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

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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 7.42, 95% CI 2.69–20.46, p<0.0001; adjusted: 66% [n=28] vs 19% [n=8], 8.17, 2.88–23.16, p<0.0001), with number needed to treat of 2·17 (95% CI 1·60–3·97). For injectable methadone (39% [n=16]; adjusted: 30% [n=14]) versus oral methadone, the difference was not significant (OR 1·74, 95% CI 0·66–4·60, p=0·264; adjusted: 1·79, 0·67–4·82, p=0·249). For injectable heroin versus injectable methadone, a significant difference was recorded (4·26, 1·63–11·14, 7·42, 95% CI 2·69–20·46, p<0·0001; adjusted: 66% [n=28] vs 19% [n=8], 8·17, 2·88–23·16, p<0·0001), but the study was not powered for this comparison. Differences were evident within the first 6 weeks of treatment.

Interpretation Treatment with supervised injectable heroin leads to significantly lower use of street heroin than does supervised injectable methadone or optimised oral methadone. UK Government proposals should be rolled out to support the positive response that can be achieved with heroin maintenance treatment for previously unresponsive chronic heroin addicts.

Funding Community Fund (Big Lottery) Research section, through Action on Addiction.

Introduction

At least 5–10% of heroin addicts fail to benefit from established conventional treatments but whether they are untreatable or just difficult to treat is unknown. A scientific evidence base is emerging to support the effectiveness of maintenance treatment with directly supervised medicinal heroin (diamorphine or diacetylmorphine) as a second-line treatment for chronic heroin addiction.1 In the past 15 years, findings from five randomised trials of more than 1000 participants have shown that treatment with heroin has substantial benefits over oral methadone for individuals who have not responded to previous or continuing methadone treatment.2-4 However, these studies relied on self-reported primary outcomes and used various complex measures of benefit, leading to the report in a Cochrane review that outcomes were not comparable between the studies and, therefore, effectiveness remained uncertain.7 Furthermore, only two studies had used a control of optimised doses of oral methadone.3,4 In the UK, use of injectable methadone needs assessment since, for several decades, this treatment has been more common than has injectable heroin for treatment of addiction.3,11 The political context is also important. All recent trials in Switzerland,12 the Netherlands,13
Once daily doses of ≥80 mg actively encouraged; optimum doses individually titrated.

Features of the maintenance treatments

- Supervised injectable methadone
  - Injected methadone doses calculated with the formula: injected methadone dose = 0.8 × oral dose; dose reassessed continually
  - One injected dose per day
  - Patients encouraged to take additional doses of oral methadone on a regular basis, and instead of injectable methadone dose if unable to attend clinic
  - Maximum dose of injectable methadone: up to 200 mg/day

- Supervised injectable heroin
  - Injected heroin doses individually titrated (typically stabilising at 300–600 mg/day)
  - Daily dose divided into two (usually equally)
  - Patients encouraged to take additional doses of oral methadone doses on a regular basis, and instead of injectable heroin if unable to attend clinic
  - Maximum dose of injectable heroin: 900 mg/day (450 mg per injection)

- Provision of injectable treatments
  - All doses were self-administered under direct nursing supervision at clinic sites
  - No takeaway doses of injected medication
  - Clinics were open for supervised injecting on two sessions per day (for 365 days per year): morning (eg, 0900–1100 h) and afternoon (eg, 1400–1600 h)
  - Patients generally attended two sessions per day if receiving heroin, and one session per day if receiving methadone
  - Patient safety assessment by nursing staff for 10–20 min before and after every dose
  - Supervised treatment was combined with psychosocial support

Methods

Patients and study design

Chronic heroin addicts (aged 18–65 years) receiving conventional oral maintenance treatment (≥6 months) were eligible for the study if they were continuing to inject street heroin regularly (≥50% of days in preceding 3 months). Patients were enrolled from the local catchment areas of supervised injecting clinics in south London, Darlington, and Brighton. Patients were enrolled and screened for eligibility by the doctor or lead nurse at the study site, and patient eligibility was double-checked by a research worker. Trial design and eligibility criteria have been described elsewhere.15

Patients provided written informed consent after they were screened for eligibility and before randomisation. Ethical approval was received from the London Multi-site Research Ethics Committee. The trial was overseen by a trial steering committee, and by a data monitoring and ethics committee, comprising a statistician and two consultant addiction psychiatrists.

Randomisation and masking

Randomisation was undertaken independently by the Clinical Trials Unit (Institute of Psychiatry, King’s College London, London, UK), which generated the randomisation sequence by computer. Randomisation by minimisation was used to assign patients in a 1:1:1 ratio to one of three treatments: supervised injectable methadone, supervised injectable heroin, or optimised oral methadone (control).

Randomisation was stratified for: regular use of cocaine or crack cocaine (≥50% of days in previous 30 days); previous treatment with optimised oral methadone (≥80 mg daily; supervised ≥5 days per week); and clinic site (south London, Darlington, or Brighton). To conceal allocation, the doctor or lead nurse at the study site emailed the Clinical Trials Unit to confirm individual patient eligibility and request random allocation, and the Unit sent an email to the researchers independent of the clinical team stating the treatment allocation.

In this open-label study, researchers were unmasked to treatment allocation once the Clinical Trials Unit had randomly allocated the patient, and they informed clinicians and patients of allocation before treatment began. Urinalysis was done by laboratory personnel who were masked to treatment allocation, and the statistician analysing primary outcome data was masked to injectable group but not to oral versus injectable treatment for the entirety of the primary analysis.

Procedures

Features of the three treatments are listed in the panel. Oral methadone was available to patients receiving injectable treatment to supplement their routine injected doses (to prevent night-time withdrawal), and as takeaway alternative medication if they could not attend the clinic for their usual injected doses. All patients were assigned a case worker for scheduled follow-up visits.
weekly reviews, monthly medical reviews, and access to psychological services.

Patients received their allocated treatment for 26 weeks. This endpoint was chosen for the trial phase on the basis that any substantial differences would occur before this point, and that the robustness of these benefits (beyond 6–12 months) would be considered separately if major differences were identified. After the trial, the patient was reassessed for the most appropriate treatment (including consideration of injectable heroin or injectable methadone).

The primary outcome was the reduction of regular use of street heroin, which was defined as 50% or more of negative specimens on urinalysis during weeks 14–26. For all patients achieving this outcome, we hereafter use the term responders. Urine specimens
Table 1: Patients’ characteristics at baseline (intention-to-treat sample)

<table>
<thead>
<tr>
<th>Demographic indicators</th>
<th>Injectable methadone (n=42)</th>
<th>Injectable heroin (n=43)</th>
<th>Oral methadone (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at randomisation (years)</td>
<td>37.0 (7.0)</td>
<td>37.5 (6.6)</td>
<td>37.2 (5.9)</td>
</tr>
<tr>
<td>Men (%)</td>
<td>28 (67%)</td>
<td>32 (74%)</td>
<td>28 (67%)</td>
</tr>
<tr>
<td>Ethnic origin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>40 (95%)</td>
<td>42 (98%)</td>
<td>40 (95%)</td>
</tr>
<tr>
<td>Black</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Mixed white/Asian</td>
<td>1 (2%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Employment status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Unemployed or receiving sickness benefit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>1 (2%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Spent time in prison</td>
<td>26 (62%)</td>
<td>33 (77%)</td>
<td>34 (81%)</td>
</tr>
<tr>
<td>Number of times in prison</td>
<td>5.6 (5.5)</td>
<td>6.9 (7.3)</td>
<td>5.4 (7.9)</td>
</tr>
<tr>
<td>Treatment at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optimised oral methadone</td>
<td>16 (38%)</td>
<td>18 (42%)</td>
<td>16 (38%)</td>
</tr>
<tr>
<td>Treatment centre</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South London</td>
<td>17 (40%)</td>
<td>18 (42%)</td>
<td>16 (38%)</td>
</tr>
<tr>
<td>Darlington</td>
<td>15 (36%)</td>
<td>14 (33%)</td>
<td>16 (38%)</td>
</tr>
<tr>
<td>Brighton</td>
<td>10 (24%)</td>
<td>11 (26%)</td>
<td>10 (24%)</td>
</tr>
<tr>
<td>Previous drug use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opiate use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of first use (years)</td>
<td>20.6 (5.5)</td>
<td>19.3 (5.2)</td>
<td>20.6 (6.2)</td>
</tr>
<tr>
<td>Length of use (years)</td>
<td>15.9 (7.2)</td>
<td>17.2 (7.9)</td>
<td>16.0 (6.6)</td>
</tr>
<tr>
<td>Injecting drug use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of first use (years)</td>
<td>24.0 (7.4)</td>
<td>21.4 (6.8)</td>
<td>23.6 (7.1)</td>
</tr>
<tr>
<td>Length of use (years)</td>
<td>12.4 (7.1)</td>
<td>15.6 (9.0)</td>
<td>13.0 (7.0)</td>
</tr>
<tr>
<td>Previous treatment for drug use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of first treatment (years)</td>
<td>26.0 (7.1)</td>
<td>26.7 (6.3)</td>
<td>27.1 (7.5)</td>
</tr>
<tr>
<td>Treatment for opiate use</td>
<td>42 (100%)</td>
<td>43 (100%)</td>
<td>42 (100%)</td>
</tr>
<tr>
<td>Number of times in treatment</td>
<td>4.1 (3.8)</td>
<td>4.7 (4.7)</td>
<td>4.5 (4.1)</td>
</tr>
<tr>
<td>Length in treatment (years)</td>
<td>9.5 (5.8)</td>
<td>10.5 (7.7)</td>
<td>9.5 (6.0)</td>
</tr>
<tr>
<td>Abstinence-based residential rehabilitation</td>
<td>21 (50%)</td>
<td>15 (35%)</td>
<td>16 (38%)</td>
</tr>
<tr>
<td>Number of relapse treatments</td>
<td>1.3 (0.7)</td>
<td>1.7 (1.8)</td>
<td>2.3 (2.9)</td>
</tr>
<tr>
<td>Drug use in past 30 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular use of cocaine or crack cocaine</td>
<td>18 (43%)</td>
<td>18 (42%)</td>
<td>18 (43%)</td>
</tr>
<tr>
<td>Heroin use</td>
<td>42 (100%)</td>
<td>43 (100%)</td>
<td>42 (100%)</td>
</tr>
<tr>
<td>Number of days use</td>
<td>27.0 (4.1)</td>
<td>28.0 (3.0)</td>
<td>27.5 (3.7)</td>
</tr>
<tr>
<td>Crack cocaine</td>
<td>29 (69%)</td>
<td>34 (79%)</td>
<td>31 (74%)</td>
</tr>
<tr>
<td>Number of days use</td>
<td>15.0 (11.4)</td>
<td>13.2 (10.7)</td>
<td>14.2 (10.9)</td>
</tr>
<tr>
<td>Benzodiazepine use</td>
<td>13 (31%)</td>
<td>13 (30%)</td>
<td>18 (43%)</td>
</tr>
<tr>
<td>Number of days use</td>
<td>6.2 (8.0)</td>
<td>5.3 (5.5)</td>
<td>9.7 (13.0)</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>24 (57%)</td>
<td>19 (44%)</td>
<td>21 (50%)</td>
</tr>
<tr>
<td>Number of days use</td>
<td>13.9 (10.4)</td>
<td>15.1 (10.6)</td>
<td>15.5 (11.6)</td>
</tr>
</tbody>
</table>

Data are number (%) or mean (SD).

were obtained at random once a week for 26 weeks. Specimens were analysed with laboratory urinalysis that uses liquid chromatography mass spectrometry to detect opioid impurities (eg, noscapine, papaverine), and thereby differentiate between medicinal and street heroin (detection to 10 ng/mL). Analysis was undertaken by the pathology service at King’s College Hospital, London, UK.

As secondary outcomes, we also examined more stringent tests of reduction of regular use of street heroin, which were defined as two, one, or zero (abstinent) positive specimens during weeks 14–26, and a test of zero positive specimens during weeks 23–26. Self-reported abstinence from street heroin (zero use) in the past 30 days was obtained by independent researchers in face-to-face interviews with patients at baseline (0 weeks), 13 weeks, and 26 weeks. Patients were reimbursed for their time and travel for attending the research interviews at baseline, 13 weeks, and 26 weeks with a £20 store voucher.

Statistical analysis

The sample size was calculated to allow comparison of oral methadone with each of injectable methadone and injectable heroin. Comparison of the two injectable treatments would have needed a substantially larger sample size, and was judged to exceed available clinical resources in the supervised injecting clinics. We assumed that regular use of street heroin would reduce (defined by at least 50% of negative urine samples during weeks 14–26) in 69% of patients on injectable methadone, 85% of those on injectable heroin, and 33% of those on oral methadone on the basis of previous trials. With α=0.05 (two-sided) and possible loss to follow-up of 20%, we calculated that a total of 150 patients would be needed for 90% power, and 114 patients for 80% power.

All data were analysed with Stata (version 10). For the primary analysis, data were analysed by intention to treat. For analysis of the primary outcome, missing data were handled with multiple imputation for cases in which urine samples were missing because of hospital admission, imprisonment, agreed absence (holiday), safety reasons, or clinical omission or error (eg, leakage, no label, failure to ask patient for sample, sample not sent for analysis). Missing urine samples were managed in the same way for the one patient attempting abstinence without any treatment contact. Urine samples that were not provided because of non-compliance (refusal to provide or unplanned failure to attend) were presumed to be positive.

For multiple imputation, missing data on a variable is replaced with values drawn from an estimate of the distribution of the variable. In Rubin’s method for multiple imputation, several simulated datasets are analysed and the results combined to generate estimates and confidence intervals incorporating uncertainty caused by missing data. Under the assumption that data are missing at random, multiple imputation results in unbiased estimates of study associations.

Multiple imputation with chained equations (ICE) was achieved with the ICE command in Stata; 100 imputations were created from the imputation model for the urinalysis outcomes during weeks 1–26. Dichotomous covariates were regular crack cocaine use at baseline, treatment...
with optimised oral methadone at baseline, and self-reported use of street heroin at 26 weeks. Continuous measures were time from first ever use of opiates to randomisation and number of previous treatments. After exploration of predictors for missing data, an interaction between treatment centre and per-protocol status was also included.

Most missing outcome data were handled at the item level. Any missing outcome data were assumed to be missing at random on the basis of the variables included in the imputation model. Consequently, a sensitivity analysis was done to assess the adequacy of the imputation model for prediction of whether outcome data were missing or not. We assessed the validity of our assumption that data were missing at random by analysis of statistical associations between whether or not data were missing, and any additional potential predictors generated by examination of the data or the comment fields in the database.

The unadjusted absolute differences in the percentages of participants who achieved responder status were calculated with Rubin’s rules to account for the 100 imputations. To calculate the odds ratio (OR) of being a responder, a logistic regression model was fitted on the intention-to-treat sample for the dichotomous outcome of regular use of street heroin (≥50% or <50% of positive specimens for street heroin on random weekly urinalysis). The model included fixed contrasts for each of injectable methadone and injectable heroin versus oral methadone, and was adjusted by fixed randomisation stratification factors. The number of patients who would need to be treated to achieve a responder status (number needed to treat) during weeks 14–26 was calculated as the reciprocal of the absolute risk difference (the proportion of non-responders in the treatment group minus the proportion of non-responders in the control group).

In the secondary analysis, data were analysed per protocol. Participants were excluded from the per-protocol sample if they: did not receive treatment for 28 days continuously; missed the assessment at 13 weeks or 26 weeks, or both, after all follow-up attempts had been made; failed to supply more than half of the urine samples requested during weeks 14–26; failed to attend clinic at least 3 days per week without explanation for at least 50% of the time every 4 weeks during the 26 weeks after randomisation; or failed to provide 26-week outcome data within 30 weeks of randomisation. Any substantial differences between the intention-to-treat and per-protocol analyses are reported alongside the results of the intention-to-treat analysis. We recorded adverse events and serious adverse events, and the treating doctor (local principal investigator) decided whether the events were related to the trial drug (not related, unlikely to be related, or likely to be related).

This study is registered, number ISRCTN01338071.
Role of the funding source
The study sponsor and funders had no role in the trial design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication. The corresponding author had full access to data and made the final decision on where to submit for publication.

Results
Figure 1 shows the trial profile. Patients were recruited between September, 2005, and August, 2008, and 301 patients were screened for eligibility. 174 (58%) patients were excluded (89 ineligible, 85 failed to attend appointments), and 127 (42%) were enrolled and randomly allocated to the three treatment groups.

Most patients were men (93 [73%]), white (122 [96%]), and unemployed (121 [95%]), had spent time in prison (93 [73%], mean of 3·9 times [SD 7·0]), and had a mean age of 37·2 years (6·3; table 1). Patients had used opiates for a mean of 16·6 years (SD 7·3), had injected drugs for a mean of 13·7 years (7·8), and had received treatment for mean of 9·8 years (6·7). 127 (100%) patients had been previously treated for opiate use (mean of 4·4 times [SD 4·2]), and 52 (41%) had received residential drug-free rehabilitation (mean of 1·8 times [1·8]). All were using street heroin virtually daily (mean 27·5 days per 30 days [3·6]), and many (54 [43%]) also reported regular use of cocaine or crack cocaine. All patients were receiving methadone treatment at enrolment (continuously for ≥6 months), and 50 (39%) were receiving optimised methadone treatment (table 1).

Of 1651 scheduled urine samples (13 samples during weeks 14–26 for 127 participants), 588 (36%; most in oral methadone group) were not obtained because of non-compliance and were classed as positive (webappendix p 1). Additionally, 142 (9%) were missing because of planned absence, and 152 (9%) were missing because of clinical error (proportions comparable between all treatment interventions); these data were imputed to enable statistical analyses (webappendix p 1). All available self-report data (ie, completed interviews) from baseline, 13 weeks, and 26 weeks were analysed, since few data were missing (data available for 42 patients on injectable methadone, 42 on injectable heroin, and 38 on oral methadone). A generalised estimating equations model was fitted in to maintain the correlation between participants, and an exchangeable correlation structure was implemented.

At 26 weeks, 101 (80%) patients remained in the assigned trial treatment: 34 (81%) on injectable methadone, 38 (88%) on injectable heroin, and 29 (69%) on oral methadone. 12 patients did not start treatment, of whom eight continued in their previous methadone treatment (outside the trial; figure 1). Of the 14 patients who discontinued their assigned treatment (four on injectable methadone, four on injectable heroin, six on oral methadone), four were imprisoned, four discharged themselves from assigned treatment, one moved out of the catchment area, two were discharged for medical reasons, one violated the protocol, and two missed 28 days’ treatment (figure 1). Patients on oral methadone were significantly more likely to not start treatment than were those on injectable heroin (p=0·030; figure 2; webappendix p 2). After exclusion of patients who did not start treatment, the proportions of participants retained at 13 and 26 weeks did not differ significantly between treatment groups (figure 2; webappendix p 2).

Table 2: Logistic regression model of the probability of participants becoming responders

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Intention-to-treat sample (n=127)</th>
<th>Per-protocol sample (n=89)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted odds ratio (95% CI)</td>
<td>p value</td>
</tr>
<tr>
<td>Injectable methadone vs oral methadone</td>
<td>1·79 (0·67–4·82)</td>
<td>0·249</td>
</tr>
<tr>
<td>Injectable heroin vs oral methadone</td>
<td>8·17 (2·88–23·16)</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>Injectable heroin vs injectable methadone*</td>
<td>4·57 (1·71–12·19)</td>
<td>0·002</td>
</tr>
<tr>
<td>Centre</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Darlington vs south London</td>
<td>1·37 (0·46–4·06)</td>
<td>0·572</td>
</tr>
<tr>
<td>Brighton vs south London</td>
<td>1·32 (0·44–3·92)</td>
<td>0·622</td>
</tr>
<tr>
<td>Regular vs no crack cocaine use at baseline</td>
<td>2·06 (0·85–4·99)</td>
<td>0·108</td>
</tr>
<tr>
<td>Treatment vs no treatment with optimised oral methadone at baseline</td>
<td>0·75 (0·28–1·97)</td>
<td>0·557</td>
</tr>
</tbody>
</table>

A full logistic regression model fitted on the sample was used to calculate predicted probabilities of responders in the reference categories (south London, no regular crack cocaine use at baseline, and no treatment with optimised oral methadone at baseline); model adjusted for centre, regular crack cocaine use at baseline, and treatment with optimised oral methadone at baseline. From the logistic regression model, in the injectable heroin, injectable methadone, and oral methadone groups, respectively, 66%, 30%, and 19% of the intention-to-treat sample, and 75%, 38%, and 30% of the per-protocol sample are expected to be responders. *Study was not powered for this comparison. 150% or more of days in previous 30 days. 150% or more of urine samples negative for street heroin during weeks 14–26.
Overall the per-protocol sample included 89 (70%) patients from the intention-to-treat sample: 18 (43%) clients receiving oral methadone did not meet the per-protocol definition, compared with 12 (29%) of those on injectable methadone, and 8 (19%) of those on injectable heroin.

We aimed to provide treatment with full therapeutic power from adequate daily doses. Dose stabilisation was mostly achieved within 6–8 weeks, with only minor adjustments thereafter (figure 3). Mean daily doses during weeks 7–26 were 128·3 mg (SD 38·3) injectable methadone plus 31·4 mg (13·0) supplementary oral methadone, 398·9 mg (163·6) injectable heroin plus 41·8 mg (12·7) supplementary oral methadone, and 107·3 mg (39·9) optimised oral methadone.

In the intention-to-treat analysis for weeks 14–26, a higher proportion of patients (72% [n=31]) on injectable heroin were responders at follow-up than were those on injectable methadone (39% [n=16]) or oral methadone (27% [n=11]). The difference was significant for injectable heroin versus oral methadone (OR 7·42, 95% CI 2·69–20·46, p<0·0001), but not for injectable methadone versus oral methadone (1·74, 0·66–4·60, p=0·264). For injectable heroin versus oral methadone, number needed to treat was 2·17 (95% CI 1·60 to 3·97), whereas for injectable methadone versus oral methadone, number needed to treat was 8·33 (12·17 to 3·20). For injectable heroin versus injectable methadone, number needed to treat was 2·93 (1·92 to 7·74).

With the full logistic regression model fitted on the intention-to-treat sample, data adjusted for centre, regular crack use at baseline, and other variables held constant, 30% (n=14) of participants on injectable methadone, 66% (n=28) of those on injectable heroin, and 19% (n=8) of those on oral methadone were responders (figure 4). Patients on injectable heroin were significantly more likely to be responders than were those on oral methadone, but the difference was not significant between patients on injectable methadone and oral methadone (table 2). Additionally, patients on injectable heroin were significantly more likely to be responders than were those on injectable methadone, but the trial was not powered for this comparison (unadjusted OR 4·26, 95% CI 1·63–11·14, p=0·003; table 2). Similar results were produced from per-protocol analysis with adjusted data (figure 4) and unadjusted data: 48% (n=20) of participants on injectable methadone, 79% (n=34) of those on injectable heroin, and 38% (n=16) of those on oral methadone were responders, with a significant difference between the participants on injectable heroin and oral methadone, but not between those on injectable methadone and oral methadone.

In examination of the extent to which responders achieved abstinence or near abstinence from street heroin, an eighth of patients on injectable heroin achieved complete abstinence, and two-fifths achieved almost complete sets of urine samples negative for street heroin, with two or fewer positive samples during weeks 14–26 (table 3). Abstinence or near abstinence was higher in patients on injectable heroin than in those on injectable methadone or oral methadone, and patients on injectable heroin were significantly more likely to be near abstinent from street heroin than were those on oral methadone (table 3). However, we recorded no significant differences in abstinence for injectable heroin versus oral methadone, or differences in abstinence or near abstinence for injectable methadone versus oral methadone (table 3).
We also assessed abstinence from street heroin during weeks 23–26 (figure 5, webappendix p 3), which we judged to be comparable with self-report data obtained for weeks 23–26. With the logistic regression model fitted on the intention-to-treat sample, and other covariants held constant, 18% (n=8) of patients on injectable methadone, 37% (n=16) of those on injectable heroin, and 8% (n=3) of those on oral methadone were abstinent from street heroin (figure 5). Significantly more patients on injectable heroin were abstinent than were those on oral methadone (OR 6.54, 95% CI 1.91–22.34, p=0.003), but the differences were not significant for injectable methadone versus oral methadone (2.37, 0.63–8.86, p=0.199) or for injectable heroin versus injectable methadone (2.76, 0.98–7.77, p=0.055). Per-protocol analysis produced similar results (figure 5).

Self-reported abstinence from street heroin at weeks 23–26 was recorded in a significantly higher proportion of patients on injectable heroin (51% [n=22]) than in those on injectable methadone (29% [n=12]; OR 2.69, 95% CI 1.06–6.85, p=0.038) or oral methadone (17% [n=7]; 6.32, 2.09–19.18, p=0.001). The difference was not significant for injectable methadone versus oral methadone (2.34, 0.76–7.29, p=0.140). Weekly urinalysis results showed that, for all three treatments, increasing proportions of participants had urine samples negative for street heroin during the first 6 weeks of treatment, with only slight further improvement during weeks 7–26 (figure 6). However, injectable heroin was associated with the greatest proportion of participants with urine samples negative for street heroin within the first 6 weeks of treatment and thereafter (figure 6). The injectable heroin group was associated with the largest increase in abstinence by the end of 6 weeks.

Overall, 20 serious adverse events were reported (table 4): four on injectable methadone, seven on injectable heroin, and nine on oral methadone. Of the three that were judged to be related to trial treatments by the local principal investigators, all were immediate overdoses after injection. One occurred in a patient on injectable methadone at 64 days into treatment, after the patient’s regular dose of 160 mg intravenous methadone. Two occurred in patients on injectable heroin, one at 17 days into treatment after the patient’s regular dose of 200 mg intramuscular heroin, and the other at 42 days into treatment after the patient’s regular dose of 200 mg intravenous heroin. In all overdoses, patients were treated with oxygen and intramuscular naloxone, and did not need admission to hospital. After correction for differing frequencies of drug administration, the rate of serious adverse events was one in every 5551 injections for injectable methadone, and one in every 6613 injections for injectable heroin; for oral methadone, none of the serious adverse events was judged to be related to treatment.

Discussion
We have shown that treatment with supervised injectable heroin leads to significantly lower use of street heroin than does supervised injectable methadone or optimised oral methadone. Furthermore, this difference was evident within the first 6 weeks of treatment.

This randomised controlled trial of treatment with supervised injectable opiates builds on the findings of five randomised trials of supervised injectable heroin versus oral methadone (table 5). Our trial focuses on reduced use of street heroin as the explicit primary
outcome, and also includes a comparison with supervised injectable methadone. Further, we used a laboratory test to objectively detect use of street heroin in our trial. In response to the impossibility of masking patients to treatment allocation (injected versus oral routes of administration), urine assays have been developed and validated to differentiate prescribed from street heroin.\textsuperscript{17,18} We recorded good retention in the trial treatments; retreatment was similar to that in the Canadian trial,\textsuperscript{6} and Germany\textsuperscript{5} and Canada,\textsuperscript{6} in which patients were not already on oral methadone at enrolment.

Several study limitations should be noted. The study was open-label, which meant that patients’ awareness of their treatment allocation could have affected expectancy and behaviour. Nevertheless we used a laboratory test to achieve an objective primary outcome measure. The study also had a smaller sample size than had the Dutch,\textsuperscript{7} German,\textsuperscript{8} and Canadian\textsuperscript{9} trials of heroin-assisted treatment, but we achieved high retention in study treatments and good follow-up of research participants.

For supervised injectable maintenance treatment to become a small intensive part of service provision, systems would be needed to deliver treatment, and the throughput and suitability of this approach would need analysis. There is a potential logistics problem of new patients initiating long-term treatment to patients who do not subsequently progress out of treatment, thereby obstructing access for new patients, and with the provision of the prescription unintentionally impeding the natural recovery that might otherwise occur, as has previously been proposed.\textsuperscript{10–16} Our fairly short-term data cannot predict how patients will progress, but longer-term data from the Swiss\textsuperscript{5} and German\textsuperscript{9} groups suggest that many patients receiving heroin-assisted treatment progress to

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### Table 5: Randomised controlled trials of substitution treatment with a supervised injectable opioid versus an oral opioid for treatment of opioid dependence

<table>
<thead>
<tr>
<th>Country</th>
<th>Intervention groups</th>
<th>Control group</th>
<th>Follow-up</th>
<th>Study population</th>
<th>Outcomes (intervention vs control groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brink et al (2003)\textsuperscript{3}</td>
<td>Supervised injectable heroin (mean dose 548 mg) plus oral methadone (n=43)</td>
<td>Optimised oral methadone (mean dose 107 mg, n=42)</td>
<td>26 weeks</td>
<td>Long-term treatment-refractory, heroin injectors, who despite receipt of oral substitution treatment for ≥6 months continue to regularly inject street heroin</td>
<td>Retention: 81% (injectable methadone), 88% (injectable heroin) vs 66% (oral methadone); Reduction in street heroin use (responder\textsuperscript{*}): 30% (injectable methadone) vs 15% (oral methadone, p=0.249); 66% (injectable heroin) vs 19% (oral methadone, p=0.0001); Serious adverse events: 20 (three related to study drug [two on injectable heroin, one on injectable methadone])</td>
</tr>
<tr>
<td>van den Brink et al (2006)\textsuperscript{4}</td>
<td>Supervised injectable heroin (mean dose 366 mg) plus oral methadone (mean dose 71 mg, n=76)</td>
<td>Oral methadone, detox, and rehab (n=24)</td>
<td>6 months</td>
<td>Dependent illicit heroin injectors; two previous episodes of methadone treatment, not in treatment at enrolment</td>
<td>Retention: 93% vs 92% (oral methadone vs injectable methadone); 72% vs 85% (oral methadone vs injectable methadone); Self-reported illicit heroin use: 22% vs 67% (oral methadone vs injectable methadone); Serious adverse event data not reported</td>
</tr>
<tr>
<td>March et al (2009)\textsuperscript{5}</td>
<td>Supervised injectable heroin (mean dose 275 mg) plus oral methadone (mean dose 43 mg, n=31)</td>
<td>Oral methadone (mean dose 105 mg, n=31)</td>
<td>9 months</td>
<td>Dependent illicit heroin injectors; two previous episodes of methadone treatment, not in treatment at enrolment</td>
<td>Retention: 74% vs 68% (oral methadone vs injectable methadone); Self-reported illicit heroin use in past 30 days (mean days): 1.3 vs 36.9 (p=0.02); Serious adverse events: seven (two unrelated and five probably related to injectable heroin treatment) vs seven</td>
</tr>
<tr>
<td>Haasen et al (2007)\textsuperscript{6}</td>
<td>Supervised injectable heroin (mean dose 442 mg) plus oral methadone (mean dose 8 mg, n=515)</td>
<td>Oral methadone (mean dose 99 mg, n=500)</td>
<td>12 months</td>
<td>Two intake groups: illicit heroin users with no treatment in past 6 months (n=540); and patients receiving oral methadone treatment who were regularly injecting heroin (n=493); randomisation stratified by treatment status at intake</td>
<td>Retention: 67% vs 40% (oral methadone vs injectable methadone); 69% vs 55% (oral methadone vs injectable methadone); Serious adverse events: 177 (38 possibly, probably, or definitely related to injectable heroin treatment) vs 75</td>
</tr>
<tr>
<td>Oviedo-Joekes et al (2009)\textsuperscript{7}</td>
<td>Supervised injectable heroin (mean dose 392 mg, n=115, of whom 30 received supervised injectable heroin [mean dose 366 mg] plus oral methadone [mean dose 34 mg]); Supervised injectable hydromorphone plus oral methadone (mean doses not reported, n=26)</td>
<td>Oral methadone (mean dose 96 mg, n=111)</td>
<td>12 months</td>
<td>Dependent illicit opioid injectors; at least two previous episodes of opioid treatment, of which at least one was methadone treatment, not in treatment at enrolment</td>
<td>Retention: 88% (injectable heroin) vs 54% (oral methadone, p=0.001); Self-reported illicit heroin use in past 30 days (mean days): 5.3 (injectable heroin) vs 12.0 (oral methadone, p=0.001); Serious adverse events: 51 (injectable heroin), ten (injectable hydromorphone) vs 18 (oral methadone)</td>
</tr>
</tbody>
</table>

All trials were open-label. \textsuperscript{*}50% or more of negative urine specimens during weeks 14–26. \textsuperscript{†}Parallel trial with smokeable diamorphine. \textsuperscript{*}Assessed by a composite measure.
conventional treatments or abstinence. We will report observational findings for our study participants at 2 years after randomisation.

Four key findings should be noted. First, we recorded important reductions in street heroin use across all three study groups, even though patients were selected on the basis of their persistent treatment failure. Patients had chronic heroin addictions, with about 17 years since first opiate use, and had been injecting heroin virtually daily despite active maintenance treatment with methadone. They had also tried several forms of treatment, and three-quarters had served prison sentences. Despite these characteristics, about a fifth of patients randomly allocated to receive oral methadone had substantially reduced their street-heroin use at 26 weeks. The fact that doses of methadone were optimised for individual patients and the increase in direct therapeutic contact might account for some of this benefit.

Second, substantially higher proportions of patients on injectable heroin were responders and achieved abstinence than were those on injectable methadone or oral methadone. We chose the primary outcome measure of 50% or more negative specimens on random weekly urinalysis during weeks 14–26 to ensure that we detected real behaviour change. This outcome is indicative of clinically meaningful improvements in individuals who, at baseline, were in treatment but were still injecting heroin most days. Many people who reduced their heroin use did so substantially, with a high proportion who were abstinent or near abstinent, particularly in those on injectable heroin. On the basis of previous studies, the direction of effect was probably as expected, but for injectable heroin versus oral methadone, the large effect size and low number needed to treat of 2·2 are notable. Since this patient population was previously judged to possibly be beyond treatment, we are encouraged that large proportions responded to intensive treatment, and nearly half were close to abstinence from street heroin at 26 weeks.

Third, the findings for treatment with injectable methadone are important for the UK, in which injectable methadone has been prescribed more widely than has injectable heroin in the past 30 years, and for any countries considering injectable maintenance treatment. Injectable methadone treatment led to far lower reduction in street heroin use than did injectable heroin treatment, and did not lead to significantly greater improvements compared with oral methadone. Such results are in sharp contrast to the encouraging findings with injectable hydromorphone that were reported in a small sub-study within the Canadian trial.

Last, the almost immediate (within 7 weeks) improvement in self-reported abstinence in patients on injectable heroin should be investigated further, to establish whether potential responders could be identified at an early treatment stage. The smaller but consistent further improvement during weeks 7–26 is grounds for cautious optimism about the long-term trajectory with aggressive treatments, and needs long-term study.

Supervised injectable treatments are intensive for both staff and patients, and need high financial and staffing investments. However, the gain from reversal of an otherwise adverse disease trajectory is a substantial achievement, especially in view of the extensive harm of heroin addiction for the individual, family, and wider society. As the Canadian group note, to provide the necessary intensive care and prepare for medical emergencies (one in every 6000 injections, as shown by our study and Ovedo-Joekes and colleagues), treatments will need to be properly established. Furthermore, investigation of these occasional and unpredictable medical emergencies is needed beyond the 26 weeks of our study.

“Rolling out the prescription of injectable heroin and methadone to clients who do not respond to other forms of treatment”, is detailed in the UK Government’s 2008 Drug Strategy, subject to the results from this trial. In the past 15 years, six randomised trials have all reported benefits from treatment with injectable heroin compared with oral methadone (table 5). Supervised injectable heroin should now be provided, with close monitoring, for carefully selected chronic heroin addicts in the UK.

Contributors
JS and NL conceived and designed the study, were the principal investigators, and were clinicians and researchers. NM coordinated the research. LP was the statistician. NL, TC, SM, HW, DZ, and JS were local lead clinicians during some periods of the trial. VC, LF, TG, and AM were researchers. NM coordinated collection of data; and VC, TG, AM, and LF undertook data handling and entry. RE did laboratory analyses. LP undertook the first statistical analysis, after which LP, JS, and NM did general analyses and led interpretation of data. JS and NM drafted the report; and all authors participated in review of the report, and have seen and approved the final version.

Conflicts of interest
JS and NL 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 JS), and JS also chaired the broader-scope pan-UK working group preparing the 2007 Orange Guidelines for the UK Departments of Health, providing guidance on management and treatment of drug dependence and misuse. JS has provided consultancy advice to Britannia/Genus, Auralis, and Martindale Pharmaceuticals; JS and JS’s institution have received support and funding from the Department of Health (England) and National Treatment Agency (England); and JS has close associations with the charity Action on Addiction. NL has received honoraria, travel and conference support, and consultancy fees from Reckitt Benckiser and Schering-Plough. NL has an untied educational grant for research related to buprenorphine in the management of opioid dependence. JS, NM, NL, and TC have previously undertaken research study of British heroin policy and have given varied commentaries and contributed to professional and public debate. LP, SM, HW, DZ, RE, TG, VC, AM, and LF declare that they have no conflicts of interest.

Acknowledgments
We thank all participants of this trial; the staff and colleagues without whom the trial would not have been possible; research and treatment funders; Ed Day, chairman of the trial steering committee; members of the data monitoring committee (Sheila Bird, Senior Statistician, Medical Research Council Biostatistics Unit, Cambridge, UK; Louise Sell, Consultant Addiction Psychiatrist and Service Director, Greater Manchester West Mental Health NHS Foundation Trust, Manchester, UK; and Philip Robson, Consultant Addiction Psychiatrist, Greater Manchester West Mental Health NHS Foundation Trust, Manchester, UK; and Philip Robson, Consultant Addiction Psychiatrist, Greater Manchester West Mental Health NHS Foundation Trust, Manchester, UK; and Philip Robson, Consultant Addiction Psychiatrist, Greater Manchester West Mental Health NHS Foundation Trust, Manchester, UK; and Philip Robson, Consultant Addiction Psychiatrist, Greater Manchester West Mental Health NHS Foundation Trust, Manchester, UK; 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GW Pharmaceuticals, Wiltshire, UK; Jenny Hellier (Clinical Trials Unit, Institute of Psychiatry, King’s College London, London, UK) for additional statistical analysis; David Taylor, Glynn Ivin, and Godwin Achumune (South London and Maudsley NHS Foundation Trust, London, UK) for pharmacy advice, coordination, and support; and Rob van der Waal (South London and Maudsley NHS Foundation Trust, London, UK) for help with development of the clinical protocol and for training nursing staff. Diamorphine ampoules were supplied by DiaMo (Switzerland) and Auralis (UK). Research funding was provided by the Community Fund (Big Lottery) Research section, through Action on Addiction; Hedley Foundation; and UK National Health Service Research and Development support. Organisational support was provided by the Clinical Trials Unit at the Institute of Psychiatry, and by the UK Mental Health Research Network. Funding for treatment was provided through the UK National Treatment Agency for Substance Misuse for the Department of Health and the Home Office, and local commissioners. NL was partly funded by the National Health Medical Research Council, Australia. Tees, Esk and Wear Valleys Foundation NHS NIHR Flexibility and Sustainability Funding provided supplementary funding for TC. King’s College London and South London and Maudsley NHS Foundation Trust are now within the Academic Health Sciences Centre, King’s Health Partners.

References

Science and politics of heroin prescription

Heroin (diamorphine) was the trade name of a drug launched by Bayer in 1898, although it is now better known as an illicit drug responsible for infectious disease spread, fatal overdoses, and criminal activity. Methadone maintenance therapy is now the most widely investigated treatment for heroin addiction, with meta-analyses showing that such use of methadone is associated with a range of health and social benefits. However, even in countries where methadone is widely available through diverse sources, only 50–60% of heroin-dependent individuals are on methadone treatment, and 45–60% of opioid-dependent individuals who have previously failed or refused to access methadone cannot subsequently be retained in treatment, even when methadone provision is optimised.

In response, several randomised trials have compared prescribed injectable heroin with optimised methadone as a second-line treatment. Whereas some early studies implied benefits of this approach, a 2005 Cochrane review of four randomised trials of heroin prescription stated that firm conclusions about efficacy could not be made because of heterogeneity across studies. Since then, randomised trials of prescribed heroin have been completed in Germany, Spain, and Canada, with every trial showing consistently better results for prescribed heroin in reducing use of illicit heroin and criminal activity, with further favourable improvements in physical and mental health and in social functioning. The German and Canadian trials, which included more direct comparisons of methadone with heroin, also showed higher treatment retention in those randomised to prescribed heroin.

In The Lancet today, John Strang and colleagues report a UK-based randomised trial of prescribed heroin. The investigators built on past randomised trials with a novel and objective laboratory measure that distinguished pharmaceutical from illicit heroin use, with the addition of an injectable methadone group. The results showed increased reductions in illicit heroin use and treatment retention in those randomised to prescribed heroin injection compared with the injectable and oral methadone groups. These findings, together with other trial results, should help to allay concerns about this approach, including methodological issues (eg, methadone dosing, target populations), safety, and cost.

However, history tells us that availability of heroin prescription can be dictated more by special interests and politics than evidence. Despite successful experiments with heroin prescription in the 1990s in Switzerland, the programme’s sustainability has been threatened by repeated public referenda. In Australia, a federal cabinet halted the much expected trial, approved by the country’s Ministerial Council on Drug Strategy, because the initiative was deemed to be “sending the wrong message.” Similarly, the implementation of heroin prescription has been slow to develop in Germany and Spain, despite the fact that randomised trials in these settings have drawn attention to the benefits of this approach. Although protocols for heroin prescription trials have been developed in the USA, France, and Belgium, none of these countries has yet done such a trial.

Other factors delaying the implementation of heroin prescription are special interests of treatment providers, including those from within the addiction treatment community. Although heroin was prescribed widely in the UK during the 1970s, a movement by treatment providers advocating for a more confrontational and abstinence-oriented approach led to a decline in heroin prescription. In Canada, where the trial of heroin prescription showed better results for heroin than methadone, physicians in several cities sought to prevent the trial from starting, and more have criticised the trial results via internet blogs and newspaper editorials. Although those opposed
to heroin prescription seem to often misunderstand existing clinical research,\textsuperscript{14,15} they more importantly seem to disregard the limitations of methadone maintenance and the subsequent individual’s health and community harms that happen when people discontinue methadone.

This state of affairs is sad because other medical specialties commonly embrace second-line therapies, even if only for a selected group who fail first-line treatments. In the era of evidence-based decision making, moving forward will probably need those embroiled in this debate to cast aside the stigma associated with heroin prescription, and recognise that the drug was once a pharmaceutical product with physiological and chemical properties similar to other opioids that are in common clinical use. The existing interference and non-evidence-based opposition from politicians and care providers, who refuse to acknowledge the limitations of methadone maintenance and the superiority of prescribed heroin in selected populations, is arguably unethical. Denying effective second-line therapy to those in need ultimately serves to condemn many users of illicit heroin to the all too common outcomes of untreated heroin addiction, including HIV infection or death from overdose.

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JSGM has received educational grants from, has served as an ad-hoc adviser to, or has spoken at various events sponsored by Abbott Laboratories, Agouron Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals, Biokan Pharma, Bristol-Myers Squibb, DuPont Pharma, Gilead Sciences, GlaxoSmithKline, Hoffmann-La Roche, Immune Response Corporation, Incyte, Janssen-Ortho, Kucera Pharmaceutical Company, Merck Frost Laboratories, Pfizer Canada, Sanofi Pasteur, Shire Biochem, Tibotec Pharmaceuticals, and Trimeris. TK and EW declare that they have no conflicts of interest.


**Are we any closer to combating Ebola infections?**

In March, 2009, a scientist working in a high-containment laboratory in Germany pricked herself with a needle that had just been used to infect a mouse with the Ebola virus.\textsuperscript{1} Although rare, similar laboratory accidents with Ebola virus have been reported in the UK (1976), USA (2004), and Russia (2004), of which the one in Russia was fatal.\textsuperscript{2} Additionally, there have been at least three exposures to Marburg virus in laboratories, another member of the Filoviridae family, and again one of these exposures was fatal.\textsuperscript{3} The incident in Germany once again caught the high-containment research community off guard because of the lack of prophylactic and treatment options in circumstances of exposure to highly pathogenic agents. This and previous incidents coincide with increasing filovirus outbreaks in Central Africa since the mid-1990s, with at least three imported cases of filovirus infection (South Africa, Netherlands, USA), of which one was fatal and one resulted in the death of an assisting medical worker.\textsuperscript{4,5} Increases in the numbers of