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Role Reversal

Controversial, expensive, yet promising so much, interest is increasing in prescribing heroin to heroin addicts. It's the drug field's ultimate role reversal – from killer drug to lifesaving medication. Just five studies hold the answers to whether it can work.

by **Mike Ashton**
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Led by government ministers frustrated at slow progress in the fight against serious drug problems, Britain is about to revive its acquaintance with heroin not as a drug of abuse, but as a treatment for drug abuse. Heroin prescribing has traditionally been the main distinguishing feature of what was seen as the 'British system' for responding to heroin addiction. It rested on the unique legal leeway afforded doctors in Britain, until recently the only nation which allowed heroin (in its pharmaceutical form called diamorphine) to be prescribed for the treatment of addiction. Before 1968, any doctor could exercise this prerogative. Since then the treatment has been restricted to specialists who hold the requisite Home Office licence, nearly all of whom work in NHS drug dependence clinics.

At first the dominant response to the 1960s UK heroin outbreak, soon diamorphine prescribing waned to be replaced by injectable and then oral methadone. Of the 70 or more licensed doctors today, perhaps 50 prescribe diamorphine (almost entirely in injectable form[1]) to just 450 patients.[2] An increase in these numbers can be expected to flow from the commitment in the UK's latest drug strategy to ensure that "properly supervised heroin prescribing" is available "for all those who would benefit from it", regardless of where they live.[3] Clinical guidance is expected soon from the Department of Health.

Despite its unique history, British evidence on diamorphine's value is thin *The nature of the evidence*, p. 23. Worldwide there are just five directly relevant studies. Each is outlined in numbered panels on the following pages and referred to by those numbers in the main text. Where they help fill out the picture we have also drawn in other studies.

Why consider diamorphine?

The 'Why bother?' question is the main one diamorphine has to answer. After all, Britain has spent the last 30 years moving *away* from diamorphine and towards oral methadone, a treatment with substantial research backing and which benefits many thousands of patients. Only if there are substantial *extra* benefits compared to oral methadone might the extra costs and risks be justified. Even then there would remain the issue of whether injectable methadone might provide the same benefits yet permit a less drug-dominated lifestyle – injecting once rather than three times a day and less pronounced mood swings.

The potential advantages of diamorphine derive from its anticipated pulling power for heroin addicts, defined traditionally and legally in Britain as having an "overpowering desire" for the chemical.[4 5] Those who find methadone unappealing or for whom it fails to curtail heroin use might be attracted and retained by diamorphine, extending the benefits of maintenance therapy – social stabilisation, risk and crime reduction, health improvements – to yet more patients.

The same pulling power is the source of diamorphine's potential drawbacks. Once known to be an option, new patients who would have been satisfied with and done well on oral methadone may demand diamorphine. They may even deliberately fail on methadone to 'qualify' for the drug. Once in diamorphine treatment, relatively safe, hassle-free and cash-free access to their drug of choice might prolong patients' careers as addicts and as patients. Injectable diamorphine maintains the frequency of injecting with its associated risks. As in the 1960s, addicts may sell all or part of their diamorphine, spreading addiction and risking the purchasers' lives, yet preventing this by requiring thrice daily attendance for supervised injection is costly and unpopular with patients.

Establishing the validity of these hopes and fears sets the agenda for this review.

An attraction in to treatment?

No study has directly addressed whether offering diamorphine as well as or instead of methadone widens the range of heroin addicts attracted in to treatment. Only addicts *already* in methadone treatment or with prior experience of methadone have been studied. Beyond them may be an un-

known number of heroin devotees who would not enter treatment at all unless diamorphine were available.

Such evidence as there is suggests that for opiate addicts in treatment or with experience of methadone, diamorphine would rarely be a front-line treatment choice, though in London at least a quarter and perhaps as many as half wanted a prescription which included injectables.[6]

Patients for whom methadone and especially injectable methadone has failed are more likely to opt for diamorphine. Even in these samples, a substantial minority – in some cases, most – opt to try or re-try methadone in injectable form. Yet more would accept this if they had to. These findings remind us that many heroin addicts enter treatment precisely to *move away* from a drug which has now unacceptably disrupted and dominated their lives.

For example, in study ❸, 37 out of 58 patients chose injectable diamorphine but 21 opted for injectable methadone. However, the 200mg ceiling on both drugs was a much less generous dose of diamorphine.[7] This sample was selected to have had unsuccessful experiences with oral methadone and two-thirds had also tried injectable methadone, presumably with no lasting success.

Research in Manchester was uncontaminated by dose restrictions yet came up with a similar finding.[8] As in study ❸, the clinic prescribed injectable methadone or diamorphine to patients who continued to inject despite receiving oral methadone. Both in dose (ranging up to 200mg methadone daily and 480mg diamorphine) and in restrictions (patients could pick up from pharmacies and inject at home) there was a level playing field for both drugs. Yet on entering treatment half the patients were hoping for injectable methadone and just a third diamorphine, figures which might have been biased by what they felt it was realistic to hope for.

In the event, just 1 in 8 were prescribed diamorphine. After attending the clinic for on average three to four years, about half saw injectable methadone as the best treatment option, a third diamorphine. The proportions reversed when patients were simply asked which drug they would choose, suggesting a degree of ambivalence over moving away from heroin.

Even in these relatively conducive circumstances, more often than not injectable methadone was the preferred treatment. Elsewhere, diamorphine's attractions would be further eroded by the need to travel to specialist centres and by extra restrictions such as prohibiting take-home doses[9] and requiring supervised consumption[6 10] or frequent attendance.[11 12] Such restrictions may explain why in seven months a study in Geneva (study ❹) which offered the chance of high doses of diamorphine managed to attract just 61 regular heroin users.

Do patients stay longer?

Retention is important because unplanned early exits from methadone maintenance usually mean reversion to pre-treatment levels of crime and illicit drug use.[13] Staying on does not guarantee good outcomes,[14 15] but the link between the two is strong.[16 17] This also seems the case for diamorphine. In the Netherlands, wholesale relapse followed forced reversion to methadone. In Switzerland, the longer patients had stayed in diamorphine treatment, the less likely they were to leave for non-therapeutic reasons such as drop-out or discharge for breaking clinic rules, and the more likely they were to no longer be using heroin after leaving.

Findings detailed below provide strong evidence that prescribing diamorphine to patients assessed as suitable for this option (normally because they have not done well on oral methadone) does result in much longer retention than on oral methadone. There is also some evidence of longer retention compared to injectable methadone. Where available, one-year retention rates are cited to aid comparability. We also explore what people left to go to; it would be perverse to condemn an early exit to a life free of opiate dependence as 'poor retention'.

Experience in Britain

Unlike trials in the Netherlands and Switzerland, relevant British studies did not disadvantage diamorphine by imposing potentially deterrent supervised consumption regimes, but sometimes they did tip the balance by restricting dose levels. Still, diamorphine's retention benefits were clear cut.

❶ In the 1970s trial in London, 74% of patients seeking diamorphine treatment and who got what they wanted were in the same treatment 12 months later, but only 26% prescribed oral methadone. Doses were roughly equal, meaning that in practice diamorphine was being prescribed at a much lower level.[7] About 40% of treatment leavers from both groups had (for at least the time being) achieved a virtually opiate free lifestyle during the last month of the follow up.

In contrast to the early '70s, in most areas diamorphine is now effectively closed to new patients, raising the possibility that today more might feel they have no alternative but to stick with oral methadone. However, later studies have reinforced its findings.

❷ Over a six-month follow-up period, 36% of oral methadone patients at English community drug clinics left treatment, but just one (4%) prescribed diamorphine. Striking as it was, this gap might have been greater had the first interview been done at treatment intake rather than months later, when most patients who were going to drop out had probably already done so. Dose levels seem to have been roughly even but the diamorphine patients are likely to have been a more problematic group, making the drug's retention advantage all the more significant.

Conceivably, some of the oral methadone patients exited to an opiate-free lifestyle. After all, they had been in treatment for about a year and three quarters were aiming for abstinence. However, this seems an unlikely explanation for the difference in retention. Leavers were probably concentrated among those who continued to use heroin and were not aiming to stop.[i]

❸ In the latest British study, after 12 months 59% of patients who chose injectable diamorphine were still in treatment compared to 48% who chose injectable methadone. Outside a research context, retention would have been higher: ten of the 25 leavers were discharged for breaking the study's rules.

The study itself offers no comparison with oral methadone but can roughly be benchmarked against the 'poor responders' in NTORS' oral methadone maintenance

Golden Bullets

The main practice implications of this article

- Diamorphine can attract and retain heroin addicts who have not benefited from oral methadone, achieving large reductions in drug use and crime and improvements in health and social stability.
- Explicit criteria can be used to select patients for injectables based on lack of success in optimised oral regimes evidenced by continued illicit heroin use and poor social and health functioning.
- Injectable methadone often provides an acceptable and effective compromise between oral methadone and injectable diamorphine.
- Remaining addicts who will only respond well to diamorphine are likely to be a small but important minority. For these patients diamorphine is a cost-effective option.
- Guidelines encouraging supervised consumption require specialist facilities and staff trained to handle drug-related emergencies.
- A balance needs to be struck between highly controlled regimes which prevent diversion but fail to attract some patients who would benefit, and overly-relaxed regimes which risk diversion and provide no incentive for patients to move on.
- Local service networks should facilitate two-way transfer between oral and injectable regimes.

Study ❶ London clinic, early 1970s

The only British randomised comparison of diamorphine and methadone was conducted in London in the early 1970s. 96 heroin addicts seeking treatment at a clinic were randomly allocated to either injectable diamorphine or oral methadone maintenance. Patients were included in the trial only if they had been insistent that diamorphine was the drug they wanted, had rejected alternative therapies, and had been injecting heroin daily for at least three months at high enough doses to convince staff that diamorphine might be appropriate. In practice, the trial's subjects were using twice as much heroin as the 164 heroin users who did not qualify for the trial. Nearly all had criminal records (averaging about three non-drug convictions) and about half these pre-dated opiate use. A substantial minority reported serious psychological disturbance including nearly 4 in 10 who had attempted suicide.

No special anti-diversion measures or extra attendance requirements were imposed on the diamorphine patients. Diamorphine and methadone doses were modest, generally ranging from 40 to 80mg daily and averaging 60mg, meaning that diamorphine doses were much less generous.[7] However, pre-treatment use levels also seemed modest, averaging an estimated 74mg of pure heroin.[viii] All but four patients were followed up 12 months after treatment entry regardless of whether they had dropped out of treatment.

1

Hartnoll R. *et al*. "Evaluation of heroin maintenance in controlled trial." *Archives of General Psychiatry*: 1980, 37, p. 877–884.

programmes. As at treatment entry in study ❸, these patients were also continuing to use drugs heavily despite oral maintenance treatment. In NTORS just 38% were still in treatment 12 months later.[22] The implication is that many addicts resistant to oral methadone treatment will stick with injectable diamorphine, even when dose is restricted.

Experience overseas

Applicability of the next two studies to Britain suffers from their very different contexts, including the requirement to attend daily for supervised consumption. Both suggest that patients who leave highly regulated diamorphine treatment often do so because its success means they no longer have to put up with the inconvenience.

❹ 70% of Swiss diamorphine patients stayed in the treatment for at least a year. Just over half the leavers progressed to treatments entailing a move away from injecting or from opiate use. They had some success. Of those who could be contacted, 85% were no longer using heroin daily, rising to 90% among patients who had left after more than a year in treatment. However, many could not be contacted. Taking these into account, still at least half of all leavers were no longer using heroin daily. Despite the inconvenience of supervised consumption and a more problematic caseload, the 70% one-year retention rate on diamorphine bettered the 57% in Swiss oral methadone programmes.

❺ The only seemingly contradictory results come from the Netherlands. 70% of diamorphine patients completed 12 months of treatment but 86% receiving only oral methadone. However, treatment success or progression seemed major reasons for leaving diamorphine early. At 12 months well over half the diamorphine leavers were doing well[ii] but only a handful of methadone leavers. Many who left voluntarily or for health reasons did so to return to methadone.[21]

For these Dutch patients used to 'low threshold' methadone services with minimal supervision, the highly regulated diamorphine clinics must have been a shock. The 26 leavers doing well on diamorphine may have decided there was no longer any need to endure these procedures. Also tipping the retention balance against diamorphine is the fact that a quarter of patients were discharged for 'disciplinary' reasons, casualties perhaps of an inflexible and demanding regime.

Do patients do better?

Since diamorphine programmes retain patients longer than methadone programmes, outcomes too can be expected to be better. The evidence on illicit opiate use and on social, crime and health problems supports this expectation. However, outcomes are not only better because more patients are retained, but also because retained patients make greater improvements.

Here especially, what diamorphine is being compared *against* is critical. Rival methadone regimes have often been suboptimal, but to an extent the same is true of diamorphine ◤ *The nature of the evidence*, p. 23. How an optimised oral methadone regime would compare with an optimised diamorphine regime remains an open question.

Experience in Britain

❶ In the 1970s London trial, with respect to drug use, 'no difference' was the overall verdict. In the twelfth month after treatment had started, 36%[iii] of patients on injectable diamorphine and 41% on oral methadone had reduced their illicit opiate use to twice a week or less. Among the remainder, there were more relatively heavy users in the oral methadone group – 37% versus 26%. These differences were not statistically significant and nor were differences in the use of non-opiate drugs, health, or employment.

On crime, diamorphine held the lead. After a year this remained a major source of income for 43% of patients allocated to diamorphine and 61% methadone. Taking baseline levels into account, the gap was no longer statistically significant, but arrest and prison experiences across the follow-up year confirmed diamorphine's lead: half the diamorphine patients had avoided arrest and 81% imprisonment, compared to 28% and 68% on oral methadone.

On both drug use and crime, diamorphine's benefits would probably have been more evident had dosing not disadvantaged the diamorphine patients.

❷ In a later English study, when first interviewed after on average the best part of a year in treatment, fewer diamorphine than methadone patients were using illicit heroin (22% v 69%), they spent far less on illegal drugs, and they had committed non-drug crimes on just two days in the last 30 compared to six on oral methadone. Their psychological health too was significantly better.

Limitations of the study preclude strong conclusions and results are confined to patients still in treatment. The impression is of a group of diamorphine patients who probably started treatment with more problems yet who, given adequate doses and a relatively undemanding, retention-enhancing regime, ended up feeling better, using illicit drugs less, and committing fewer crimes than patients limited to oral methadone.

❸ The fact that treatment-leavers at a London clinic were not followed up hampers assessment of which group of patients benefited most from their choice of injectable diamorphine versus injectable methadone. In both groups patients who *stayed* in treatment made significant early gains in drug use, crime, and in health and social functioning, gains sustained at the one-year follow-up. However, treatment leavers were probably not doing so well. The same problem prevents meaningful comparison between diamorphine and injectable methadone.

What can be said is that both groups made significant improvements on injectables which they had not made in previous oral treatments, and that many more diamorphine patients stayed to experience these benefits. Since the regime was typical of Britain, similar outcomes can be expected at other

A Dutch patient reaches for the drugs and syringe slid to him under a glass partition.

clinics, and perhaps bettered if they abandon the study's severe diamorphine dose cap.

Interestingly, this study called into question a supposedly major advantage of injectable methadone – that patients have to inject just once a day. Continued injecting of illicit drugs and a preference for splitting their methadone meant that at first seven out of ten methadone patients actually injected two or three times a day. Splitting was a response to the discomfort caused by injecting large volumes of concentrated methadone, a problem also noted in Switzerland. However, no methadone patient injected four or more times a day, a rate seen at first in nearly half the diamorphine patients. Over time both groups reduced injecting frequency.

Experience overseas

❹ Among patients retained in treatment (and most were for at least two years), the Swiss trials showed substantial reductions in illicit drug use and crime and improvements in physical health, emotional well-being and social functioning, all the more impressive given the past failures of oral methadone. No one fatally overdosed on prescribed heroin and the death rate of 1% per treatment year compares favourably with other treatments, especially since many deaths were probably due to pre-existing disease.

Despite diamorphine retaining more problematic patients, the gains were greater than in patients retained in Swiss oral methadone programmes. For example, 18 months after entering treatment just 5% of diamorphine patients were using heroin daily compared to 21% on methadone. However, rates of heavy (daily) drinking remained high, involving about a third of patients.

But these figures concern only patients still in treatment. A sub-study attempted to contact *all* patients and former patients 13 months to four years after starting treatment. Just 3%–16% were still using illegal heroin virtually every day (compared to 40%[iv] two years after starting methadone treatment in England[18]). Cocaine use and crime too were at a fraction of their pre-treatment levels.

Only in Geneva was injectable diamorphine directly compared to a control condition consisting mainly of oral methadone treatment. Six months after starting treatment, no diamorphine client was using illicit heroin daily compared to nearly half the controls. Their spending on illicit drugs and criminal income had fallen to a tenth of pre-treatment levels while both remained high in the control group. Psychological and social functioning improved more than in the controls as did the number of overdoses and feelings of well-being. Suicide attempts were virtually eliminated in the diamorphine patients but increased in the control group.

Whether these advantages can be attributed to diamorphine itself is unclear. Extra services available to the diamorphine group seem visible in the fact that 15 of 27 were treated for mental health problems compared to just 2 out of 21 in the control group.[v] Still, this study goes part way to answering the major question hanging over the Swiss studies: whether diamorphine patients would have done just as well in a further attempt on oral methadone. If Geneva is anything to go by, most (but by no means all) would once again have found this ineffective.

❺ A similar verdict emerged from the randomised trial in the Netherlands. At the 12-month follow-up, about half the diamorphine patients had made substantial improvements in their previously poor health, social functioning or psychological adjustment, 24% more than on oral methadone only. Improvements on diamorphine were spread across all three types of outcomes but on methadone tended to be limited to just one. Some of the clearest benefits were in reduced crime. However, many patients in both groups remained immersed in drug using circles featuring cocaine.

For the first time the study showed what can happen when diamorphine patients are forced to revert to methadone. Two months later over 80% who had previously done well had returned to their poor pre-treatment levels of functioning, seemingly strong evidence that the diamorphine treatment caused the improvements.[19] The fact that in this study patients knew that relapse might lead to reinstatement (so may have engineered 'failure' on methadone) does not diminish the relevance of the findings. Unless clinics elsewhere denied reinstatement to the very patients who seemed to need it most, a similar relapse rate can be expected in normal practice.

What it was about the treatment which made the impact is harder to pin down. Factors other than the drug being prescribed could have influenced outcomes, most notably dose levels. Methadone patients received on average about 70mg a day – high by Dutch standards but below levels recommended to prevent illicit heroin use.[20] Diamorphine patients received just 10mg less plus very large doses of diamorphine, which were adjusted to eliminate illicit use. As in Switzerland, attendance requirements may also have been influential as may the new staff and facilities at the diamorphine clinics.

Critics argue that given a similar regime, methadone patients might have done just as well. In the Dutch context, they miss the point – there *could not* have been a similar methadone regime. High dose levels and attendance requirements were themselves reliant on the pulling power of diamorphine. Methadone patients would have found them unacceptable. If anything, in this study it was the diamorphine option which was disadvantaged. Equalisation of pyschosocial inputs to the generally low Dutch uptake level meant that this pulling power could not be exploited to increase engagement in interventions with the potential to lever more patients out of a drug-based lifestyle.

Study ❷ English community drug team

One of three clinics run by the same community drug team in England changed to offering the option of diamorphine maintenance for patients who did not want to stop using heroin or felt unable to do so. The other two remained restricted to oral methadone. Regimes at all three were similar, involving usually weekly attendance to review treatment and for counselling. Dosing was flexible, averaging 253mg diamorphine daily and 72mg methadone.

27 patients prescribed injectable diamorphine were matched with 39 oral methadone patients from the other two clinics to achieve roughly equivalent samples in terms of age, gender, length of opiate use (averaging 10–12 years), and duration of current treatment. At their first interview the diamorphine patients had already been in this treatment for on average 11 months, methadone patients for nine. About six months later those still in the same treatment were re-interviewed.

Despite rough matching, the diamorphine group must have been a selected set of patients able to convince an experienced psychiatrist that they needed the drug. We know that at treatment entry they all felt unwilling or unable to stop using heroin. This reluctance continued through to the in-treatment interviews when they were much less likely than methadone patients to avow abstinence as a treatment goal.

Without pre-treatment data or random allocation, in this study it is not possible to say to what degree any differences in retention or outcomes were caused by the difference in treatments. Influences such as different staff, doctors, areas and differences in the patients themselves could have affected the outcomes. Patient differences are likely to have disadvantaged outcomes for diamorphine. Patients offered this treatment were probably more severely dependent, and pre-study drop-out would probably have been higher among the methadone patients, leaving a relatively stable set of interviewees.

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McCusker C. *et al*. "Prescribing drug of choice to illicit heroin users: the experience of a U.K. community drug team." *Journal of Substance Abuse Treatment*: 1996, 13(6), p. 521–531.

OFFCUTS

Two new services aim to help you choose prevention resources and to develop the evidence base. The **Drugs Education and Prevention Information Service** (DEPIS) and the **National Drug Prevention Development Team** (NDPDT) can be accessed via www.doh.gov.uk/drugs.

DEPIS is run for the Department of Health by DrugScope. At its core is a searchable database of resources and projects with evaluation reports and expert assessments. DEPIS also offers free consultancy on the evaluation and dissemination of prevention projects – visit www. drugscope.org.uk.

NDPDT supports the development and dissemination of the drug prevention evidence base. To come are information packs on how to set up and evaluate a prevention project, a bank of useful documents and policies, and practitioner forums.

Who needs diamorphine?

Concern that some patients who meet clinical criteria for diamorphine would do just as well on oral methadone has some basis, but studies suggest these are a minority and one not clearly identifiable. To deny diamorphine to all potentially suitable patients in case some don't need it would sacrifice the gains that many only make on diamorphine.

Experience in Britain

❶ A year later, 19 of the 46 London patients denied their insistent requests for diamorphine and given oral methadone instead had nevertheless been able to move away from regular use of illicit opiates. But this study recruited patients who today would be considered insufficiently problematic to qualify for diamorphine.[vi] More exacting entry criteria would probably have cut the number who did well on oral methadone.

The oral methadone patients tended to polarise into either abandoning legal and illegal opioids altogether, or staying heavily immersed in opioid use and drug using circles. An attempt to characterise patients who did poorly on methadone came up with nothing clear cut, but they did tend to have come from families of lower socioeconomic status, to have left school early and started crime young (often before drug use), and to have been separated from their mothers. There were no such links in the diamorphine group. The implication is that people handicapped by early deviancy and family breakdown and who lack social and economic resources are least able to make use of oral methadone as a route out of addiction.

Experience overseas

❹ At the start of the randomised Swiss substudy in Geneva, presumably nearly all the patients wanted diamorphine (or they would not have volunteered for the study). Six months later those who missed out in the lottery could transfer to diamorphine, but just nine out of 24 did. Despite on average three prior attempts, most of the rest were now making what they felt was satisfactory progress on methadone. This was not self-deception. At the six-month follow-up, about half of all the patients allocated to methadone were using heroin at most only occasionally. Improved methadone programmes in Geneva and rapid admission assisted by the research project might partly explain their success this time round.

This is the only study directly relevant to whether patients will deliberately fail on methadone in order to qualify for diamorphine. It suggests not.

❺ The Dutch study provides the most comprehensive method yet for selecting patients for diamorphine, one which seems to have minimised the number prescribed diamorphine who would have done as well on oral methadone.

Twelve months after entering treatment, nearly 30% of the methadone patients were responding well. However, improvements were nearly always limited to one area of functioning while problems elsewhere remained. As a result, under 1 in 10 had (by the study's own criteria) improved enough to no longer be considered for diamorphine – perhaps the most meaningful indication yet of the proportion of addicts who 'qualify' for and want diamorphine, but would actually have done well on oral methadone.

For this minority, the diamorphine programme would have been an unnecessary inconvenience and for the health system an unnecessary expense. But to have consigned the entire sample to oral methadone on these grounds would have sacrificed the remission of nearly twice as many patients who would only have done well on diamorphine.[vii]

The risk of 'getting stuck'

Diamorphine's presumed pulling power becomes counter-productive 'stickiness' if it unduly delays the ending of opiate dependence and of its treatment. The result would be reduce the capacity of specialist clinics (virtually the only source of this treatment) to recruit new patients. Beyond this practical consideration, probably few people see a life under the influence of opiate drugs as desirable – just better if legal rather than illegal.

No study has yet assessed whether diamorphine treatment prolongs addiction by mounting a long-term follow-up comparing diamorphine patients with a similar group not given this treatment. In fact, there is very little evidence at all on the time course of diamorphine treatment. Instead we have to piece together clues from studies not designed to answer this question. British studies of relatively relaxed regimes without supervised consumption suggest that some patients do stay on who in other circumstances would have progressed to other treatments or away from drugs altogether. In contrast, Swiss studies of highly structured diamorphine programmes suggests that a few years in these is more than most people wish to experience, especially if there are good quality treatments to move on to.

Experience in Britain

❶ In the 1970s London trial, a year later 14 of the 46 patients denied their demands for diamorphine and given oral methadone instead had became virtually opioid-free. If they been granted their wishes, ten of the 14 (based on what happened to those who did get what they wanted) might still have been in treatment and dependent on diamorphine. Today, only clients more entrenched in their addiction would normally be considered for diamorphine and fewer may be able to use

Study ❸ London clinic, late 1990s

3

An injectable prescribing clinic in London recruited 58 long-term opiate dependent injectors who still regularly injected and suffered drug-related problems despite relatively high dose (at least 80mg daily) oral methadone treatment. Patients could choose either injectable diamorphine (37 did) or injectable methadone (21) and were followed up for 12 months.

Drugs were dispensed at the clinic at first daily and then less often. There was no routine requirement for supervised consumption and the diamorphine group did not have to attend more often. Doses of both drugs were capped at 200mg, disadvantaging the diamorphine patients.[7] Among patients retained for 12 months the average ending dose of diamorphine was 185mg, of methadone, 161mg.

The study's prime value is that it reflects normal British practice: only patients who had not done well on oral methadone were admitted, injectable methadone and diamorphine were both on offer, and the clinic operated a fairly typical dispensing and attendance regime. This means that its outcomes are a guide to what to expect at other clinics which decide to mount an injectable prescribing programme. The main limitation to generalisability is the unusually low cap on diamorphine doses.

Metrebian N. *et al*. "Prescribing drug of choice to opiate dependent drug users: a comparison of clients receiving heroin with those receiving injectable methadone at a West London drug clinic." *Drug and Alcohol Review*: 2001, 20, p. 267–276.

Metrebian N. *et al*. "Feasibility of prescribing injectable heroin and methadone to opiate-dependent drug users: associated health gains and harm reductions." *Medical J. of Australia*: 1998, 168(12), p. 596–600.

Study 4 Switzerland, 1994–2000

In Switzerland nearly 2000 opiate addicts started diamorphine maintenance at 21 centres as part of a national evaluation.[28] To enter the trial they had to exhibit marked social and health damage from at least two years of dependence on injecting heroin despite at least two prior treatment attempts. On average they had been addicted for 10 or more years and over 9 in 10 had unsuccessfully tried methadone maintenance. Unemployment and debt were the norm, and half had no stable housing, were raising money through crime, or in poor physical or mental health.

Patients took an average of 474mg diamorphine daily under supervision at the clinic up to three times a day. Nearly a quarter also received methadone. Weekly counselling was mandated with optional further assistance, a more intensive level of support than in oral methadone programmes. However, more often than not these services were not delivered or used at the intended level.

The most stringent test of whether injectable diamorphine improved on oral methadone was a sub-study in Geneva, where 51 patients were randomly allocated to injectable diamorphine (27) or to a six-month waiting list (24) during which time at least 19 received oral methadone from usual sources. Full six-month follow-up data was obtained from all the diamorphine patients and 21 of the controls. In this study extra services such as psychiatric care were available to and used by the diamorphine patients.

Without in any of the Swiss studies a control group given equally intensive therapy but offered only oral methadone, it is impossible to be sure that the diamorphine part of the treatment caused the improvements. The influence of non-drug elements was presumably why, despite similar prescribing regimes, outcomes differed at different clinics. The analysis failed to adjust for these differences, a possible source of bias.[29]

The findings must also be seen in the context of a well-resourced treatment system in a country whose addicts' health and social conditions compare favourably with Britain.[30] In particular, the Swiss patients committed acquisitive crimes at about one eighth of the rate of patients entering English methadone programmes.[31] Information is most complete for retained patients; reports on the full sample exclude treatment leavers and a study which did follow these up managed to interview just 61%.

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Rehm J. *et al*. "Feasibility, safety and efficacy of injectable heroin prescription for refractory opioid addicts: a follow-up study." *Lancet*: 2001, 358, p. 1417–1420.

Uchtenhagen A. *et al*. *Prescription of narcotics for heroin addicts. Main results of the Swiss National Cohort Study*. Basel: Karger, 1999.

Perneger T.V. *et al*. "Randomised trial of heroin maintenance programme for addicts who fail in conventional drug treatments." *British Medical Journal*: 1998, 317, p. 13–18. (The randomised trial in Geneva.)

oral methadone as a platform for recovery.

❷ After on average about a year in treatment at an English drug clinic, nearly 4 in 10 of the patients prescribed diamorphine saw abstinence as a current treatment goal – surprisingly high, since at treatment entry all had felt unable to try to stop using heroin. However, this 'goal' was perhaps more an ambition than an intention. In the next six months, just one of the 27 came off diamorphine. Perhaps worryingly, by then half as many (20%) were aiming for abstinence.

Experience overseas

❹ Reports on seven years of diamorphine maintenance in Switzerland provide the longest perspective. At treatment entry the patients had been addicted for 10 years and probably had no intention of ceasing to use heroin in the near future. Yet within five years, two thirds had left treatment and most of these were no longer using heroin daily. Overall, within five years perhaps half of all treatment starters were no longer dependent on heroin, legal or illegal.

Having treatments to move on to seemed important. Over the full seven years, 61% of leavers left to enter other treatments, mainly methadone maintenance. This was the norm in the first year and became more common the longer a patient had been on diamorphine. At follow-up, discharged patients who had gone on to further treatment were less likely to be using heroin daily (8% v 20%) and more likely to have divorced themselves from the drug scene and from crime.

In this study patients had a strong incentive to leave – years of having to attend a clinic up to three times a day. They also had a well stocked armoury of treatments to move on to which the diamorphine clinic helped them to access.

❺ In contrast to the mainly voluntary Swiss discharges, the Dutch experience shows that attempting to curtail treatment by forcing patients to leave is likely to be a mistake. As the one-year deadline approached, the clinics did what they could to smooth the way back to methadone. Diamorphine was tapered with almost always a parallel increase in the methadone dosage, and each patient was helped to develop a personal treatment plan.[21] Nevertheless, over 8 in 10 previously doing well relapsed so badly that re-admission to diamorphine treatment had to be considered.

Assessing local need

Having established (as far as possible) that diamorphine maintenance is both feasible and effective for selected patients, there remains the important issue of how great the need might be. A final answer can only be given after oral and injectable methadone (and perhaps too buprenorphine) regimes have been optimised. Only then will we know how many heroin addicts actually need diamorphine as opposed to a more responsive methadone regime.

Given current provision, about a fifth of patients entering English methadone programmes do not respond well to treatment.[22] From these could be subtracted those who would accept and do well on injectable methadone (as we've seen, probably the majority) leaving a residue of patients who will only do well on diamorphine. To these existing patients must be added an unknown number who would enter treatment only if diamorphine were available. How great this number is will also depend partly on the accessibility and responsiveness of current non-injectable regimes.

Once the smoke clears, the need for diamorphine is likely to extend beyond the current 450 patients,[2] but with improved methadone programmes, probably not dramatically so. Whether this need materialises in patient numbers will depend on what comes with the diamorphine. As in Geneva, programmes which require continued attendance several times a day for supervised injection can find it hard to tempt patients away from less demanding oral regimes or to recruit addicts not currently in treatment. Such regimes are also costly, limiting the number of slots health services will be prepared to fund.

Organising diamorphine services

Ideally, diamorphine prescribing will be implemented in areas which already have well functioning oral and injectable methadone services. These might also be the best location for diamorphine programmes. Integrating these options avoids patients 'losing their place' if they transfer between them, a risk likely to deter progression from diamorphine to injectable and/or oral methadone. It would also ease movement in the other direction. This could be important because cost-effectiveness and other considerations suggest that patients should be encouraged to try oral methadone first. If injectables clinics are separate, they will need to ensure that patients who transfer to another service to try oral drugs can quickly return if this does not work out.

There will also be a need for good links with detoxification, rehabilitation and aftercare services. British patients offered diamorphine have normally been approaching their fortieth birthdays and addicted to heroin for a decade or more.[8,23] Swiss experience is that,

Study 5 The Netherlands, 1998–2001

The largest randomised diamorphine trial conducted so far involved 549 patients treated in six cities in the Netherlands between 1998 and 2001. Patients were long-term heroin users who used heroin daily and evidenced poor physical, mental, or social functioning. All had been treated repeatedly with oral methadone at doses of at least 60mg (or 50mg for smokers) for at least four consecutive weeks and were currently enrolled in a methadone programme. In separate studies for injectors and smokers, patients were randomly allocated to diamorphine (injectable or smokable) plus supplementary oral methadone for 12 months, or placed on a waiting list and prescribed oral methadone only.

Diamorphine up to 1000mg daily was consumed under supervision three times day at special clinics with newly recruited staff. Doses were adjusted with the aim of eliminating illicit heroin use. Oral methadone was prescribed daily by existing services using normal protocols up to a maximum of 150mg daily. Dutch methadone services generally restrain dose levels to allow patients to continue to experience heroin. In practice, therefore, the trial was largely a comparison of oral methadone plus either prescribed or illicit heroin. Diamorphine doses averaged 549mg daily supplemented by 60mg of oral methadone; methadone-only patients averaged about 70mg a day. Counselling and other therapies were made equally available to both groups.

A 40% improvement in at least one of the problem areas where the patient was doing badly before treatment, without deterioration elsewhere or increased resort to stimulant drugs, were the criteria for a 'good' response to treatment.

The 12-month follow-up collected information from over 90% of subjects, including treatment leavers. After 12 months methadone patients could transfer to diamorphine while diamorphine patients were switched back to oral methadone and reviewed after two months. Those who had been doing well on diamorphine but then relapsed would be considered for reinstatement to diamorphine. There was no evidence that outcomes suddenly improved in preparation for this deadline.

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Van den Brink W. *et al.* *Medical co-prescription of heroin: two randomized controlled trials.* Utrecht: Central Committee on the Treatment of Heroin Addicts, 2002.

especially after the first few months, a substantial minority who leave treatment will opt to end drugtaking altogether via abstinence-based treatments, and that patients do best when this is arranged beforehand.

For any UK diamorphine service, a doctor licensed to prescribe the drug for addiction is essential. These will normally be experienced in addiction and should be backed by a multidisciplinary team able to cater for the needs of what are likely to be among the most problematic of heroin patients.[24] For Britain, a major rationale for prescribing diamorphine will be to prevent continued regular illicit heroin use. Monitoring this requires urinalysis equipment capable of distinguishing illicit heroin from diamorphine; such tests are feasible but require further development.

On site or not?

Normally services will be expected to have measures to prevent diversion of diamorphine on to the illicit market. How big this problem will be is unclear, but it is certainly a possibility – diversion fuelled the original upsurge of heroin addiction in Britain in the 1960s. In the early 1970s, study 1 noted that five out of its 42 diamorphine patients were selling some of their prescription.

The Swiss (4) and Dutch (5) studies plus work in Britain[24] show that avoiding diversion by requiring on-site injecting or smoking is feasible. However, this can only work for patients who can cheaply, easily and quickly get to the clinic. Unless the network of diamorphine 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. 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.[27]

Clinics which supervise consumption will need suitable facilities and staff trained to advise on safer injecting and to intervene in the event of overdose or other mishaps.

The Swiss (study 4) tempered the inconvenience of on-site consumption by allowing patients to skip visits and take oral medication instead, an opportunity most took advantage of. Insisting instead on the return of used ampoules – a tactic used in London (study 3) – may be a less intrusive and less expensive way to prevent diversion.

Selecting suitable patients

Clear, explicit and measurable criteria based on the patient's history and current functioning will help reserve the diamorphine option for those least likely to do well on oral methadone. Making the criteria explicit also creates the opportunity to refine them in the light of experience.

The Dutch study (5) provides the most comprehensive model. Selection was based on a history of at least five years of heroin addiction, continued daily heroin use despite (in Dutch terms) adequate oral methadone treatment, and the persistence of severe drug-related problems as measured by standard assessment tools. Similar measures can later be reapplied to assess whether the patient is benefiting from the treatment.

Justifying the cost

In the UK oral methadone maintenance costs around £1000 a year compared to about £6000 a year for diamorphine ampoules.[25] These estimates cover only medication and dispensing fees; staff and facilities for supervised consumption would increase the gap. However, patients selected for diamorphine will usually exhibit severe health problems and illicit heroin use (often entailing high levels of crime) which have not responded to methadone. For these patients, the potential savings for the community of moving on to diamorphine will also be much greater than from persisting with methadone.

In Switzerland, a day in diamorphine treatment with supervised consumption cost £20 per patient and the benefits (mainly savings to the criminal justice system) were nearly £40 a day.[26] Since this is a partial accounting of benefit, and because many patients left to go to lower cost treatments and achieved lasting improvements, the long-term benefit-to-cost ratio is likely to have been much higher. With typical British addicts (much more criminal) the scope for cost savings is even greater.

Conclusion: small but important

Gazing into the future, it seems likely that diamorphine will continue to be an option reserved for a small minority of heroin-dependent patients who do not benefit from non-injectable formulations such as oral methadone or sublingual buprenorphine. Despite the failure of their prior treatments, most of these patients will respond well to diamorphine and the treatment will net savings for society which would not be achieved by another try at oral methadone.

The main limiting factors will be cost and practicality and these in turn depend partly on how much weight is placed on the risk of diamorphine being diverted on to the illicit market. If this is felt to mandate continued on-site consumption at the prescribing clinic, then making the treatment available to all who might need it will be very costly and probably impossible.

Given the volume of heroin on the illicit market, it can be argued[25] that some diversion from a small minority of addicts will make no real difference to the extent of heroin addiction, and that the risk does not warrant restrictions which consign addicts to

oral programmes which for them are ineffective or which fail to attract them in to treatment. Society, too, would be the loser in this scenario. Unduly restricting diamorphine would mean drug-driven crime and drug-related health problems continue to impose costs which could have been reduced by diamorphine treatment.

NOTES

i By interview two, 14 had left oral methadone treatment and among the remaining patients there were 17 fewer using heroin. It seems likely that most or all of the leavers had been among this 17 and that they continued to use heroin illegally – early rather than delayed reductions in illicit heroin use are the norm in methadone treatment. Also, at interview two a lower proportion of retained methadone patients said abstinence was a goal than at treatment entry. On the assumption of some continuity in treatment goals, this suggests that drop-out was most pronounced in patients who were not at first aiming for abstinence.

ii According to the study's response to treatment criteria.

iii In the paper 24%, but unaccountably this excludes five patients "selling some of their prescription every day (and not buying other opiates instead)".

iv In the previous three months.

v This gap cannot be accounted for by greater mental health problems among the diamorphine patients; the reverse was the case.

vi There was no requirement for previous failures on oral methadone or for serious drug-related problems, and on average they had been using opiates for about six years compared to the decade or more seen in other trials.

vii In the two arms of the study, 20% and 17% more patients remitted on diamorphine than on methadone.

viii How accurate this estimate was is unclear. The paper implies that quantities were assessed on the basis of expenditure rather than directly.

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The nature of the evidence

No recent British studies have directly compared methadone and diamorphine maintenance and elsewhere gaining permission to mount such a trial is extremely difficult. The upshot is that few studies have been done and none is a definitive guide to practice in Britain.

Since *extra* value relative to oral (or in some studies, injectable) methadone is the key issue, the quality of the regimes against which diamorphine is benchmarked is critical. Often these have been sub-optimal. No study has attempted to construct a rival more capable of competing with diamorphine. Such attempts could have made a big difference. Flexible, individualised dosing,[32 33 34 35] quality counselling and therapy[36 37 38 39 40 41 42] and a well run, responsive regime[43 44 45] can improve retention and turn methadone 'failures' into successes.

However, this line of argument has its limits. Patients sometimes resist very high doses of methadone and find frequent counselling and clinic attendance unappealing. One of the benefits of diamorphine could be that it has sufficient pulling power to overcome these resistances and to engage patients in regular therapeutic contact and a highly structured regime. Just as studies to date have not optimised methadone regimes, neither did any fully exploit this potential. The exception seems to have been the Swiss studies (❹), but these also required long-term supervised consumption, an imposition which studies in Britain suggest is often unnecessary. Such regimes risk deterring some patients, elevating drop-out in those who do enter treatment, and disrupting normalisation of the lifestyles of retained patients. The upshot is that no study can yet claim to have compared an optimised oral methadone programme with an optimised diamorphine programme.

LINKS Nuggets 8.7 5.10 3.2 1.5

The value of the results from UK studies (❶❷❸) is compromised by the generally low doses of diamorphine offered to patients. Results from study ❹ in Switzerland (less criminal addict population and more extensive welfare provision) and study ❺ in the Netherlands (where methadone programmes do not set doses high enough to eliminate illicit heroin use) are an uncertain guide to what to expect in Britain. Studies generally do not report alcohol use outcomes and there are no analyses of differential impact on men and women or on different ethnic groups.