DRUG & ALCOHOL FINDINGS *Review analysis*

This entry is our analysis of a review or synthesis of research findings considered particularly relevant to improving outcomes from drug or alcohol interventions in the UK. The original review was not published by Findings; click Title to order a copy. Free reprints may be available from the authors – click prepared e-mail. The summary conveys the findings and views expressed in the review. Below is a commentary from Drug and Alcohol Findings.

Heroin on trial: systematic review and meta-analysis of randomised trials of diamorphine-prescribing as treatment for refractory heroin addiction.

Strang J., Groshkova T., Uchtenhagen A. et al.

The British Journal of Psychiatry: 2015, 207, p. 5–14.

The UK has a long history of prescribing heroin for the treatment of heroin dependence. What has research from six countries concluded about this intensive intervention intended for patients who would otherwise be considered 'unresponsive' to treatment?

SUMMARY Diamorphine hydrochloride (pharmaceutical heroin) has been prescribed for more than a century in the treatment of heroin dependence (though only on a routine and continued basis in the UK). However, *supervised* injectable heroin treatment was not properly established until the 1990s in Switzerland.

Two features characterised the new approach: (1) supervised injectable diamorphine was not the first-line treatment, but an option for patients who had not responded to standard treatments such as oral methadone maintenance or residential rehabilitation; and (2) all doses (typically 150–250 mg diamorphine per injection) were taken under direct medical or nursing supervision, thereby ensuring compliance, monitoring, and safety, and preventing possible diversion of prescribed diamorphine to the illicit market.

Reviews conducted according to rigorous Cochrane Collaboration procedures have included all trials of heroin prescribing, regardless of whether administration of the drug was supervised or intended for take-home administration. In 2005 the first review concluded that, even though there were some results in favour of heroin treatment, "no definitive conclusions about the overall effectiveness of heroin prescription (was) possible". The second in 2011 (see Effectiveness Bank analysis) found that, on the basis of an expanded evidence base, "heroin prescription should be indicated to people who [are] currently [failing to benefit from] or have previously failed maintenance treatment, and it should be provided in clinical settings where proper follow-up is ensured".

Key points
From summary and commentary

In trials conducted over the past 15 years, supervised injectable heroin treatment has emerged as an effective treatment for people dependent on heroin who have not benefitted (in the desired way) from standard treatments such as oral methadone maintenance or residential rehabilitation.

Across six trials in six countries, supervised injectable heroin has been associated with a greater reduction in the use of illicit 'street' heroin in patients receiving supervised injectable heroin treatment than people receiving an alternative (typically methadone maintenance).

The featured paper examined trials of *supervised* injectable heroin treatment. Findings were summarised and where possible combined from similar studies to arrive at a single outcome measure. It also analysed the political and scientific response to the published findings. All trials followed a randomised controlled trial design – randomly allocating people to one of at least two groups – enabling researchers to compare the outcomes of injectable heroin with alternative treatments (typically methadone maintenance).

Main findings

Six trials in six countries over 15 years

Results were generally consistent, with each trial progressively strengthening the evidence base for the treatment approach.

Switzerland (1998). This small study was the first randomised controlled trial of supervised injectable heroin (free source at the time of writing), and contributed to establishing the safety of administering high doses of diamorphine and positive short-term outcomes. A total of 51 participants were allocated to receive either injectable diamorphine or oral methadone maintenance therapy, then followed up over a six-month period. The two groups had equivalent rates of retention, but the diamorphine-prescribed group had significantly greater reductions in illicit heroin use and crime. Continued illicit heroin use was reported by only 22% of those receiving diamorphine versus 67% of those in the methadone control group. [See Effectiveness Bank analyses: 1 2 3]

The Netherlands (2003). Representing a significant step-change in the evidence-base, two Dutch randomised controlled trials brought sufficient sample size (594 participants) and study rigour to reach more robust conclusions around diamorphine prescribing. However, only one studied the efficacy and safety of injectable diamorphine (174 participants); the other tested inhalable diamorphine (375 participants), and was therefore not included in the featured review. The retention rate at 12 months was higher for methadone maintenance therapy (85%) than for supervised injectable heroin treatment (72%), but a much larger proportion of the heroin-prescribed group (57% vs 32%) were classified as responding to treatment [showing at least 40% improvement in at least one of the three domains (physical, mental, and social) at the end of treatment]. In addition, the Dutch trials showed that supervised injectable heroin treatment was cost-effective for this target population. [See Effectiveness Bank analyses: 1 2]

Spain (2006). A small trial of 62 participants was undertaken in Andalucia, an autonomous community in southern

Spain. It found equivalent retention rates among people allocated to injectable heroin and oral methadone, but a significantly greater reduction in self-reported illicit heroin use in the prescribed heroin group at their nine-month follow-up. Despite the small sample size and the reliance on self-reported use or non-use of illicit heroin, these findings provided further evidence of benefit. [See Effectiveness Bank analysis]

Germany (2007). The largest trial to date (1015 participants) found slightly higher rates of retention in the heroin group than the methadone group. Furthermore, greater proportions of people prescribed injectable heroin reported reduced illicit heroin use. An advance in this trial was the attention to ensuring appropriate dosage for participants randomised to oral methadone maintenance therapy, thereby addressing concern that the apparent advantage of heroin-prescribing may be an artefact of suboptimal treatment in the control group. This trial was also the first to include laboratory tests for illicit heroin use, where previously there had been a reliance on self-reported heroin use; however, these results were not available for all participants. [See Effectiveness Bank analyses: 1 2 3]

Canada (2009). The Canadian North American Opiate Medication Initiative (NAOMI) trial, which recruited 226 participants, was the first trial to be conducted outside Europe. Compared with patients allocated to methadone, patients allocated to injectable heroin had significantly higher rates of retention, and a greater reduction in rates of illicit drug use and other illegal activity. [See Effectiveness Bank analysis]

England (2010). The UK Randomised Injectable Opioid Treatment Trial (RIOTT) was the first trial (see Effectiveness Bank analysis) to use laboratory tests as the primary measure of illicit opioid use. Conducted at three different locations, with 127 participants in total, the trial compared two forms of supervised injectable maintenance therapy (injectable heroin and injectable methadone) against an optimised version of oral methadone maintenance therapy. Good retention was achieved in all groups. At months four to six, the heroin-treated group was significantly more likely to provide urine specimens that tested negative for illicit heroin than the optimised methadone maintenance therapy group. [See Effectiveness Bank analyses: 1 2 3 4]

Effects of supervised injectable heroin

Opiate use. Each study reported that supervised injectable heroin was associated with a positive effect on illicit heroin use. Results could not be pooled into a single measure due to the use of different outcomes for opiate use reduction and/or abstinence.

Retention in treatment. Based on available data from four studies, there was a significant advantage of supervised injectable heroin over oral methadone maintenance therapy in terms of retention in treatment. Studies from Spain and the Netherlands were excluded because participants in the methadone maintenance therapy groups were offered supervised injectable heroin at the end of the trial period, confounding the effect of the different treatments on retention. The UK study, however, was not excluded; while in practice requests for injectable maintenance at the end of the trial period were considered sympathetically, there was no automatic right to be offered.

Mortality. The six trials collectively identified 16 events of death (six in supervised injectable heroin; 10 in oral methadone maintenance therapy) resulting in a slight (and not statistically significant) advantage of supervised injectable heroin over oral methadone maintenance therapy.

Side effects. Five trials showed a significantly higher risk of side effects – serious adverse events either probably or definitely related to the study medication – among those assigned to supervised injectable heroin compared with oral methadone maintenance therapy. The Swiss study did not report data on side effects.

Impact on clinical practice and policy

Countries where diamorphine is recognised as a medicinal product. The medical use of heroin is (and has always been) recognised in the UK as a legitimate medicine which a doctor may prescribe for the relief of pain and suffering, as well as for the treatment of opioid dependence. However, since the late 1960s, the authority to prescribe diamorphine for heroin depependence has been restricted to doctors with a special licence (essentially being addiction specialists), while all medical practitioners continue to have the authority to prescribe diamorphine for other conditions (eg, severe pain).

Countries where diamorphine is approved as a medicinal product for 'treatment-refractory heroin dependence'. In 2001, injectable heroin was registered in Switzerland as a maintenance treatment for opioid dependence. A similar process has been followed and completed over the last decade in the Netherlands and in Germany. In 2008, the Controlled Substances Act was amended in Denmark, allowing the provision of supervised heroin-prescribing.

Obstacles to implementation and optimal impact

The introduction of effective interventions can sometimes, at first, be viewed as controversial. Supervised injectable heroin treatment is an example of one such 'controversial' treatment:

'Diamorphophobia'. A critical concern relates to public and political anxiety about the acceptability of the idea of heroin being a medicinal product. While diamorphine has existed as a pharmaceutically-manufactured product in the UK for more than a century, the situation is very different in most other countries where heroin is usually seen exclusively as an illicitly manufactured drug with addictive properties. This has restricted the ability to establish clinical research trials and contributed to the refusal to provide continuity of diamorphine treatment for people beyond the end of trials. In Canada, the identification of similar benefits with injectable hydromorphone [a semi-synthetic derivative of morphine prescribed in the UK for severe pain in cancer] may show a route to circumvent more severe expressions of such 'diamorphophobia'.

Concerns about the adequacy of the scientific evidence. This was previously a major obstacle, but has now largely been addressed by the series of trials described above. Where these have been studied, all the trials have broadly shown similar benefits with regard to use of 'street' heroin and other drugs, as well as physical and mental health and social functioning. Confidence in the effectiveness of injectable heroin treatment has also increased over time; for example the 2011 Cochrane review reached a more positive conclusion than the 2005 review. However, questions and gaps in the literature still remain. While longer term data is available from eight extended follow-up studies in four countries – Switzerland (1 2), the Netherlands, Spain, and Germany (1 2 3) – more recent evidence from randomised trials on heroin treatment has tended to focus on short-term outcomes, with participants being randomly allocated to

treatment for a maximum of 12 months. Further research is needed to understand what factors influence remission from illicit drug use and how quality of life and social functioning can be enhanced among people dependent on heroin.

Concerns about safety. While much concern has been expressed over security, public safety and potential for the diversion of prescribed heroin, findings to date suggest no negative effects of the new supervised injecting clinics on public safety, and reports of growing local public support (1 2 3).

Concern that prescribed diamorphine would preferentially attract people who use heroin and undermine other treatments. This has not been borne out by evidence. Most of the six trials actually experienced difficulty in recruiting participants, either failing to reach target recruitment (1 2 3) or needing to extend the planned recruitment time (1 2). It appears that for many marginalised people using heroin, the attraction of prescribed diamorphine is rarely sufficient to promote engagement in highly structured treatment. Recent documented experience (1 2 3 4 5) suggests that many patients attending the new injecting clinics aim for sobriety in the longer term, or return to healthier stability in methadone maintenance programmes. However, this still needs to be studied further. A suitable response to the needs and aspirations of this patient group will involve investing time and resources in developing recovery-oriented heroin maintenance – an approach that would combine heroin pharmacotherapy and a sustained menu of recovery support services to assist patients and families in achieving long-term recovery.

Financial costs. In the context of ever-increasing health costs and competing health priorities, heroin prescribing might be difficult for governments to embrace. Findings of international research (1 2 3) have consistently demonstrated a considerable economic benefit of supervised injectable heroin treatment because of the reduction in the costs of criminal justice involvement, imprisonment, and healthcare. Different models of service provision of heroin treatment may identify variants of supervised injectable heroin treatment that are more affordable. This was being explored in England up until 2015 after which the central funding for this new treatment was not renewed (1 2).

Being co-opted by campaigning groups. Encouraging findings from randomised trials have been picked up by groups campaigning for major changes in the law, and in some cases the trials have been misrepresented as being about legalisation (which they were not). The trials were not about legalisation of non-medical use but about legalising access to heroin for the treatment of dependence. Careful attention to accurate secondary reporting of the findings of the heroin trials is important so that they are properly understood and the potential for advancement properly identified.

Safety. Several of the trials reported instances of sudden-onset respiratory depression in people receiving injectable diamorphine, at a rate of about 1 in every 6,000 injections (1 2) – less risky than injecting street heroin, but nevertheless producing clinically critical events. These were all safely managed with resuscitation measures, but, as noted in the 2011 Cochrane review, these findings necessitate specific attention and emphasise the importance of appropriately trained staff supervising injections.

The authors' conclusions

Based on trials conducted over the past 15 years, heroin-prescribing is a feasible and effective treatment when part of highly-regulated regimen for people dependent on heroin who have repeatedly not benefitted (in the desired way) from orthodox treatment.

At the time of publication, diamorphine hydrochloride was registered as a medicinal product for the above patient group in five European countries: Switzerland, the Netherlands, Germany, the UK, and Denmark.

FINDINGS COMMENTARY Unlike earlier Cochrane reviews (1 2), the featured paper focused solely on evidence of the effectiveness of supervised injectable diamorphine, as opposed to both supervised and unsupervised diamorphine. *Why* this would be desirable was implied in the description of what characterised the supervised approach: heroin is consumed under the watch of medical/nursing professionals, ensuring compliance, monitoring, and safety, and preventing possible diversion of prescribed diamorphine to the illicit market. Yet the British experience has predominantly been one of unsupervised consumption. Furthermore, practice has not always been to reserve diamorphine as a 'last resort' for a small minority of patients – patients with persistently poor outcomes despite optimised oral programmes – as current treatment guidelines advise (unfold the supplementary text). The findings of the review therefore reflect the best tests of diamorphine prescribing to date under the current status quo – necessarily excluding evidence of the effectiveness of diamorphine under different (and original British practice) conditions.

History of heroin maintenance in the UK

The classic 1924 Rolleston report secured a uniquely extensive space for clinical discretion in the medical response to opioid addiction, as the tightening up of drug supply laws initiated during the First World War threatened to extend to the consulting room. Two years later the outcome was a set of government-endorsed guidelines which supported doctors in continuing to supply opiates not just to treat dependence but also to 'maintain addiction' in patients who could lead a "fairly normal and useful life" with the drugs, but not without them. It was a formula which lasted more or less unaltered for 40 years and remains an important legacy, underpinning the highly unusual right of British doctors to prescribe heroin to people dependent on heroin. The key was to enshrine the view that dependence on drugs was a disease and therefore a fit target not just for treatment but also for compassion, a condition distinct from base craving, indulgence or habit. From this flowed the conclusion that, like any other disease, doctors should be free to respond as they saw fit.

However, since Rolleston's time the UK has moved away from maintenance regimens that followed the grain of the 'original addiction' by prescribing the same drug to be taken in the same manner and, if patients wanted, in their own homes (for more of which see *Prescribing opiate-type drugs to*

opiate addicts: good sense or nonsense?). In 1968 heroin prescribing became almost exclusively restricted to a few hundred specialists working from hospital clinics, easier to control than independent GPs and private practitioners. Having attracted people dependent on heroin into these more controlled settings, in the 1970s the UK moved decisively to switch them to the more 'normalising' oral methadone option pioneered in the USA.

From the mid-1990s, mainland European countries trialled and then adopted the heroin prescribing option Britain had largely abandoned, adding the requirement that the heroin be injected under medical supervision at the clinic. This continental approach cycled back to Britain via the RIOTT trial, which found that for patients who had previously not done well on methadone, heroin prescribing featuring supervised consumption suppressed illegal heroin use much more effectively than oral methadone.

Prior to the Randomised Injecting Opioid Treatment Trial (RIOTT), findings of British studies suggested that requiring patients to attend for supervised injection (sometimes multiple times a day) was often unnecessary, risked deterring patients, made it difficult for those who did start treatment to continue, and obstructed normalisation of the lifestyles of retained patients. Studies in continental Europe and Britain have shown that requiring on-site injecting or smoking of heroin several times a day *is* feasible, but this can only work for patients who can get to the clinic easily and quickly. Unless the network of heroin prescribing centres is greatly expanded, on-site consumption would leave large parts of Britain unserved, especially rural areas. 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. 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 a study in London – may be a less intrusive and less expensive way to prevent diversion.

If we needed it, RIOTT provided an indication that important keys to transforming maintenance outcomes into more like the government's recovery ambitions lie outside the treatment clinic. Despite its greater success in curbing illegal heroin use, at least in the short term heroin prescribing did not do more to improve wider drug use outcomes, crime outcomes, social reintegration, and physical and mental health. Whether prescribed oral methadone or injectable heroin, patients still faced the same housing, education, employment, financial, mental health and stigma barriers to a more fulfilling life.

An important English trial

Thoroughly analysed in the Effectiveness Bank, RIOTT was conducted at clinics in London, Darlington, and Brighton between 2005 and 2008, and recruited 127 people who continued to frequently inject illicit heroin despite being prescribed substitute oral opiate-type drugs. The aim was to tease out what worked and didn't work – were their current oral treatments sub-optimal, would they not respond to any available treatments, or would they only do well if prescribed injectable medications (either methadone or heroin)?

The biggest question mark over the results of the trial was the assumption in the primary analysis that all unexplained missing tests were positive for illicit 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 illicit heroin. It seems possible that this advantage was due largely – perhaps even entirely – to the assumption that missed tests would have indicated illicit 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.

A new wave of heroin prescribing?

In October 2019, a heroin-assisted treatment programme was launched in Middlesbrough – aimed at "people with a long-term dependency on heroin, who have failed to respond to any other drug treatment" and initially targeting up to 15 of the most 'at risk' people in the locality who were "causing most concern to criminal justice agencies and health and social care services".

> *"Individuals selected to take part in the treatment will be asked to attend a specialist facility in Middlesbrough twice a day, seven days a week, where they*

will be assessed to determine the dose of diamorphine (medical grade heroin) they will be prescribed that visit."

"Participants will then be taken to a dedicated treatment room, where they will self-administer the diamorphine under supervision of medically trained staff. They will be assessed for 10–15 minutes to ensure there is no adverse reaction to the medication."

"Once their drug use has stabilised, participants will spend time with specialists from other agencies to help them rebuild their lives and reintegrate into society."

Supervised heroin prescribing has been supported in Middlesbrough by Police and Crime Commissioner Barry Coppinger, who said "The time is right to try a new approach to reduce the impact drug misuse has on services and communities".

In November 2019, a similar initiative was rolled out in Glasgow (1 2 3), with plans to work with up to 20 people by the end of the first year who would receive tailored doses of diamorphine for injection on the premises under supervision. Dr Saket Priyadarshi, associate medical director and senior medical officer of Glasgow Alcohol and Drug Recovery Services described the facility as "much-needed", but also expressed "frustration" that the path to a complementary service (drug consumption rooms) had so far been blocked. Drug consumption rooms are hygienic and supervised spaces for people to inject or otherwise consume illicit drugs. The point of having both drug consumption rooms and supervised diamorphine prescribing within the portfolio of services is that they appeal to and are designed to benefit different groups of people. Dr Priyadarshi said, "We have new cases of HIV every year and our drug-related death rate is rising too, and the people who are experiencing the most significant harms are those who would benefit from a drug consumption room".

For further reading, search for analyses of heroin prescribing or the prescribing in injectable drugs in the treatment of opioid dependence.

Thanks for their comments on this entry in draft to Dr Tom Carnwath, Consultant Psychiatrist with accreditation in general adult psychiatry and addiction psychiatry. Commentators bear no responsibility for the text including the interpretations and any remaining errors.

Last revised 20 December 2019. First uploaded 23 September 2019

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