The N-ALIVE randomised prison-release naloxone trial: testing pre-provision of naloxone to prevent heroin overdose deaths

Professor John Strang
National Addiction Centre, London, UK
(on behalf of co-investigators Max Parmar, Sheila Bird and John Strang and the N-ALIVE trial team)
Declaration (personal & institutional)

• DH, NTA, Home Office, NACD, EMCDDA, WHO, UNODC, NIDA

• NHS provider (community & in-patient); also Phoenix House, Lifeline, Clouds House, KCA (Kent Council on Addictions)

• Reckitt-Benckiser, Schering-Plough, Napp, Martindale, Auralis, Lundbeck, Alkermes, UCB, Mundipharma Europe, Lannacher, iGen, Lightlake & others, including trying to work with possible pharma-manufacturers

• UKDPC (UK Drug Policy Commission), SSA (Society for the Study of Addiction); and two Masters degrees (taught MSc and IPAS) and an Addictions MOOC

• Work also with several charities (and received support) including Action on Addiction, and J Paul Getty Charitable Trust (JPGT) and Pilgrim Trust

• Support from EMCDDA for this event
Acknowledgements

• All participants and those who expressed interest in the trial
• N-ALIVE workers, Principal Investigators and all staff involved at each of our prisons
• N-ALIVE trial team: mrcctu.nalivepilot@ucl.ac.uk
• TMG and TS-DMC
• MHRN network co-ordinators
Structure of today’s talk:

- Why do people die?
- When does it occur?
- Could we improve interim emergency care?
<table>
<thead>
<tr>
<th>Drug</th>
<th>Prevalence in gen population (last year, age 16-59)</th>
<th>No. 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 (inc 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 = 400mg
Structure of today’s talk:

• Why do people die?

• When does it occur?

• Could we improve interim emergency care?
When in particular excess?

- During methadone early treatment
- Post-detox/rehab
- Prison release
Persistence of drug use during imprisonment: relationship of drug type, recency of use and severity of dependence to use of heroin, cocaine and amphetamine in prison

John Strang¹, Michael Gossop¹, Joan Heuston², John Green³, Christopher Whiteley⁴ & Anthony Maden¹,⁵

National Addiction Centre (Institute of Psychiatry/Maudsley Hospital), London,¹ formerly National Addiction Centre,² Paterson Centre, Paddington, London,³ Hackney Specialist Addiction Unit (formerly National Addiction Centre), Homerton Hospital, London⁴ and The Academic Centre, WLMH NHS Trust, Southall, Middlesex, UK⁵

ABSTRACT

Aim To investigate the persistence of use of heroin, cocaine and amphetamine drugs during imprisonment, and to identify factors associated with increased levels of persistence. Design The use of heroin, cocaine and amphetamine by current prison inmates has been examined and, in particular, the relationship between drug use within prison and the type of drug used prior to imprisonment, recency of use and severity of dependence. Setting and participants A randomly selected sample of 1009 adult male prisoners in 13 prisons in England and Wales during 1994/95; structured confidential interviews conducted by independent research staff. Enquiry about prior use of heroin, cocaine or amphetamine focused on three time-periods (ever, last year and last month pre-prison) and the use of these drugs during the first month of imprisonment. Findings A total of 557 (55%) of the 1009 prisoners had used previously one of the three drugs selected for study: 58% had used heroin, 69% cocaine and 75% amphetamine. More than half (59%; 327/557) had used these drugs in the month before the current imprisonment. Drug use in prisons was most likely to occur among those who had used in the month prior to imprisonment. The persistence of heroin use in prison occurred more frequently (70%) than use of cocaine (20%) or amphetamine (15%). Of those using heroin pre-imprisonment, 67% considered they were dependent, compared to 15% and 22%, respectively, for cocaine and amphetamine users.
<table>
<thead>
<tr>
<th>Ever used</th>
<th>Year before prison</th>
<th>Month before prison</th>
<th>First month in prison</th>
<th>Ever used it in prison</th>
<th>Ever injected it in prison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heroin (n = 324)</td>
<td>63% (n = 204)</td>
<td>52% (n = 169)</td>
<td>36% (n = 118)</td>
<td>71% (n = 230)</td>
<td>16% (n = 51)</td>
</tr>
<tr>
<td>Cocaine (n = 387)</td>
<td>72% (n = 280)</td>
<td>54% (n = 209)</td>
<td>11% (n = 41)</td>
<td>35% (n = 135)</td>
<td>3% (n = 10)</td>
</tr>
<tr>
<td>Amphetamines (n = 417)</td>
<td>52% (n = 216)</td>
<td>30% (n = 125)</td>
<td>5% (n = 19)</td>
<td>26% (n = 108)</td>
<td>4% (n = 15)</td>
</tr>
</tbody>
</table>

All percentages are calculated based on the numbers who have ever used the specific drug.
Mortality from overdose among injecting drug users recently released from prison: database linkage study

S R Seaman, R P Bettle, S M Gore

Abstract

**Objective:** To assess whether injecting drug users have a higher than usual risk of death from overdose in the 2 weeks after release from prison.

**Design:** Soundex coding of surnames and information on date of birth were used to link entry and release dates from the local prison between 1983 and 1994 with clinical data from Edinburgh City Hospital's cohort of male injecting drug users who are infected with HIV.

**Setting:** Edinburgh City Hospital and Edinburgh Prison.

**Subjects:** 316/332 male injecting drug users infected with HIV in the City Hospital HIV cohort; 16 were excluded because they were enrolled after developing AIDS or because their precise date of death was not available.

**Main outcome measure:** Relative risk of dying from overdose before developing AIDS and relative risk of dying of all causes before developing AIDS during the 2 weeks after release from prison; this was compared and 0.029/1000 days during other times of liberty. The relative risk of death from overdose became 7.7 (1.5 to 39.1) after temporal matching (when the comparison was limited to the first 2 weeks after release or the next 10 weeks). The crude relative risk in an analysis combining stratified prison term and the 2 weeks after release was 4.5 (1.7 to 11.7) for death from overdose. After temporal matching these risks became 1.8 (0.4 to 9.2).

**Conclusion:** Prisons should evaluate interventions to reduce the risk of death from overdose after release.

Introduction

The risk of death from overdose may be greater in injecting drug users who resume drug use after a period of abstinence during which their tolerance may have declined. Imprisonment is an enforced period of abstinence from, or may lead to a radical reduction in, drug use. We investigated the risk of death from overdose among male injecting drug users in the Edinburgh City Hospital HIV cohort in the 2 weeks...
Acute risk of drug-related death among newly released prisoners in England and Wales

Michael Farrell & John Marsden
National Addiction Centre, Division of Psychological Medicine and Psychiatry, Institute of Psychiatry, King’s College London, UK

ABSTRACT

Aims To investigate drug-related deaths among newly released prisoners in England and Wales. Design Database linkage study. Participants National sample of 48 771 male and female sentenced prisoners released during 1998–2000 with all recorded deaths included to November 2003. Findings There were 442 recorded deaths, of which 261 (59%) were drug-related. In the year following index release, the drug-related mortality rate was 5.2 per 1000 among men and 5.9 per 1000 among women. All-cause mortality in the first and second weeks following release for men was 37 and 26 deaths per 1000 per annum, respectively (95% of which were drug-related). There were 47 and 38 deaths per 1000 per annum, respectively, among women, all of which were drug-related. In the first year after prison release, there were 342 male deaths (45.8 were expected in the general population) and there were 100 female deaths (8.3 expected in the general population). Drug-related deaths were attributed mainly to substance use disorders and drug overdose. Coronial records cited the involvement of opioids in 95% of deaths, benzodiazepines in 20%, cocaine in 14% and tricyclic antidepressants in 10%. Drug-related deaths among men were more likely to involve heroin over methadone, and were more likely to involve amphetamines in women. Conclusions Despite a decrease in the prevalence of drug use and overdose during index incarceration, drug-related deaths were common in the year following release and were associated with the use and co-use of multiple drugs.
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

MRC Biostatistics Unit, Cambridge, UK,1 National Centre in HIV Epidemiology and Clinical Research, Sydney, NSW, Australia,2 Division of General Internal Medicine, University of Colorado at Denver School of Medicine, Denver, CO, USA,3 School of Population Health, The University of Western Australia, Crawley, WA, Australia,4 National Addiction Centre, Division of Psychological Medicine and Psychiatry, Institute of Psychiatry, King's College London, London, UK,5 Health Protection Scotland, Glasgow, UK,6 Department of Statistics and Modelling Science, Strathclyde University, Glasgow, UK7 and Denver Health Medical Center, Denver, CO, USA8

ABSTRACT

Aims The transition from prison back into the community is particularly hazardous for drug-using offenders whose tolerance for heroin has been reduced by imprisonment. Studies have indicated an increased risk of drug-related death soon after release from prison, particularly in the first 2 weeks. For precise, up-to-date understanding of these risks, a meta-analysis was conducted on the risk of drug-related death in weeks 1 + 2 and 3 + 4 compared with later 2-week periods in the first 12 weeks after release from prison. Methods English-language studies were identified that followed up adult prisoners for mortality from time of index release for at least 12 weeks. Six studies from six prison systems met the inclusion criteria and relevant data were extracted independently. Results These studies contributed a total of 69,093 person-years and 1,033 deaths in the first 12 weeks after release, of which 612 were drug-related. A three- to eightfold increased risk of drug-related death was found when comparing weeks 1 + 2 with weeks 3–12, with notable heterogeneity between countries: United Kingdom, 7.5 (95% CI: 5.7–9.9); Australia, 4.0 (95% CI: 3.4–4.8); Washington State, USA, 2.3 (95% CI: 1.6–3.5); and New Mexico State, USA, 1.5 (95% CI: 1.0–2.3). See Appendix section, table 1 for more details.
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</td>
<td>7.5 (5.7, 9.9)</td>
</tr>
</tbody>
</table>

*Subtotal (I-squared = 0.0% (0.0-99.8%), P = 0.958)*

<table>
<thead>
<tr>
<th><strong>Australia</strong></th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<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</td>
<td>4.0 (3.4, 4.8)</td>
</tr>
</tbody>
</table>

*Subtotal (I-squared = 0.0% (0.0-99.6%), P = 0.838)*

<table>
<thead>
<tr>
<th><strong>USA</strong></th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<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</td>
<td>3.1 (1.3, 7.1)</td>
</tr>
</tbody>
</table>

*Subtotal (I-squared = 74.8% (0.0-94.3%), P = 0.046)*
Structure of today’s talk:

• Why do people die?

• When does it occur?

• Could we improve interim emergency care?
First serious consideration:

RESEARCH REPORT

Preventing opiate overdose fatalities with take-home naloxone: pre-launch study of possible impact and acceptability

JOHN STRANG, BEVERLY POWIS, DAVID BEST, LOUISA VINGOE, PAUL GRIFFITHS, COLIN TAYLOR, SARAH WELCH & MICHAEL GOSSOP

National Addiction Centre (The Maudsley/Institute of Psychiatry), London, UK

Abstract

Aims. Before proceeding with the introduction of an overdose fatality prevention programme including teaching in cardio-pulmonary resuscitation and distribution of naloxone, a pre-launch study of treatment and community samples of injecting drug misusers has been undertaken to establish (i) the extent of witnessing overdoses, (ii) the acceptability of naloxone distribution and training; and (iii) the likely impact of such measures. Design and setting. Structured interview of two samples: (a) a community sample of injecting drug misusers recruited by selected privileged access interviewers (PAI) and interviewed by them in
Why is take-home naloxone so important?

- Most heroin overdoses are witnessed
- Most witnesses intervene actively (often wrongly)
- Many family members witness overdose
Twelve Scenarios

• (A1) patient commencing OST;
• (A2) patient concluding OST;
• (A3) client finishing rehab or hospital care;
• (B1) named client at syringe exchange scheme;
• (B2) named resident at hostel for homeless;
• (B3) unnamed contact of outreach worker;
• (C1) individual leaving prison;
• (C2) family member (e.g. parent) for their at-risk son/daughter/etc;
• (D1) stock supply for hostel staff or day centre;
• (D2) open availability at a syringe exchange scheme;
• (E1) to be carried by a taxi driver or non-clinical 'first responder';
• (F1) over-the-counter from a community pharmacy.
British Red Cross
Community Based First Aid Film

Interview Based Inspiration

The MRC N-ALIVE Pilot Trial: NALoxone InVEstigation

• N-ALIVE Chief Investigators
  – Prof. John Strang, Prof. Mahesh Parmar, Prof. Sheila Bird

• N-ALIVE CTU Trial Team
  – Dr. Angela Meade and many crucial others

• Funding and support: MRC with research support from MHRN
Heroin-related deaths account for 8% of all UK deaths in individuals aged 15-44 yrs.

About 30% of prisoners have previously used heroin.

One in 200 prisoners with history of heroin use by injection dies from a drugs-related death (DRD) within 2–4 weeks of leaving prison.

Current approaches have not prevented high rate of post-release overdose deaths.
N-ALIVE trial – pilot & main phase

• N-ALIVE research trial to test/prove reduced deaths post-release

• Pilot – current (n=approx 1,000; mar 2014)
• Main study n=30,000 (15k + 15k)

• Large randomised trial to test **effectiveness** of Naloxone-on-release to prevent deaths from overdose post-release
N-ALIVE Outcome Measures

• Primary:
  – DRDs within 12 weeks of the prisoner’s N-ALIVE release date

• Secondary:
  – DRDs within 4 weeks of the prisoner’s N-ALIVE release date
  – NFOAs to A&E within the first 12 weeks after release
Why have an RCT?

Main Reasons:

• Naloxone-on-release is not currently prescribed in English Prisons

• RCT is stronger trial design than uncontrolled observational study

• Prisoners realise that in order for prisons to improve their health services, effectiveness has to be beyond question

• Prison-based research deals with a ‘captive population’ – the highest ethical and scientific standards must apply

• Observational study would not answer whether prisons and prisoners would actually use naloxone-on-release as intended
N-ALIVE Pilot Trial Approvals/Collaborations

- Medical Research Council: peer-review to fund
- National Ethics Approval: Updated REC approval was obtained in September 2011 (protocol changed due to the introduction of the Scottish programme)
- Ministry of Justice Research Quality Assurance (Nov 2010)
- National Research Committee (approval to approach governors) (Aug 2011)*
- Formal adoption of the N-ALIVE trial into the Mental Health Research Network (MHRN) trial portfolio
- Global Research & Development (R&D) approval
- Office for National Statistics - for linkage with Register of Deaths
- NHS HSCIC: Hospital Episode Statistics – for A&E data on NFOAs
- Local Prison Governor Approval/including engaging a local Principal Investigator
- Local R&D approval

* Home Office/Ministry of Justice split required the N-ALIVE team to re-obtain relevant permissions
Eligibility Criteria

**Inclusion criteria**
- History of heroin use by injection
- Aged 18 years or older
- Have been in prison for at least seven days
- Likely release date within three months
- Not previously randomised and then withdrawn their consent prior to release
- Written informed consent

**Exclusion criteria**
- History of anaphylactic reaction to Naloxone
- Pregnant or planning to become pregnant within 6 months
- Resident outside of Scotland, England and Wales
- Most recent N-ALIVE release date is within 6 months
- Most recent N-ALIVE release date is missing but participant was randomised in N-ALIVE in the past year

Participants receiving opiate substitution treatment are **not** excluded from participating in **N-ALIVE**
Trial Design

**Consent & Randomisation**
(prisoners incarcerated ≥7 days, & randomised <3 months prior to release date)

1:1

**Naloxone Group**

**Control Group**

**Prisoner’s N-ALIVE Release Date**
Prisoner given pack on release from custody

Optional: Once-only Phone Contact in either weeks 1-2 or 3-4 post-release. Ratio: 2:1:1

Pre-paid Anonymised N-ALIVE Reply Card: re critical events

12 Weeks Post-Release
- National Death Record Review
- Retrospective prisoner consented A&E database linkage

Up to 3 months pre-release

Prison release date

Up to 6 months after prisoner’s N-ALIVE release date

Returned Prisoner Self-Questionnaire - completed next time in prison

12 weeks post-release
Naloxone saves lives

"I was with a friend who collapsed. We tried to revive him but the ambulance took 20 minutes to arrive, by which time he had died."

"...when the medics came I told them I had given him the naloxone. The medics said ‘Wow!’ We had probably just saved the guy’s life."

"I used naloxone and it saved his life."

ABC

Ambulance
Breathing
Recovery position
Naloxone
Take-Home Emergency Naloxone to Prevent Heroin Overdose Deaths after Prison Release: Rationale and Practicalities for the N-ALIVE Randomized Trial

John Strang, Sheila M. Bird, and Mahesh K. B. Parmar

ABSTRACT  The naloxone investigation (N-ALIVE) randomized trial commenced in the UK in May 2012, with the preliminary phase involving 5,600 prisoners on release. The trial is investigating whether heroin overdose deaths post-prison release can be prevented by prior provision of a take-home emergency supply of naloxone. Heroin contributes disproportionately to drug deaths through opiate-induced respiratory depression. Take-home emergency naloxone is a novel preventive measure for which there have been encouraging preliminary reports from community schemes. Overdoses are usually witnessed, and drug users themselves and also family members are a vast intervention workforce who are willing to intervene, but whose responses are currently suboptimal due to a range of factors. N-ALIVE is designed to improve on this.
N-ALIVE Milestones

• First site opened
  – HMP Nottingham opened on 28\textsuperscript{th} May 2012

• First participant randomised
  – HMP Nottingham randomised first 3 participants on 29\textsuperscript{th} May 2012
N-ALIVE Milestones

• **15 sites open to recruitment**
  – HMP Oakwood opened on 11\textsuperscript{th} Feb 2014
  – Five sites opened in Jan/Feb 2014

• **First female prison**
  – HMP Holloway opened on 17\textsuperscript{th} Jan 2014
  – First female randomised on 27\textsuperscript{th} Feb 2014
HOT OFF THE PRESS

A FANTASTIC ACHIEVEMENT—THANK YOU ALL!
HMP Lincoln randomised the 1000th participant
Well done to all the staff at HMP Lincoln!

Well done also to HMP Liverpool, HMP Nottingham and HMP Bristol who randomised on the same day; sorry you missed out this time, better luck for the 1500th participant!

We would like to thank all staff at our recruiting prisons for helping us to reach this ground-breaking milestone. Keep up the good work; April has been a record-breaking month! HMP Exeter randomised our 100th participant in this month alone!
N-ALIVE trial – YouTube clips

Three trigger videos on Youtube

• (i) explanation of the trial  
  https://www.youtube.com/watch?v=Xbnx5Q3vZek

• (ii) how to put your naloxone kit together and give the injection  
  https://www.youtube.com/watch?v=w_qAHdjfFUE

• (iii) how to manage an overdose  
  https://www.youtube.com/watch?v=S4kQ3iVUFMs
Thank you