonged OAT

<table>
<thead>
<tr>
<th></th>
<th>Concurrent</th>
<th>Unadjusted</th>
<th>Adjusted a</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong> Exposure with OAT</td>
<td>HR (95% CI)</td>
<td>p</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Drug-related poisoning</td>
<td>None</td>
<td>1 (ref)</td>
<td>0.0005</td>
</tr>
<tr>
<td></td>
<td>Benzodiazepines</td>
<td>1.98 (1.35 to 2.90)</td>
<td>3.34 (2.14 to 5.20)</td>
</tr>
</tbody>
</table>

*a Adjusted for sex, year, comorbidity, region, OAT type, OAT treatment period, off treatment prescription of benzodiazepine, z-drugs and gabapentinoids and, concurrent prescription of z-drugs and gabapentinoids.

Macleod et al., Plos Med in press
Implications – Evidence that:

- OAT in the community reduces OD risk
- Bup reduces OD risk compared to methadone
  - But retention poorer
- OAT retention in UK is sub-optimal
  - Public health benefit uncertain
- Comorbidity increases risk of death (doh)
  - Even with OD & may interact with OAT modality
- Co-prescribing benzos increases mortality risk
  - Need alternative interventions
Implications – Evidence that:

- **Prison OAT works**
  - OAT in prison *almost entirely eliminates* deaths of opioid dependent prisoners in 1\textsuperscript{st} weeks of prison
  - OAT on release *removes excess mortality* risk in 1\textsuperscript{st} 4 weeks after release & increases community OAT

- **Model projections on scaling-up community /prison OAT retention & coverage**
  - Reduce OD, HIV, self-harm and injury deaths
  - Develop/introduce interventions to address excess in other causes of death
Implications:

- Public health framework to OAT and OD prevention
- Intervention programme not working / needs overhaul and investment
- [more applied epidemiology]
- Cross country comparisons
### OST modality x Treatment Period

<table>
<thead>
<tr>
<th>Treatment Period</th>
<th>OST Type</th>
<th>Drug related mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>IRR (95% CI)</td>
</tr>
<tr>
<td>1-4w on</td>
<td>M</td>
<td>1 (ref)</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>0.08 (0.01 to 0.48)</td>
</tr>
<tr>
<td>Rest on</td>
<td>M</td>
<td>1 (ref)</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>0.37 (0.17 to 0.79)</td>
</tr>
<tr>
<td>1-4w off</td>
<td>M</td>
<td>1 (ref)</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>0.78 (0.36 to 1.66)</td>
</tr>
<tr>
<td>Rest off</td>
<td>M</td>
<td>1 (ref)</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>0.23 (0.12 to 0.48)</td>
</tr>
<tr>
<td>$P$</td>
<td></td>
<td>0.014</td>
</tr>
</tbody>
</table>

IPW: inverse proportional weighting based upon propensity scores derived from all previous confounders (age, sex, comorbidity, year, prescription for benzo, gabapentoid prescription, self-harm, evidence of overdose, alcohol problems, prison, homeless, OST patients in practice, Practice size. Additionally adjusted for age x OST type and comorbidity x OST type interactions. MR unadjusted mortality rates weighted using IPW.
Implications for practice

- Evidence support Ho that buprenorphine safer than methadone at treatment initiation
  - But residual confounding by indication possible
- Beneficial effects of buprenorphine on mortality risk after treatment less clear
  - Duration of treatment episodes lower for buprenorphine so may offset benefits
- Experimental evidence needed on:-
  - how to combine bup/meth to reduce mortality risk
  - retain people in OST so that deaths in population fall
Implications for practice

• Opioid dependent patients prescribed benzos had increased OD risk of death from overdose, despite staying in treatment longer.
  • Evidence of dose response association
  • Specific to OD not ACM
  • Contributor to increase mortality risk in population
  • BUT residual confounding/ confounding by indication?
• Clinicians should be more cautious about prescribing benzos to opioid dep patients
CONCLUSIONS
Relative Reduction in Deaths among PWID over 2020-2040

- **Kentucky**: 63%, 17%, 17%
- **Kyiv**: 65%, 24%, 7%
- **Tehran**: 54%, 37%, 6%

**Status quo**: 0.3% Relative Reduction in Deaths Compared to No OAT Scenario (%)

**Scale-up OAT to 40% in the community (A)**

- Overdose: 2.4%
- Suicide: 4.4%
- Injury: 7.7%

**Scale-up OAT to 40% in the community (A) + improve OAT retention (B)**

- Overdose: 8.6%
- Suicide: 11.7%
- Injury: 14.5%

**Scale-up OAT to 40% in the community (A) + improve OAT retention (B) + provide OAT in prisons (C)**

- Overdose: 12.5%
- Suicide: 16.7%
- Injury: 25.9%

Degenhardt et al., Lancet 2019
Stone et al… under review
Conclusions

• Injecting drug use causes significant health loss which can be significantly reduced through scaling-up OAT.

• Our findings highlight the importance of:
  • Scaling-up OAT
  • Improving OAT retention
  • Increasing the availability of OAT in prisons

• The impact of scaling-up OAT on all-cause mortality varies substantially between the three settings

• Primarily because of differences in how the varied harms associated with drug use contribute to
Conclusions

• Even after scaling-up OAT, mortality rates among PWID would still far exceed that among the general population.

• There is a need to scale-up and develop other interventions to improve the health of PWID.

• However, unlikely other interventions will have as strong effects on a wide range of different outcomes.

• Given extremely low global coverages of OAT\(^1\), a key priority in most countries must be to first scale-up OAT.

\(^1\) Larney Lancet Global Health 2017
…in the United States (rate per 100,000)

Age-adjusted rates of drug overdose deaths\(^a\) and drug overdose deaths involving any opioid\(^b\) for all intents and for unintentional intent by year — United States, 1999–2016

~120 deaths per million, 2016
Most important effects of OAT

- Overdose Mortality: 16%
- Suicide Mortality: 5%
- Injury Mortality: 27%
- Other Mortality: 2%
- Incarceration: 6%
- HCV Transmission: 0%
- HIV Transmission: 22%
- HIV Cascade of Care: 15%

Graph shows the contribution to deaths averted in Kentucky, Kyiv, and Tehran for different outcomes.
Leaving prison on OST & entering community treatment: independent benefits

- 6295 (42%) people entered drug treatment in 1st 4 weeks after prison release
- Leaving on OST more likely to enter community Rx:
  - HR 2.13, (95%CI 2.01-2.25)
  - Community Rx reduces DRP:
    - HR 0.39 (95% CI 0.1-1.4)
  - Mutually beneficial – no evidence of an interaction/or mediation