Opioid overdose deaths: exploring potential new elements of response

Professor Sir John Strang
National Addiction Centre, King’s College London, UK
Declarations (personal & institutional)

- NHS provider (community & in-patient); also Phoenix House, Lifeline, Clouds House, KCA (Kent Council on Addictions).
- Dept of Health, PHE, Home Office, NACD, EMCDDA, WHO, UNODC, NIDA.
- Dialogue and work with pharmaceutical companies re actual or potential development of new medicines for use in the addiction treatment field (incl re naloxone products), including (past 3 years) Martindale, Indivior, MundiPharma, Braeburn/Camurus and trial product supply from iGen and Camurus.
- SSA (Society for the Study of Addiction); UKDPC (UK Drug Policy Commission), 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 also with J Paul Getty Charitable Trust (JPGT) and Pilgrim Trust.
- The university (King’s College London) has registered intellectual property on a buccal naloxone formulation, and JS has been named in a patent registration by a Pharma company as inventor of a novel concentrated naloxone nasal spray.
Structure of lecture

1. Drug deaths: where are they concentrated?
2. Understanding heroin/opioid overdose
3. Mobilisation: responding to prevent
4. Challenges still to be addressed
### With which drugs do the overdose deaths occur?

→ Concentration of opiate overdose among drug-related deaths

<table>
<thead>
<tr>
<th>Drug</th>
<th>Prevalence in general population (use in last year, age 16-59)</th>
<th>No. of deaths in the last 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannabis</td>
<td>10.8%</td>
<td>78</td>
</tr>
<tr>
<td>Cocaine</td>
<td>2.4%</td>
<td>508</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>1.5%</td>
<td>436</td>
</tr>
<tr>
<td>Ecstasy</td>
<td>2%</td>
<td>200</td>
</tr>
<tr>
<td>Opiates (incl. heroin, morphine &amp; methadone)</td>
<td>0.2%</td>
<td>6,194</td>
</tr>
</tbody>
</table>
Drug Overdose & Motor Vehicle Accident Deaths

Data: CDC
National Overdose Deaths

Number of Deaths from Heroin & Prescription Opioids

Source: National Center for Health Statistics, CDC Wonder
When in particular?

- Prison release
- Post-detox/rehab
- During medication induction
- After medication termination
Mortality from overdose among injecting drug users recently released from prison: database linkage study
S R Seaman, R P Brettle, 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 with the expected number of deaths in the Edinburgh region.

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.1 Imprisonment is an enforced period of abstinence from, or may lead to a radical reduction in, drug use.2 We investigated the risk of death from overdose among male injecting drug users in the Edinburgh City Hospital HIV cohort3 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, while drug-related deaths among women were more likely to involve benzodiazepines. Conclusions  Drug-related deaths are a common and serious problem among released prisoners, and prevention strategies are needed.
When? Clustering in time and space

Excess mortality ratio

Time since release (weeks)

Singleton et al, 2002
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, UK.⁷ and Denver Health Medical Center; Denver; CO, USA.⁸

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 1033 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, 2.6 (95% CI: 1.7–3.8); and Malaysia, USA, 2.3 (95% CI: 1.6–3.3). Regression analysis in Spain did not find an increased risk.
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>
<tr>
<td>(I-squared = 0.0% (0.0-99.8%), $P = 0.958$)</td>
<td></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</td>
<td>4.0 (3.4, 4.8)</td>
</tr>
<tr>
<td>(I-squared = 0.0% (0.0-99.6%), $P = 0.838$)</td>
<td></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</td>
<td>8.0 (5.0, 14.2)</td>
</tr>
<tr>
<td>(I-squared = 74.8% (0.0-94.3%), $P = 0.046$)</td>
<td></td>
</tr>
</tbody>
</table>
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,¹³ Matt Hickman, professor in public health and epidemiology¹

ABSTRACT
Objective To investigate the effect of opiate substitution treatment at the beginning and end of treatment and according to duration of treatment.
Design Prospective cohort study.
Setting UK General Practice Research Database.

INTRODUCTION
Opiate users have a high risk of death and contribute
Risk of death during and after OST treatment

“The task of the Recovery Orientated Drug Treatment Expert Group has been to describe how to meet the ambition of the Drug Strategy 2010 to help more heroin users to recover and break free of dependence...”

MEDICATIONS IN RECOVERY
RE-ORIENTATING DRUG DEPENDENCE TREATMENT
Structure of lecture

1. Drug deaths: where are they concentrated?
2. Understanding heroin/opioid overdose
3. Mobilisation: responding to prevent
4. Challenges still to be addressed
Understanding Heroin Overdose: A Study of the Acute Respiratory Depressant Effects of Injected Pharmaceutical Heroin

Caroline J. Jolley¹‡*, James Bell²⁻, Gerrard F. Rafferty¹, John Moxham¹, John Strang²⁻³

¹ Division of Asthma, Allergy and Lung Biology, Faculty of Life Sciences and Medicine, King’s College London, King’s Health Partners, Denmark Hill, London, United Kingdom, ² National Addiction Centre, Institute of Psychiatry, Psychology and Neuroscience, King’s College London, King’s Health Partners, Denmark Hill, London, United Kingdom, ³ Addictions Services, South London & Maudsley NHS Foundation Trust, King’s Health Partners, Denmark Hill, London, United Kingdom

‡ CJJ and JB are joint first authors on this work.
* caroline.jolley@kcl.ac.uk

Abstract

Opioids are respiratory depressants and heroin/opioid overdose is a major contributor to the excess mortality of heroin addicts. The individual and situational variability of respiratory depression caused by intravenous heroin is poorly understood. This study used advanced respiratory monitoring to follow the time course and severity of acute opioid-induced respiratory depression. 10 patients (9/10 with chronic airflow obstruction) undergoing supervised injectable opioid treatment for heroin addiction received their usual prescribed dose of injectable opioid (diamorphine or methadone) (IOT), and their usual prescribed dose of oral opioid (methadone or sustained release oral morphine) after 30 minutes. The main outcome measures were pulse oximetry (SpO₂%), end-tidal CO₂% (ETCO₂%) and neural respiratory drive (NRD) (quantified using parasartal intercostal muscle electromyography). Significant respiratory depression was defined as absence of inspiratory airflow >10s, SpO₂% < 90% for >10s and ETCO₂% per breath >6.5%. Increases in ETCO₂% indicated significant respi-
Oxygen saturation: IV versus IM

**Figure 1** Oxygen saturation after intravenous (IV) and intramuscular (IM) injection of heroin
Subject 21 (41 year old male) injected 180mg heroin intravenously on both occasions. Subject 31 (42 year old female) injected 150mg intramuscular heroin in session 1 and 160mg heroin in session 2. (unpublished)
Structure of lecture

1. Drug deaths: where are they concentrated?
2. Understanding heroin/opioid overdose
3. Mobilisation: responding to prevent
4. Challenges still to be addressed
• We have the technology, but ....
Why take-home naloxone matters

• Overdose is the major cause of death among drug users – mainly opiates

• Most heroin overdoses are witnessed

• Most witnesses intervene actively (often wrongly)

• Many family members witness overdose

• We know why it happens and we know how to treat it
First serious consideration:


*** key points ***
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...
Take home naloxone and the prevention of deaths from opiate overdose: two pilot schemes

Kerstin Dettmer, Bill Saunders, John Strang

Doctors routinely give naloxone during emergency resuscitation after opiate overdose. The distribution of naloxone to opiate addicts has recently been addressed,¹ ² and a survey of drug users shows extensive support for the provision of supplies to take away.¹ We present the preliminary results of two pilot schemes to provide take home naloxone to opiate users.

Methods and results

The Berlin project
In January 1999 drug users in Berlin were given naloxone to take home. Opiate misusers attending a healthcare project (operating from a mobile van or ambulance) were offered training in emergency resuscitation after overdose, provided with naloxone (two 400 µg ampoules), needles, syringes, an emergency handbook, and information on naloxone. They were asked to report on any use of the drug. After 16 months, 124 opiate misusers had received training in resuscitation and were provided with supplies of naloxone to take away; 40 reported back, with 22 having given emergency naloxone (two on two occasions, one on three, and one on four).

The methods of administration were diverse.

Case 1 (Berlin)
“Three days ago, I was walking along the canal with a friend of mine. We saw a guy lying on the ground, with two people trying to help him—they were trying to help him breathe by mouth to mouth. When we ran over to them, we could tell it wasn’t really working. The guy was blue in the face and hardly breathing anymore. I could barely feel his pulse. Right away I gave him one ampoule of naloxone—I didn’t think I could find a vein so I just shot it real slow into his upper arm. We tried to give him CPR and we called 911. Then the guy started to wake up and he started to breathe and shake a little bit. He was so thankful, he wanted to give me 50 Marks, but I wouldn’t take it. When the medics came I told them I had given him the naloxone. The medics said ‘Wow! So you guys have even got naloxone now?’ But he thought it was great. He said we had probably just saved the guy’s life.” The ambulance staff then took the overdose victim to hospital for further observation.

The Jersey project
From October 1998 over the next 16 months naloxone (one minijet ready filled with 800 µg naloxone) was provided to 101 drug misusers in contact with local

Publications

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

National Addiction Centre (Institute of Psychiatry/The Maudsley), Addiction Sciences Building, Denmark Hill, London, UK

ABSTRACT

Aim To examine the impact of training in overdose management and naloxone provision on the knowledge and confidence of current opiate users; and to record subsequent management of overdoses that occur during a 3-month
Changes in knowledge after training

***All significant at p<0.001

- Before training
- After training

<table>
<thead>
<tr>
<th>Category</th>
<th>Clinicians</th>
<th>Clients</th>
</tr>
</thead>
<tbody>
<tr>
<td>risks (7)</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>signs (8)</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>actions (11)</td>
<td>7</td>
<td>11</td>
</tr>
</tbody>
</table>

- Clinicians
- Clients
Client confidence in administering naloxone

![Graph showing client confidence levels](image)
Family carers and the prevention of heroin overdose deaths: Unmet training need and overlooked intervention opportunity of resuscitation training and supply of naloxone

JOHN STRANG, VICTORIA MANNING, SORAYA MAYET, EMILY TITHERINGTON, LIZ OFFOR, CLAUDIA SEMMLER, & ANNA WILLIAMS

National Addiction Centre (Institute of Psychiatry/The Maudsley), Denmark Hill, London, UK
Carers – the overlooked intervention workforce

102 carers attending 4 organisations

- 80% parents, 20% other relative/partner
- 96% of opiate users, 87% IDU, 57% in Tx,
- 1/3 used in presence of carer, 47% had past OD
- 20% of carers had witnessed an OD
- 5 had lost user to fatal OD (3 children 2 partners)
- 16% would ‘panic’ or ‘not know what to do’
- 83% expressed an interest OD management & N training

Evidence of potential to extend naloxone life-saving potential …

The naloxone programme: Investigation of the wider use of naloxone in the prevention of overdose deaths in pre-hospital care

FINAL REPORT: June 2007

Commissioned by:

The National Treatment Agency for Substance Misuse

Research Team: Professor John Strang, Victoria Manning, Dr Soraya Mayet, Dr Mike Kelleher Claudia Semmler, Liz Offor, Emily Titherington, Laura Santana, Dr David Best, (NAC London),
MEDIA RELEASE FROM THE NATIONAL TREATMENT AGENCY

National media release: Thursday 25 June 2009

Life saving kits to be given to families of injecting drug users in groundbreaking scheme

The families and carers of injecting drug users will be given training in how to respond to overdoses and how to administer a drug called naloxone in the event of a heroin overdose in a groundbreaking new scheme to help save lives, the National Treatment Agency (NTA) announced today. 16 sites in England have been given the go ahead to pilot the scheme, involving around 950 family members and carers, who are often the ones to encounter someone overdosing.

Naloxone works by reversing the effects of heroin and other opioids for long enough for medical help to arrive. These projects will increase the amount of naloxone available to drug users, family members and carers involved in the scheme, and train them in its use and other life saving measures. They will also encourage drug users to think about the risks they take and ways of avoiding them, including drug treatment options to overcome their addiction.

Naloxone is very safe and is regularly carried by ambulance crews for use in the event of a suspected overdose. The establishment of such demonstration sites is fully supported by UK clinical guidelines. Naloxone does not cause dependency and has no euphoria-inducing side effects. It would have to be used in enormous quantities in order to be harmful, and protocols will be in place so that the naloxone is stored safely.
“Pilot sites trained the carers and relations of opiate misusers to respond to overdoses and use the antidote naloxone. This appears to have helped save lives…”

THE NTA OVERDOSE AND NALOXONE TRAINING PROGRAMME FOR FAMILIES AND CARERS

National Treatment Agency for Substance Misuse
Naloxone kits issued across Scotland

31/07/2012

The Scottish Government today welcomed figures that show naloxone is being distributed the length and breadth of Scotland and is being made available to those at risk of opiate overdose.

Scotland was the first country in the world to announce a national naloxone programme, in November 2010. The programme is centrally coordinated and funded by the Scottish Government, empowering individuals, families, friends and communities to reverse an opiate overdose. Naloxone provides more time for an ambulance to arrive and further treatment to be given to those in opiate overdose situations.

Figures published today show that 3,445 naloxone kits were issued in Scotland in 2011/12 through this national programme. Scottish Government investment in the programme funds a national coordinator based at the Scottish Drugs Forum and support to Alcohol and Drugs Partnerships and Health Boards to enable them to deliver naloxone training and supply naloxone kits to people at risk.
PROPOSALS FOR AMENDMENTS TO THE HUMAN MEDICINES REGULATIONS 2012 TO ALLOW WIDER ACCESS TO NALOXONE FOR USE IN EMERGENCIES

Regulations 2012 to allow people providing drug treatment services to supply naloxone to anyone requiring access to it for use in an emergency. The amendment is aimed at making stocks of naloxone available in settings which drug users are likely to access, for example, hostels. It will also allow family members or carers to receive direct supplies of naloxone which they can administer in an emergency if needed. The proposal will apply to publicly

Regulatory Impact Assessment

9. The proposal is intended to improve public health by widening access to naloxone.
Naloxone for Outpatient Use: Data Required to Support an NDA

Sharon Hertz, M.D.
Deputy Director
Division of Anesthesia, Analgesia, and Addiction Products
CDER
Opioid overdose: preventing and reducing opioid overdose mortality
Community management of opioid overdose

**Recommendation**

People likely to witness an opioid overdose should have access to naloxone and be instructed in its administration to enable them to use it for the emergency management of suspected opioid overdose.
The emergence of stronger science
Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis

Alexander Y Walley assistant professor of medicine, medical director of Massachusetts opioid overdose prevention pilot, Ziming Xuan research assistant professor, H Holly Hackman epidemiologist, Emily Quinn statistical manager, Maya Doe-Simkins public health researcher, Amy Sorensen-Alawad program manager, Sarah Ruiz assistant director of planning and development, Al Ozonoff director, design and analysis core

1Clinical Addiction Research Education Unit, Section of General Internal Medicine, Boston University School of Medicine, Boston, MA, USA; 2Department of Community Health Sciences, Boston University School of Public Health, USA; 3Massachusetts Department of Public Health, USA; 4Data Coordinating Center, Boston University School of Public Health, USA; 5Design and Analysis Core, Clinical Research Center, Children's Hospital Boston, USA; 6Department of Biostatistics, Boston University School of Public Health, USA

Abstract

Objective To evaluate the impact of state supported overdose education and nasal naloxone distribution (OEND) programs on rates of opioid related death from overdose and acute care utilization in Massachusetts. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis

(2013)
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, London, UK

ABSTRACT

Aims To evaluate a heroin overdose management training programme for family members based on emergency recovery procedures and take-home naloxone (THN) administration. Design A two-group, parallel-arm, non-blinded, randomized controlled trial of group-based training versus an information-only control. Setting Training events delivered in community addiction treatment services in three locations in England. Participants A total of 187 family members and carers allocated to receive either THN training or basic information on opioid overdose management \((n = 95\) and \(n = 92\), respectively), with 123 participants completing the study. Measurements The primary outcome measure was a self-completion Opioid Overdose Knowledge Scale (OOKS; range 0–45) and an Opioid Overdose Attitudes Scale (OOAS; range 28–140) was the secondary outcome measure. Each group was assessed before receiving their assigned condition and followed-up 3 months after. Events of witnessing and managing an overdose during follow-up were also recorded. Findings At follow-up, study participants who had received THN training reported greater overdose-related knowledge relative to those receiving basic information only [OOKS mean difference, 4.08 (95% confidence interval, 2.10–6.06; \(P < 0.001\)); Cohen’s \(d = 0.74\) (0.37–1.10)]. The mean change in scores was −1.11 (standard error 0.46) on the self-completion Opioid Overdose Knowledge Scale.
Results

Changes in Knowledge and Attitudes total score: between groups and across follow-ups.

Interaction Effect = $F_{[2, 320]} = 23.78$, $p < .001$

Interaction Effect = $F_{[2, 320]} = 24.33$, $p < .001$
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. Over 13,000 people died from heroin overdoses in the UK in 2011, and this was accompanied by over 2,000 underreporting incidents.
Structure of lecture

1. Drug deaths: where are they concentrated?
2. Understanding heroin/opioid overdose
3. Mobilisation: responding to prevent
4. Challenges still to be addressed
Challenges:

1) Can it be non-injectable?
Identification of non-injectable routes

Drug and Alcohol Dependence

Review

Naloxone without the needle – systematic review of candidate routes for non-injectable naloxone for opioid overdose reversal

John Strang, Rebecca McDonald, Abdulmalik Alqureshi, Paul Royall, David Taylor, Ben Forbes

ARTICLE INFO

ABSTRACT

Introduction: Deaths from opioid overdose can be prevented through administration of the antagonist naloxone, which has been licensed for injection since the 1970s. To support wider availability of naloxone in community settings, novel non-injectable naloxone formulations are being developed, suitable for emergency use by non-medical personnel.

Objectives: 1) Identify candidate routes of injection-free naloxone administration potentially suitable for emergency overdose reversal; 2) consider pathways for developing and evaluating novel naloxone formulations.

Methods: A three-stage analysis of candidate routes of administration was conducted: 1) assessment of all 112 routes of administration identified by FDA against exclusion criteria. 2) Scrutiny of empirical data for identified candidate routes, searching PubMed and WHO International Clinical Trials Registry Platform
Identification of non-injectable routes

Stage 1: Examination of all routes against exclusion criteria

Stage 2: PubMed & WHO ICTRP search

Stage 3: Examination against inclusion criteria

112 routes of administration (see FDA, 1992)

4 routes excluded (no analytical meaning)

102 routes excluded

6 routes of administration

2 routes excluded (duplications)

1 route excluded: respiration (inhalation)

3 routes included: buccal, nasal, sublingual

Fig. 1. Selection process of candidate routes of administration.
university-industry collaboration

- New PK analysis of concentrated naloxone nasal spray

Mundin, McDonald et al. (Addiction, 2016). *Pharmacokinetics of concentrated naloxone nasal spray over first 30 minutes post-dosing: analysis of suitability for opioid overdose reversal.*
Pharmacokinetics of concentrated naloxone nasal spray for opioid overdose reversal: Phase I healthy volunteer study

Rebecca McDonald\textsuperscript{1} (ID), Ulrike Lorch\textsuperscript{2}, Jo Woodward\textsuperscript{3}, Björn Bosse\textsuperscript{4}, Helen Dooner\textsuperscript{3}, Gill Mundin\textsuperscript{3}, Kevin Smith\textsuperscript{3} & John Strang\textsuperscript{1}

National Addiction Centre, Institute of Psychiatry, Psychology and Neuroscience, King’s College London, London, UK;\textsuperscript{1} Richmond Pharmacology Ltd, Croydon University Hospital (Woodcroft Wing), Croydon, UK;\textsuperscript{2} Mundipharma Research Ltd, Cambridge Science Park, Cambridgeshire, UK;\textsuperscript{3} and Mundipharma Research GmbH and Co. KG, Limburg, Germany\textsuperscript{4}

ABSTRACT

Background and Aims Take-home naloxone can prevent death from heroin/opioid overdose, but pre-provision is difficult because naloxone is usually given by injection. Non-injectable alternatives, including naloxone nasal sprays, are currently being developed. To be effective, the intranasal (i.n.) spray dose must be adequate but not excessive, and early absorption must be comparable to intramuscular (i.m.) injection. We report on the pharmacokinetics (PK) of a specially produced concentrated novel nasal spray. The specific aims were to: (1) estimate PK profiles of i.n. naloxone, (2) compare early systemic exposure with i.n. versus i.m. naloxone and (3) estimate i.n. bioavailability. Design Open-label, randomized, five-way cross-over PK study Setting Clinical trials facility (Croydon, UK). Participants Thirty-eight healthy volunteers (age 20–54 years; 11 female). Intervention and comparator Three doses of i.n. (1 mg/0.1 ml, 2 mg/0.1 ml, 4 mg/0.1 ml) vs i.m. (4 mg)
Looking at PK data over 2 hours (left-hand graph); or concentrating on the first 20 minutes (right-hand graph)

Concentrated naloxone nasal spray pharmacokinetics

**Figure 1** Mean plasma naloxone concentrations (observed values): dosing to 120 minutes (left) and dosing to 20 minutes (right)
## Key findings: Bioavailability

<table>
<thead>
<tr>
<th></th>
<th>IN 1 mg</th>
<th>IN 2 mg</th>
<th>IN 4 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ratio (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>90% CI (lower, upper)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Absolute Bioavailability IN : IV</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IN 1 mg</td>
<td>50</td>
<td>47</td>
<td>48</td>
</tr>
<tr>
<td>(44.6, 56.6)</td>
<td>(41.7, 52.6)</td>
<td>(43.3, 53.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Relative Bioavailability IN : IM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IN 1 mg</td>
<td>51</td>
<td>47</td>
<td>48</td>
</tr>
<tr>
<td>(45.2, 57.1)</td>
<td>(41.7, 53.5)</td>
<td>(43.2, 54.1)</td>
<td></td>
</tr>
</tbody>
</table>

*IV 0.4 mg used as the reference treatment for the comparison

**IM 0.4 mg used as the reference treatment for the comparison
Key findings: Simulation of 2\textsuperscript{nd} dose

- IN Naloxone 2mg given at 0 and 3 mins
- IM Naloxone 0.4 mg given every 3 mins x 5 doses
Amorphous Formulation and *in Vitro* Performance Testing of Instantly Disintegrating Buccal Tablets for the Emergency Delivery of Naloxone

Abdulmalik Alqureshi, † Zahrae Kumar, † Rebecca McDonald, ‡ John Strang, ‡ Asma Buanz, § Shagufta Ahmed, †† Elizabeth Allen, †† Peter Cameron, † James A. Rickard, † Verity Sandhu, † Chris Holt, † Rebecca Stansfield, † David Taylor, † Ben Forbes, † and Paul G. Royall* †

† Institute of Pharmaceutical Science, King’s College London, Franklin-Wilkins Building, 150 Stamford Street, London, U.K., SE1 9NH
‡ Institute of Psychiatry, Psychology & Neuroscience (IoPPN), King’s College London (National Addiction Centre), Addictions Sciences Building, 4 Windsor Walk, Denmark Hill, London, U.K., SE5 8BB
§ UCL School of Pharmacy, University College London, 29-39 Brunswick Square, London, U.K., WC1N 1AX
†† Quintiles Ltd, Quintiles Drug Research Unit at Guy’s Hospital, 6 Newcomen Street London, U.K., SE1 1YR
† Guy’s and St Thomas’ NHS Foundation Trust Pharmacy Manufacturing Unit, Guy’s Hospital, Great Maze Pond, London, U.K., SE1 9RT
Stock solution
Naloxone and pharmaceutical grade excipients in water for injection

Solution pipetted into blister wells (top) and frozen (bottom) ready for lyophilisation

Frozen tablets lyophilised using tailored temperature and pressure cycle

Instant melt tablet
Figure 5. Effect of (A) temperature [volume 0.7 mL; medium: phosphate buffered saline], (B) fluid volume [temperature 35 °C; medium: phosphate buffered saline], (C) disintegration medium [temperature 35 °C; volume 0.7 mL] on the disintegration profile of the naloxone instant disintegrating tablet; using a digital image disintegration assay. Data represent mean ± standard error, n = 3.
Preventing opioid overdose deaths with take-home naloxone

Editors
John Strang and Rebecca McDonald
National Addiction Centre, Addictions Department, Institute of Psychiatry, Psychology & Neuroscience, King’s College London, United Kingdom

EMCDDA project group
Dagmar Hedrich and Roland Simon

Take-home emergency naloxone to prevent deaths from heroin overdose
Now enough experience to justify it

John Strang professor\(^1\), Sheila M Bird professor\(^2\), Paul Dietze professor\(^3\), Gilberto Gerra chief\(^4\), A Thomas McLellan chief executive officer\(^5\)

\(^1\)National Addiction Centre (Institute of Psychiatry and The Maudsley), King’s College London, London SE5 8AF, UK; \(^2\)Biostatistics Unit, Cambridge CB2 0SR, UK; \(^3\)Burnet Institute, Melbourne, Australia; \(^4\)UNODC Drug Prevention and Health Branch Division, United Nations Office on Drugs and Crime, Vienna, Austria; \(^5\)Treatment Research Institute, Philadelphia, PA 19106, USA

A paradigm shift is occurring in the treatment of heroin overdose. On 5 November the World Health Organization launched guidelines on the community management of heroin overdose which included recommended administration of naloxone. In 2012, a United Nations resolution identified the need for more effective prevention of drug overdose, including the use of naloxone. The same year, the first large scale randomised trial of take-home naloxone (NALIVF) started its pilot phase.
Conclusions: preventing heroin overdose deaths

• Effective treatments effectively treat; reduce overdose events

• Develop interventions to prevent fatal outcome when OD occurs

• Identify high-risk contexts, high-risk periods, risk enhancers

• Naloxone (the ‘heroin EpiPen’) - make it public, make it portable

• Engage - users, family, government, industry, law-makers
Thank you