Heroin-Assisted Treatment: the RIOTT trial and its findings

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

- Special thanks to the many patient/participants, clinical and policy colleagues, research colleagues
- Wider international community of interest and commitment to science
- EMCDDA - commissioning ‘Insights’ Monograph (complimentary copies available on request)
Declaration (personal & institutional)

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

- DH, NTA, Home Office, NACD, EMCDDA, WHO, UNODC, FDA, NIDA.

- Consultation and work with pharmaceutical companies re actual or potential development of new medicines for use in the addiction treatment field, including (past 3 years) Martindale Pharma, Indivior, MundiPharma, Alkermes, Rusan/iGen, Braeburn/Camurus.

- 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 also with Pilgrim Trust.

- The university (King’s College London) has registered intellectual property on a novel buccal naloxone, and JS has been named in a patent registration by a Pharma company as inventor of a concentrated nasal naloxone spray formulation.
RIOTT funding support & declarations

• Research Funding
  – Community Fund (Big Lottery) & Action on Addiction & Hedley Foundation

• Clinical Services Funding
  – National Treatment Agency, Department of Health, and Home Office
  – Local DATs & PCTs

• Medications:
  – Diamo, Switzerland; Cardinal, UK; Auralis, UK; also Genus, UK

• Other support
  – The Band Trust – DVD
  – EMCDDA – European analysis and ‘Insights’ report

• Clinical colleagues:
  – Marina House, Maudsley; Darlington; Brighton

• Service users/patients/study subjects:
RIOTT Team & Collaborators

- Investigators/trial coordination
  - Prof John Strang
  - Dr Nicholas Lintzeris
  - Dr Nicola Metrebian

- Local Investigators
  - Dr Deborah Zador / Dr James Bell
  - Dr Tom Carnwath/Dr Soraya Mayet
  - Dr Hugh Williams

- Research staff
  - Vikki Charles
  - Luciana Forzisi
  - Teodora Groshkova
  - Chris Hallam
  - Anthea Martin

- Clinical Trial Pharmacist
  - Glynis Ivin, Maudsley Hospital
  - Godwin Achunine, London clinic

- Diamorphine suppliers
  - DiaMo Narcotics GmbH, Switzerland
  - Auralis, UK

- RIOTT clinical team leaders
  - Rob van der Waal, London
  - Anne McNutt, Darlington
  - Ian Wilson, Brighton

- Trial co-ordination
  - National Addiction Centre, Institute of Psychiatry, KCL

- Statistician
  - Laura Potts, Clinical Trials Unit, Institute of Psychiatry, KCL

- Health Economics
  - Dr Sarah Byford Institute of Psychiatry, KCL
  - Barbara Barrett, Institute of Psychiatry

- Randomisation
  - Clinical Trials Unit, IoP

- Pathology
  - Dr Andy Marsh & Richard Evers, Kings College Hospital
Credit where credit’s due

- Ambros Uchtenhagen and Swiss Ministry of Health - public health policy drive
- Wim Van den Brink and Dutch CCHB – serious research trial (and Germans and Canadians)
To complement the development of existing services, heroin should be available on prescription to all those who have a clinical need for it.

The number of people receiving heroin will increase as overall numbers in treatment grow.

The administration of prescribed heroin for those with a clinical need will take place in safe, medically supervised areas with clean needles. Strict and verifiable measures will be in place to ensure there is no risk of seepage into the wider community.

*UK Government Drug Strategy, 2002*
Target population

Entrenched heroin addicts who have repeatedly been found to fail to benefit from existing treatments

(despite treatment, continuing to inject heroin on all/most days per month)
RIOTT trial randomisation

Injecting heroin User in opioid Maintenance Treatment for 6 months

- Diamorphine IV/IM +/- oral methadone
- Methadone Ampoules IV/IM +/- oral methadone
- Enhanced Oral Methadone
Primary outcome

Retention in treatment X

Reducing/quitting ‘street heroin’

Other drug use; well-being;

Criminal behaviour ?

Wider recovery
## Primary outcome measure

<table>
<thead>
<tr>
<th>Primary outcome</th>
<th>Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in street heroin use</td>
<td>The proportion of subjects in each group who cease regular street heroin use</td>
</tr>
</tbody>
</table>
‘responder’ or ‘abstinent’?

Major reduction in frequency of use of ‘street heroin’

Completely abstinent from ‘street heroin’
Which measure of primary outcome?

- Urine test results
- Observations and measurements
- Self-report
Validation of techniques to detect illicit heroin use in patients prescribed pharmaceutical heroin for the management of opioid dependence

S. Paterson\textsuperscript{1}, N. Lintzeris\textsuperscript{2,3}, T. B. Mitchell\textsuperscript{2}, R. Cordero\textsuperscript{1}, L. Nestor\textsuperscript{2} & J. Strang\textsuperscript{2}

Toxicology Unit, Imperial College London, UK\textsuperscript{1} and National Addiction Centre, Institute of Psychiatry, Kings College London, South London and Maudsley Trust, UK\textsuperscript{2} and National Drug and Alcohol Research Centre, University of New South Wales, Australia\textsuperscript{3}

\textit{Correspondence to:}
Nicholas Lintzeris
c/o National Addiction Centre
PO Box 48
4 Windsor Walk
Denmark Hill
London SE5 8AF
UK
E-mail: n.lintzeris@iop.kcl.ac.uk

Submitted 5 November 2004; initial review completed 31 March 2005; final version accepted 9 May 2005

\textbf{ABSTRACT}

\textbf{Background} The clinical implementation and evaluation of heroin substitution programmes have been confounded by the lack of objective and validated biomarkers for illicit heroin use in patients prescribed pharmaceutical heroin. This study examined the capacity to detect illicit heroin use by gas chromatography–mass spectrometry (GC-MS) analysis of urine samples for the presence of opium impurities common to illicit, but not pharmaceutical heroin.

\textbf{Aims} To characterize the diagnostic properties of the metabolites of noscapine and papaverine in comparison to morphine as a gold-standard marker of illicit heroin use; and to examine the relationships between the self-reported time since most recent heroin use and the detection of these opioids in urine.
Metabolism of “illicit” Heroin

Diamorphine → Morphine
Noscapine → 6-Desmethylmeconine
Papaverine → 4,6-Dihydroxypapaverine
Supervised injectable heroin or injectable methadone versus optimised oral methadone as treatment for chronic heroin addicts in England after persistent failure in orthodox treatment (RIOTT): a randomised trial

John Strang, Nicola Metrebian, Nicholas Lintzeris, Laura Potts, Tom Carnwath, Soraya Mayet, Hugh Williams, Deborah Zador, Richard Evers, Teodora Groshkova, Vikki Charles, Anthea Martin, Luciana Forzisi

Summary

Background Some heroin addicts persistently fail to benefit from conventional treatments. We aimed to compare the effectiveness of supervised injectable treatment with medicinal heroin (diamorphine or diacetylmorphine) or supervised injectable methadone versus optimised oral methadone for chronic heroin addiction.

Methods In this multisite, open-label, randomised controlled trial, we enrolled chronic heroin addicts who were receiving conventional oral treatment (≥6 months), but continued to inject street heroin regularly (≥50% of days in preceding 3 months). Randomisation by minimisation was used to assign patients to receive supervised injectable methadone, supervised injectable heroin, or optimised oral methadone. Treatment was provided for 26 weeks in three supervised injecting clinics in England. Primary outcome was 50% or more of negative specimens for street heroin on weekly urinalysis during weeks 14–26. Primary analysis was by intention to treat; data were adjusted for centre, regular crack use at baseline, and treatment with optimised oral methadone at baseline. Percentages were calculated with Rubin’s rules and were then used to estimate numbers of patients in the multiple imputed samples. This study is registered, ISRCTN01338071.

Findings Of 301 patients screened, 127 were enrolled and randomly allocated to receive injectable methadone (n=42 patients), injectable heroin (n=43), or oral methadone (n=42); all patients were included in the primary analysis. At 26 weeks, 80% (n=101) patients remained in assigned treatment: 81% (n=34) on injectable methadone, 88% (n=38) on injectable heroin, and 69% (n=29) on oral methadone. Patients on injectable heroin were significantly more likely to have achieved the primary outcome (72% [n=31]) than were those on oral methadone (27% [n=11], OR...
Findings - to begin at the end

Four important conclusions, as I see them

• SIH (heroin) group strongest achievement

• SIM (inj methadone) better than OOM group

• OOM (optimised oral) – still show benefit

• Rapid onset of benefit and gain
Results
Figure 1 shows the trial profile. Patients were recruited between September, 2005, and August, 2008, and

Figure 4: Proportion of responders* at weeks 14–26
Error bars are 95% CIs. Analysis adjusted for centre, regular crack use at baseline, and treatment with optimised oral methadone at baseline. *50% or more of urine samples negative for street heroin during weeks 14–26.
Figure 5: Proportion of participants who were abstinent* from street heroin at weeks 23–26
Error bars are 95% CIs. Analysis adjusted for centre, regular crack use at baseline, and treatment with optimised oral methadone at baseline. *Negative results in all four samples taken in weeks 23–26.
Figure 6: Proportion of participants abstinent from street heroin per week by data for urine drug screen (intention-to-treat sample)
Operating costs

- Optimised oral methadone maintenance – c 5k pppa
- Supervised injectable methadone maintenance – c 10k pppa
- Supervised injectable heroin maintenance – c 15k pppa
Operating costs

• ‘bog-standard’ oral methadone maintenance – c 3k pppa

• DTTO/DIP methadone treatment + monitoring – c 10k pppa

• Optimised oral methadone maintenance – c 5k pppa

• Supervised injectable methadone maintenance – c 10k pppa

• Supervised injectable heroin maintenance – c 15k pppa

• Prison – c 44k pppa
Operating costs

• ‘An ineffective service is inefficient and cannot be cost-effective, no matter how cheaply it is provided’

• Cochrane, 1972
Cost-effectiveness of injectable opioid treatment v. oral methadone for chronic heroin addiction†

Sarah Byford, Barbara Barrett, Nicola Metrebian, Teodora Groshkova, Maria Cary, Vikki Charles, Nicholas Lintzeris and John Strang

Background
Despite evidence of the effectiveness of injectable opioid treatment compared with oral methadone for chronic heroin addiction, the additional cost of injectable treatment is considerable, and cost-effectiveness uncertain.

Aims
To compare the cost-effectiveness of supervised injectable heroin and injectable methadone with optimised oral methadone for chronic refractory heroin addiction.

Method
Multisite, open-label, randomised controlled trial. Outcomes were assessed in terms of quality-adjusted life-years (QALYs). Economic perspective included health, social services and criminal justice resources.

addiction. The choice between supervised injectable heroin and injectable methadone is less clear. There is currently evidence to suggest superior effectiveness of injectable heroin but at a cost that policy makers may find unacceptable. Future research should consider the use of decision analytic techniques to model expected costs and benefits of the treatments over the longer term.

Declaration of interest
J.S. and N.L. have contributed to UK National Treatment Agency for Substance Misuse and Department of Health guidelines on the role of injectable prescribing in the management of opiate addiction (2003; chaired by J.S.). J.S. has chaired the broader-scope pan-UK working group preparing the 2007 Orange Guidelines for the UK Departments of Health, providing guidance on management...
Fig. 1 Supervised injectable heroin v. optimised oral methadone (a) bootstrapped cost and effectiveness pairs for quality-adjusted life-years (QALYs) and (b) cost-effectiveness acceptability curve for QALYs.
Heroin on trial: systematic review and meta-analysis of randomised trials of diamorphine-prescribing as treatment for refractory heroin addiction

John Strang,* Teodora Groshkova,* Ambros Uchtenhagen, Wim van den Brink, Christian Haasen, Martin T. Schechter, Nick Lintzeris, James Bell, Alessandro Pirona, Eugenia Oviedo-Joekes, Roland Simon and Nicola Metrebian

Background
Supervised injectable heroin (SIH) treatment has emerged over the past 15 years as an intensive treatment for entrenched heroin users who have not responded to standard treatments such as oral methadone maintenance treatment (MMT) or residential rehabilitation.

Aims
To synthesise published findings for treatment with SIH for refractory heroin-dependence through systematic review and meta-analysis, and to examine the political and scientific response to these findings.

Method
Randomised controlled trials (RCTs) of SIH treatment were identified through database searching, and random effects pooled efficacy was estimated for SIH treatment. Methodological quality was assessed according to criteria set out by the Cochrane Collaboration.

Results
Six RCTs met the inclusion criteria for analysis. Across the trials, SIH treatment improved treatment outcome, i.e. greater reduction in the use of illicit 'street' heroin in patients receiving SIH treatment compared with control groups (most often receiving MMT).

Conclusions
SIH is found to be an effective way of treating heroin dependence refractory to standard treatment. SIH may be less safe than MMT and therefore requires more clinical attention to manage greater safety issues. This intensive intervention is for a patient population previously considered unresponsive to treatment. Inclusion of this low-volume pharmaceutical companies including current and potential future suppliers of diacetyl morphine and methadone (ViroPharma, Martindale, TEVA, Reckitt Benckiser) and have conducted research involving collaboration with the pharmaceutical industry to investigate possible new treatment medications (Martindale, Mundipharma, iGen). J.S., N.M. and N.L. have previously undertaken research study of British heroin policy and have given varied commentaries and contributed to professional and public debate. A.U. has been mandated to document and evaluate the Swiss cohort study on heroin-assisted treatment by the Federal Office of Public Health, resulting in (unpaid) scientific publications and (unpaid) presentations at conferences (expenses reimbursed); expert consultation and project participation for the World Health Organization and United Nations Office on Drugs and Crime on substitution treatment for opioid addiction. W.vdB. is chair of the working group that is currently preparing the Netherlands Interdisciplinary Guideline on Opioid Addiction Treatment. He also was the scientific director of the Central Committee on the Treatment of Heroin Addiction (CCBH), which was responsible for the planning, execution and reporting on the Dutch trial on heroin-assisted treatment. W.vdB. has separately provided consultancy advice and received honoraria, travel and conference support, and consultancy fees from various pharmaceutical companies including current and potential future suppliers of buprenorphine (Reckitt Benckiser), extended-release naltrexone (Alkermes) and nalmefene (Lundbeck). C.H. has contributed to the German guidelines on opioid substitution treatment of the German Medical Association and has...
“... rolling out the prescription of injectable heroin and methadone to clients who do not respond to other forms of treatment, subject to the findings, due in 2009, of pilots exploring the use of this type of treatment”.

(H.M.Government Drug Strategy, 2008)
News story

Invitation to Tender: the piloting of supervised injectable Opioid Treatment

The DH is looking to contract with Service Providers to develop a cost-effective model of delivering a high intensity treatment intervention...

The DH is looking to contract with Service Providers to develop a cost-effective model of delivering a high intensity treatment intervention to a thinly spread population, with a view to demonstrating how IOT can be appropriately commissioned in the future. The nature of the service to be delivered requires hours of opening which enable twice daily supervised injecting, 7 days per week.

The proposed programme will explore how to maximise the cost-effectiveness of IOT to secure future commissioning arrangements:

1. We intend to award between two and six contracts, on the basis of service organisation, bidding until 31 March 2015.
Drug misuse and dependence

UK guidelines on clinical management
4.7.5 Injectable opioid treatments

There is a compelling evidence base in support of making injectable heroin treatment available for those who continue to be at risk despite optimised oral OST. A small section of the OST treatment population, despite being given access to optimised treatment with oral opioid maintenance, can fail to make adequate progress and continue to be involved in high levels of injecting drug misuse and other risk-taking behaviour. These patients may benefit from specialist assessment and reconsideration of their treatment options.

In some instances, clinical benefit can be improved simply by correcting sub-optimal dosing or enhancing and targeting psychosocial interventions to better meet the individual’s needs. For other patients however, addiction specialists with the appropriate competencies, with access to appropriate facilities and skilled support, could decide to initiate a trial of injectable maintenance treatment. Injectable opioid treatment is not currently available in all specialist services and in all parts of the UK.
New heroin-assisted treatment

Recent evidence and current practices of supervised injectable heroin treatment in Europe and beyond

Authors
John Strang, Teodora Groshkova and Nicola Metrebian
Thank you