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### ► [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.](#)

Strang J., Metrebian N., Lintzeris N. et al. [Request reprint](#)

Lancet: 2010, 375, p. 1885–1895.

Controversial and expensive it might be, but in the first British randomised trial, a continental-style heroin prescribing programme featuring on-site supervised consumption suppressed illegal heroin use much more effectively than oral methadone.

**Abstract** This abstract also draws on an earlier description of the [featured study's methodology](#). Conducted at clinics in London, Darlington, and Brighton, between 2005 and 2008 the Randomised Injecting Opioid Treatment Trial (RIOTT) [recruited](#) 127 opiate addicts who continued to frequently inject illegal heroin despite being prescribed substitute oral opiate-type drugs. The aim was to test whether they were simply beyond available treatments, whether it was just that their current oral treatments were sub-optimal, or whether they would only do well if prescribed injectable medications, either methadone or heroin.

#### [Rationale, methodology and patients](#)

In Britain injectable prescribing has for decades been legal and accepted practice in the treatment of opiate addiction, though currently it accounts for [very few](#) patients. Rather than this traditional approach, the study tested programmes of the kind recently developed in continental Europe. Their distinctive feature is that all injectable medication must be injected at the clinic under [medical supervision](#), usually requiring in the featured study twice daily attendance for heroin patients and once daily for those prescribed injectable methadone. To tide them over at night or if they could not attend for their injections, patients were also prescribed oral methadone to be taken at home.

Patients were almost all unemployed. About three quarters were men and the same

proportion had been in prison. All were using street heroin virtually daily; 43% also reported regular cocaine use. Aged on average 37 years, they had used opiates for 17 years and injected for 14. As required to join the study, all had previously been treated for their opiate use. On average each had tried treatment four times for in total 10 years; 4 in 10 had tried drug-free residential rehabilitation.

For six months these 127 patients were randomly allocated either to injectable methadone or heroin, or to continue on oral methadone. If necessary doses were individually adjusted to **high levels** to achieve maximal comfort and suppression of illicit opiate use. Regular psychosocial support was also available. Additionally, to optimise the oral methadone option, at first patients were required to take all weekday doses under supervision at the clinics, supervision continued on at least three days a week, and they were offered frequent keyworking sessions and medical reviews. After the six months of the trial, patients were reassessed for the most appropriate treatment, including possible injectable prescribing for those previously allocated to oral methadone.

### Heroin improves retention and suppresses illegal use

The featured report dealt with retention in treatment and the degree to which the three treatments suppressed illegal heroin use. An innovation was a urine test capable of identifying whether a patient had taken illegal as opposed to prescribed heroin, meaning that (unlike other similar studies) the study did not have to rely on patients' own accounts, though these too were obtained through interviews half way through and at the end of the six-month trial.

By the end of the trial, 88% of the patients assigned to injectable heroin remained in treatment, 81% on injectable methadone, and 69% on oral methadone, differentials largely due to more patients not starting their methadone treatments rather than more dropping out part way through.

Poor attendance among the oral methadone patients meant that 58% of the urine tests were missed due to non-compliance, far more than among the injectable heroin (15%) or methadone (35%) patients. For the main analysis, these tests were **counted as positive** for illegal heroin. On this basis, the proportion of tests free of illegal heroin increased over the first six weeks as medication doses were adjusted, and then levelled off. The initial increase in the heroin-free tests was steepest and the final level highest among patients allocated to injectable heroin. After adjusting for other factors, 66% met the study's criterion for responding well to treatment – at least half the tests free of illegal heroin from week 14 on, considered a clinically meaningful improvement. In contrast, this criterion was satisfied by just 30% on injectable and 19% on oral methadone, creating a statistically significant advantage for the heroin patients. The more stringent criterion of no more than two tests indicative of illegal heroin use ("near abstinence") was met respectively by 41%, 9% and 7% of patients in the three treatments.

Urine tests corroborated the patients' own accounts over the last month of the trial. Of the heroin patients, 51% said they had not used illegal heroin at all compared to 29% allocated to injectable and 17% to oral methadone.

All three serious adverse events related to the medications prescribed in the study were non-fatal overdoses immediately after patients had injected at the clinics, two after injecting heroin. Patients were treated on-site and did not require admission to hospital.

These events occurred after one in every 6613 injections of heroin and one in every 5551 of methadone.

### The authors' conclusions

The authors said the study had shown that treatment with supervised injectable heroin leads to significantly and substantially lower use of street heroin than supervised injectable methadone or optimised oral methadone. The differential was evident within the first six weeks, potentially meaning that people who are (or are not) going to benefit from the expensive injectable heroin option can rapidly be identified. From a baseline of near-daily heroin use despite being in treatment, heroin patients generally achieved clinically meaningful improvements; by the end of the study, nearly half were close to abstinent from street heroin. But about a fifth of patients previously not doing well on oral methadone also greatly improved on the study's optimised oral methadone programme. Though outcomes were also better with injectable rather than oral methadone, this advantage was not great nor statistically significant.

Though rare per injection, the incidence of overdoses after injection mandates provision for medical emergencies in the form of trained and vigilant staff and resuscitation equipment, adding to an expense justified by the severity of the addiction of this minority of patients and the consequences for the patient and society if it remains inadequately treated. With other similar trials overseas, the results of this trial suggest that supervised injectable heroin should now be provided, with close monitoring, for carefully selected, chronic heroin addicts in Britain previously unresponsive to mainstream treatments.

### FINDINGS

The questions posed by the study were whether these patients, who remained wedded to illegal heroin despite extensive treatment, were simply beyond available treatments, whether they needed injectable medications, or whether it was just that their current oral treatments were sub-optimal. For some, each of these three propositions was true. A third did seem beyond current treatments even as extended and optimised by the study. For a fifth, 'all' it took was to individualise and optimise dosing, psychosocial support and treatment planning in a continuing oral methadone programme. But despite these attempts to make the most of oral methadone, nearly half the patients only did well if prescribed injectable medications. Of these medications, heroin was superior to methadone at suppressing illegal heroin use. The upshot was that the most reliable way to divorce the patients from regular illegal heroin injecting was to prescribe the same drug to be taken in the same way, but legally and under medical supervision. Given this, two thirds of these seemingly intractable patients responded well as defined by the study.

Other heroin prescribing trials have been reviewed by [Findings](#) and [more recently](#) by one of the researchers from the featured study. The conclusion was that while it does not always 'rescue' previously intractable patients, and other more conventional treatments can help if optimally delivered, heroin prescribing does usually improve on the substance use and psychosocial outcomes achieved with oral drugs. However, there are safety concerns and it is an expensive option to be reserved for the minority of patients who do not benefit from mainstream maintenance prescribing. These lessons from the research have been reflected in [UK national clinical guidelines](#) and in [guidance](#) issued by England's National Treatment Agency for Substance Misuse.

## Is a 'so what' reaction justified?

The main question over these findings (see below) are their apparent reliance on the assumption that missed tests were positive for heroin. But taking them at face value, they represent major achievements which transformed the lives of many patients and probably also saved some lives. Yet with respect to the key issue – the advantages of heroin prescribing relative to methadone – one reaction to the findings might be, 'No surprise: why *would* people continue to buy illegal heroin, risking their health and freedom, when they can have it for free?' That things are not so simple is indicated by the fact that a third of the patients allocated to legal heroin continued to frequently use illegal supplies, that recruitment to the study was unexpectedly slow, and that 40% of patients otherwise eligible to join the trial and get a chance of injectable heroin missed the required intake appointments. It is not a foregone conclusion that an offer of legal injectable heroin will be accepted by patients dependent on illegal supplies, even if they are already in treatment, or that once accepted and implemented, legal supplies will displace illegal use.

Findings published so far from the study leave it vulnerable to the accusation that it simply showed that legal heroin can substitute for illegal heroin, not a great step forward. Such reactions heighten the importance of the other outcomes promised by the trial, especially crime, health, quality of life and social reintegration. These were in part at least presented at a conference in September 2009. On such measures it seems injectable medications and heroin in particular had a far less clear-cut advantage, possibly due to the short-term nature of the trial and the small sample. If the choice (as for many patients it was) is between heroin self-injection in a hygienic, controlled and medically supervised environment with a pharmaceutical product, versus similar injections of street heroin outside the clinic, the former is certainly less risky to immediate and long-term health – a point which seems to have been made by the incidence of overdoses. Outside the clinic these might have been more serious.

## Implementing heroin treatment

Accepting that (as per national guidelines) heroin prescribing will remain a niche option for patients not doing well in optimised oral programmes, the hope is that this trial will pave the way for a revival of the treatment in Britain by showing that it can be done safely, with the expected benefits for patients and society, and without the risk that the drug will be sold on the illicit market. Supervised consumption is a presumed requirement for meeting these criteria; if heroin prescribing is to make a revival, the feasibility of implementing this requirement will be critical.

Studies in continental Europe and Britain have shown that requiring on-site injecting or smoking of heroin several times a day is feasible. However, this can only work for patients who can quickly and easily get to the clinic. Unless the network of heroin prescribing centres is greatly expanded, on-site consumption will leave large parts of Britain unserved, especially rural areas. There are other options (such as supervised consumption in a pharmacy, local surgery or drug service) but these will not be easy to organise and may be considered unsafe. The same problem arises even if on-site consumption is limited to the early stages of treatment, a precaution which may be considered necessary on patient safety grounds and one recommended by national

[guidelines](#). The inconvenience of on-site consumption can be tempered by allowing patients to skip visits and take oral medication instead, an opportunity most took advantage of in [Swiss trials](#). Insisting instead on the return of used ampoules – a tactic used with seeming success in [London](#) – may be a less intrusive and expensive way to prevent diversion.

### Methodological issues

The biggest question mark over the results of the trial is the assumption in the primary analysis that all unexplained missing tests were positive for illegal heroin. An extra 43% were missed by the oral methadone patients as opposed to the heroin patients. In the unadjusted figures, an extra 45% on heroin met the criterion for responding to treatment, a benchmark which required at least half the tests to be free of illegal heroin. It seems possible that this advantage was due largely – perhaps even entirely – to the assumption that missed tests would have indicated illegal heroin use. Though a usual assumption to make, it might be incorrect, especially if disappointed patients allocated to methadone sought treatment elsewhere. In a German heroin prescribing trial, this is exactly what [seems to have happened](#). In this study many patients allocated to oral methadone never started treatment. Partly as a result, after a year significantly more patients remained on injectable heroin. However, the same proportions were in some kind of treatment.

Inevitably, a highly controlled trial like this raises questions about its applicability to routine clinical care. The study is probably best seen as a test of what happens when people who want injectable opioids are randomly allocated instead to oral methadone, rather than of what happens when people who want oral medications are randomised instead to injectables. The kudos and *esprit de corps* associated with a groundbreaking national trial, the desire to influence service provision by demonstrating that heroin prescribing can work, and the prospect that if one could show one benefited, the treatment would continue past the end of the trial, may all have raised the performance of patients allocated to heroin. For the other groups, the prospect of a chance of injectable heroin at the end of the trial if they stuck with the study and stayed in treatment and out of prison may also have been influential. Patients may have been deterred from joining the trial by the burden of research assessments and by the fact that they had a two in three chance of not being offered heroin. In normal practice more may come forward, though still it seems likely that few would both be suitable for and accept heroin prescribing on terms similar to those offered in the study. Also the strict 'no take-aways' policy of the study could in normal practice perhaps be relaxed for patients who are stable and socially integrated and especially for those in education, training or employment, making the treatment more palatable and offering an incentive to reintegration. Patients (as many methadone patients are) who were dependent on alcohol or regularly abusing benzodiazepines [were excluded](#) from the trial.

*Thanks for their comments on this entry in draft to David Best of the University of the West of Scotland. Commentators bear no responsibility for the text including the interpretations and any remaining errors.*

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