Determining the impact of opioid substitution therapy upon mortality: Evaluation during key risk periods

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Collaborators and funding sources

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- **External collaborators**: Don Weatherburn, Amy Gibson, Deborah Randall, Tony Butler

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Outline

• Overview of rationale for this work
• Brief orientation to the Australian context

1. Describe work we did to examine the potential impact of opioid substitution therapy on mortality post-release from prison

2. Summarise other recent relevant work
   a) Cost-effectiveness of OST in reducing mortality in the six months post-release from prison
   b) Impact of OST on mortality during incarceration
   c) Differences between OST medication types in mortality risk during certain risk periods
Background

- Overdose is a significant risk faced by people who are opioid dependent.
- People with opioid dependence are also at increased risk of coming into contact with the criminal justice system.
  - High risk of death following release, most due to overdose.
- Many people with opioid dependence also have some form of contact with opioid substitution therapy (OST) – typically methadone or buprenorphine.
  - OST reduces mortality risk of opioid-dependent people.
  - Does OST reduce risk of death among opioid dependent prisoners when they are released from prison?
  - Are there differences in mortality risk between OST medications during discrete periods of risk during treatment e.g. induction?
Background

• Although mortality is a significant risk, it is nonetheless rare
  o randomised controlled trials will arguably never be sufficiently
    powered to examine impacts on mortality
    • especially during specific risk periods
    • or among specific sub-populations

• Data linkage represents a unique method with sufficient
  power to examine rare outcomes, specific time periods, and
  small populations
  o Typically involves the use of administrative datasets
  o Linkage via details such as date of birth and name

• To ascertain potential causal relationships one must use
  statistical approaches to adjust for potential confounding

• We have used this approach to examine mortality among
  opioid dependent people in New South Wales, Australia
A brief overview of the NSW situation
Datasets used in our linkage studies

<table>
<thead>
<tr>
<th>Domain</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone and buprenorphine treatment</td>
<td>• Every authority to dispense methadone or buprenorphine in NSW as OST approved by NSW Health, 1985-2010</td>
</tr>
<tr>
<td></td>
<td>• All entries into or out of treatment are recorded</td>
</tr>
<tr>
<td></td>
<td>• Changes in medications (methadone or buprenorphine) must also be submitted and are recorded</td>
</tr>
<tr>
<td>NSW Ministry of Health Pharmaceutical Drugs of Addiction System (PHDAS)</td>
<td></td>
</tr>
<tr>
<td>Criminal charges and incarceration</td>
<td>• All finalised criminal court appearances in the Local, District and Supreme Courts of NSW between 1993-2011</td>
</tr>
<tr>
<td></td>
<td>• nature of criminal charges recorded</td>
</tr>
<tr>
<td></td>
<td>• All custody episodes obtained from the NSW Department of Corrective Services from 2000-2011</td>
</tr>
<tr>
<td></td>
<td>• Dates of entry into and out of custody recorded</td>
</tr>
<tr>
<td>NSW Bureau of Crime Statistics and Research (BOCSAR) Reoffending Database (ROD)</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>• Mortality data collected from Births, Deaths and Marriage Registers</td>
</tr>
<tr>
<td></td>
<td>• Information includes date, State, and causes of death</td>
</tr>
<tr>
<td>Australian Institute of Health and Welfare National Deaths Index (NDI)</td>
<td>• Primary causes for all records, secondary causes for deaths occurring 1997 and later) up to March 2012.</td>
</tr>
</tbody>
</table>
The New South Wales (NSW) situation

- Opioid dependent people have relatively good access to opioid substitution therapy (OST)
  - Surveys suggest three quarters of opioid dependent people have a history of OST
  - Methadone since 1985, buprenorphine since 2001
  - Around 50,000 people have entered OST at some point
- Our data linkage work has found that:
  - Three quarters (76%) of OST entrants have had >=1 criminal charge
    - cohort accounted for 13% of criminal court appearances since 1994
    - 20-25% appeared in court each year vs. ~2.8 per 100 NSW pop.
  - Between 2000-12, nearly four in ten (37%) had at least one episode of incarceration
  - An increasing number of new OST entrants are inducted onto buprenorphine

Degenhardt et al (2013). Engagement with the criminal justice system among opioid dependent people: Retrospective cohort study. *Addiction*

Mortality among opioid dependent people in NSW

- Overdose is the most common cause
  - 43% of ALL deaths are accidental opioid overdoses
  - An additional 9% are other drug overdoses (intentional, or other drugs)
- Suicide is the next single largest cause of death (13%)

1. Does OST reduce mortality risk post-release from prison?
Cohort definition

All people seeking OST, 1985-2012

People seeking OST who were released from prison, 2000-2012
N=16,453
79% men
30% Indigenous
60,161 prison releases
OST was prescribed in 51% of releases

People seeking OST who died, 1985-2012
1,050 deaths after a prison release
Method

- Cohort: people with an episode of OST who had also been released from prison at least once (n=16,453)
- Followed up until death or end of follow-up period
  - Assumes chronic opioid dependence
  - Any resulting bias would produce more conservative results, as people no longer using opioids would have lower baseline mortality risk
  - This assumption has been one we have used throughout our analyses examining potential causal impacts of OST
- Only those releases from prison during or after the first episode of OST were included (n= 60,161 prison releases)
Method

- Crude mortality rates in and out of treatment
- Association between OST and mortality:
  - Extended Cox models that allowed for discontinuous risk intervals
  - Post-release OST exposure coded as a time-dependent variable
- Other variables:
  - sex, Indigenous status, age at release, and variables relating to treatment and criminal justice history
  - to account for potential differences in mortality risk among people with differing histories of criminal involvement, e.g. violent crime).
Mortality first year after release (n=411 deaths)
Mortality first month after release (n=96 deaths)
Mortality according to OST in the first 4 weeks post-release

<table>
<thead>
<tr>
<th></th>
<th>Extent of OST exposure 1 month post-release</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Full</td>
</tr>
<tr>
<td></td>
<td>N per 100 PY</td>
</tr>
<tr>
<td>All-cause</td>
<td>8.8</td>
</tr>
<tr>
<td>Accidental overdose</td>
<td>3.5</td>
</tr>
<tr>
<td>Suicide</td>
<td>1.0</td>
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<tr>
<td>Accidental injury</td>
<td>1.6</td>
</tr>
<tr>
<td>Violence</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>Partial</td>
</tr>
<tr>
<td></td>
<td>N per 100 PY</td>
</tr>
<tr>
<td>All-cause</td>
<td>11.5</td>
</tr>
<tr>
<td>Accidental overdose</td>
<td>10.4</td>
</tr>
<tr>
<td>Suicide</td>
<td>-</td>
</tr>
<tr>
<td>Accidental injury</td>
<td>-</td>
</tr>
<tr>
<td>Violence</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>N per 100 PY</td>
</tr>
<tr>
<td>All-cause</td>
<td>36.7</td>
</tr>
<tr>
<td>Accidental overdose</td>
<td>26.5</td>
</tr>
<tr>
<td>Suicide</td>
<td>0.8</td>
</tr>
<tr>
<td>Accidental injury</td>
<td>1.3</td>
</tr>
<tr>
<td>Violence</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Full exposure: Was in OST for the full month post-release (or else until death or re-incarceration)

Partial exposure: Was in OST for part of the month post-release (or else until death or re-incarceration)
Mortality according to OST in the first 4 weeks post-release

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<thead>
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<th>Extent of OST exposure 1 month post-release</th>
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<th>Partial</th>
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<tbody>
<tr>
<td>N per 100 PY</td>
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<td>N</td>
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</tr>
<tr>
<td>All-cause</td>
<td>8.8</td>
<td>11.5</td>
<td>36.7</td>
</tr>
<tr>
<td>N per 100 PY</td>
<td>16</td>
<td>5</td>
<td>75</td>
</tr>
<tr>
<td>Accidental overdose</td>
<td>3.5</td>
<td>10.4</td>
<td>26.5</td>
</tr>
<tr>
<td>N per 100 PY</td>
<td>6</td>
<td>4</td>
<td>46</td>
</tr>
<tr>
<td>Suicide</td>
<td>1.6</td>
<td>-</td>
<td>0.6</td>
</tr>
<tr>
<td>N per 100 PY</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Accidental injury</td>
<td>1.6</td>
<td>-</td>
<td>1.3</td>
</tr>
<tr>
<td>N per 100 PY</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Violence</td>
<td>0.6</td>
<td>-</td>
<td>0.5</td>
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<tr>
<td>N per 100 PY</td>
<td>2</td>
<td>0</td>
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</tr>
</tbody>
</table>

Full exposure: Was in OST for the full month post-release (or else until death or re-incarceration)
Partial exposure: Was in OST for part of the month post-release (or else until death or re-incarceration)
The impact of OST on mortality post-release: results of multivariable Cox regressions

• First 4 weeks post-release
  o Each day spent in OST was independently associated with a **75% reduction in hazard of death**
    (adj. HR 0.25; 95% CI: 0.12, 0.53)

• Total time at liberty post-release from prison
  o Each day spent in OST was independently associated with an **83% reduction in hazard of death**
    (adj. HR 0.17; 95% CI: 0.14, 0.20)

Adjusted for sex, Indigenous status, age, no. prior incarcerations, duration of most recent incarceration, prior drug, violent or property offences, OST history
2. a. Is the impact of OST upon mortality post-release from prison a cost-effective one?

Cost effectiveness analysis

- This is an economic method used to assess the additional cost (or the cost savings) required (or gained) in order to achieve a given outcome.
- It involves comparing the costs and outcomes of two alternatives.
- Core metric: incremental cost effectiveness ratio (ICER).
  - ICER = \([\text{Cost}_A - \text{Cost}_B] / [\text{Outcome}_A - \text{Outcome}_B]\)
- We assessed the cost-effectiveness of OST as a strategy to prevent mortality post-release from prison, using the same cohort.
  - Outcome – mortality
  - Timeframe – 6 months post-release from prison
  - Perspective – treatment provider and criminal justice system
Is OST post-release cost-effective as a strategy to reduce mortality risk?

- Comparator groups
  - Those who received OST within a week of prison release (N = 7,892)
  - Those who did not receive OST within a week (N = 8,181)
- Costs of OST and criminal justice system counted
- Analyses:
  - Propensity score matching across comparator groups, followed by
    - multivariate logistic regression (mortality)
    - generalised linear model (costs)
  - ICER calculated
    - bootstrapping to estimate uncertainty around ICER (n=10,000)
  - Sensitivity analyses to see whether still cost-effective if criminal justice system costs excluded
Is OST post-release cost-effective as a strategy to reduce mortality risk?

- Following adjusted analyses, we found:
  - Among those who began on OST immediately post-release, costs were lower in the six months post-release
  - Deaths were also lower
  - ICER = -$1401

- This means that OST immediately post-release both saved lives and it was less costly.

Bootstrapping showed that OST was cheaper and saved lives in nearly 90% of 20,000 modelled iterations.

2. b. Does OST have an impact upon mortality in custody?

Mortality and OST in custody

• Deaths in prison raise questions as to the quality of care provided by correctional authorities
  • ‘Unnatural’ deaths (suicide, overdose) of particular concern (48-59% of deaths)
  • Opioid dependent people may be at particular risk
    • Drug withdrawal as a trigger for suicide
    • Opioid overdose in custody
• OST might serve not only to improve clinical outcomes but also reduce mortality risk
  • In NSW, OST is available in prison
  • Among OST clients in NSW, 75% of those with some in custody received OST at some point in custody
Does OST reduce mortality risk in custody?

- We examined this in our cohort
  - Almost one in four (37%, n=16,715) were incarcerated at least once, 2000-2012
  - We could examine time in custody spent in and out of OST
- Multivariable cox regressions to examine impact of OST on mortality risk overall, and during the first month
  - In the first 4 weeks of custody (the time in custody for our cohort with highest mortality risk), being in OST reduced mortality risk by 93% (multivariable cox regression)

2. c. Is there a difference in mortality risk during key risk periods according to type of OST medication?

Background

- Background
  - Clinical guidance recommends methadone over buprenorphine as the first line of treatment as it is more cost-effective
  - Variations in treatment cost reimbursement have also influenced prescribing preferences
  - However, methadone, a full opioid agonist, can cause potentially hazardous respiratory depression during treatment induction
- There has been no well-powered, direct comparison of mortality risks during key risk periods
  - During induction
  - Following cessation
  - Following in-treatment switching from one medication to another
  - …that considered potential confounders across patient groups
Does OST medication affect mortality risk during key periods in and out of treatment?

• Methadone was first prescribed in 59% of treatment episodes
• One in five (19%) patients switched medications within a treatment episode
  o 46% of these were from buprenorphine to methadone
• Analyses:
  o Does risk of death differ during induction/cessation?
    ▪ Poisson regression estimated mortality rate ratios adjusted for confounders
  o Does the risk of mortality in patients who switched medications? vs. those who did not
    ▪ Nested case-control design that adjusted for confounders
  o Sensitivity analyses to examine how large unmeasured confounding would need to be to explain differences

Does OST medication affect mortality risk during key periods in and out of treatment?

Adjusted analyses

- During first 4 weeks of treatment:
  - Overdose risk 5 times higher in those inducted onto methadone (MRR = 4.88)
- 4 weeks after cessation of treatment:
  - Overdose risk half that in those leaving methadone (MRR = 0.50)
- Sensitivity analyses suggested confounding could not explain the differences found
  - Despite varying the relative risk, and prevalence of the confounder
- During the remainder of treatment:
  - No difference in mortality risk
- Following a switch in medication:
  - No difference in mortality risk

Summary and conclusions
We found clear evidence that:

1. OST in prison AND post-release is critical to reduce post-release mortality
2. OST post-release saves lives and is cheaper
3. OST in prison almost entirely eliminates deaths of opioid dependent prisoners in the first 4 weeks of prison

Additional lines of evidence to argue for OST in prison and co-ordination of post-release programmes

There are also differential periods when different OST medications might be related to higher/lower overdose risk

Useful to consider in clinical practice?
Thank you!
My email: l.degenhardt@unsw.edu.au