Heroin maintenance treatment. From idea to research to practice

Uchtenhagen, A A
Heroin maintenance treatment: From idea to research to practice

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Abstract

Maintaining opiate addicts on opiates has a long history. The idea to prescribe pharmaceutical morphine as a substitute for street heroin started in USA and was abolished on the basis of prohibitionist legislation. A new approach to maintain opiate addicts on substitution therapy was initiated in USA in 1963, with the prescription of methadone. This approach found, although slowly, increasing acceptance, and is nowadays considered to be a cornerstone in the management of opiate dependence and for the prevention of HIV/AIDS in opiate injectors. Since 1975, the concept of heroin maintenance treatment was re-activated in order to reach out to treatment-resistant heroin addicts. Research projects were performed in Switzerland, the Netherlands, Germany, Spain, Canada and in England, another one is planned in Belgium. Based on the unanimously positive outcomes, heroin maintenance has become routine treatment for otherwise untretable heroin addicts in Switzerland, the Netherlands, Germany and England, and Denmark has set up heroin maintenance without new research trials. [Uchtenhagen AA. Heroin maintenance treatment: From idea to research to practice. Drug Alcohol Rev 2011;30:130–137]

Key words: heroin dependence, heroin maintenance treatment, opioid substitution treatment, drug policy.

The origins

Prescribing and using opiates as an effective medication for a range of ailments goes back to the origins of Chinese, Sumeric and Egyptian medicine, and probably beyond. In Homeric times, opium in wine (‘Nepenthes’) was offered against all evils, and the opium-made ‘Theriak’ was still considered to be the most essential drug at the dawn of modern medicine by Paracelsus. It was inevitable that its addictive potential had to become manifest, but we do not know when and where opiate addiction was first observed and when the use of opiates as a maintenance regime started. We do know however, that the Roman emperor Marcus Aurelius was maintained on opium by the eminent Galenus, and that the Mughal emperor Jahangir received opium maintenance. And far into the 20th century, opium dispensing was practised in some countries like Pakistan and Laos, providing dependent people with their daily dose.

Once heroin (diacetylmorphine) was developed in 1874, it was again used as an effective medication for many conditions, frequently prescribed as ‘patent medicines’. In Europe, it was also considered to be a cure for morphine, cocaine and opium dependence, until its own addictive potential became obvious. In the USA, 44 narcotic clinics were set up, most of them after the Harrison Act, which left the dependent persons without supply, and introduced tapering off morphine for detoxification purposes. But then, the maintenance concept was re-invented, based on the frequency of relapses (the ‘Tennessee system’ of 1914, see [1]). While the southern clinics, treating mainly iatrogenic morphine dependents, were quite successful, the New York clinics failed in maintaining young heroin addicts from minority groups [1,2].

Prohibition against maintenance

While all US narcotic clinics, successful or not, were closed by law in 1923, a few doctors continued to
The idea of maintaining heroin addicts on opioids became increasingly acceptable, instead of restricting treatment to ‘abstinence-only’ approaches. In 2003, there were 462,412 patients in substitution treatment [6], and the number increased to an estimated 650,000 in 2007 [7]. By 2007, substitution treatment is available in all Member States of the EU; in nine countries, it is open to nearly all heroin addicts, and in seven more countries to the majority of them [7]. Finally, in 2006 the World Health Organisation (WHO) succeeded in putting methadone and buprenorphine on the list of essential medicines. While earlier the main objective had been to reduce criminality and to curb the illegal heroin market, this was replaced by a major public health concern [8].

The quest for prescribing the ‘original drug’: new research

The increasing number of methadone patients led inevitably to an increased though still smaller number of ‘methadone-resistant’ patients who continued to inject heroin in spite of the availability of adequate methadone dosages and care. At the same time, the HIV epidemic made it a priority to increase coverage, that is, to reach out to as many injectors as possible. In this circumstance, the idea of prescribing heroin as the original and preferred substance of addicts was raised.

Even if the AIDS epidemic is at the origin of all initiatives to prescribe heroin in Switzerland, the Netherlands, Germany, Canada and Spain, the revival of the idea of heroin maintenance had come up before and was ready to be taken up again. The debate started in Canada in the early 1950s and again in the 1970s in the Netherlands and in the USA. The arguments mainly focused on heroin addiction as a chronic condition and the need to restrict its negative health and social consequences. Three attempts to start heroin prescribing in US cities have not succeeded [3]. Non-medical options providing heroin to addicts in the Netherlands (tolerated ‘home dealers’ and ‘heroin bars’) were started, but then considered to be failures [3]. The only project under medical control was a compromise between new thinking and political concerns: the Amsterdam morphine prescription experiment for highly problematic heroin addicts, starting 1983 [9].

In the UK, where pharmaceutical diamorphine as a substitute for street heroin was gradually replaced by methadone after the early 1970s, and where a first randomised trial comparing injectable heroin with methadone had produced ambiguous results [10], a new experiment in prescribing heroin ‘reefers’ was successfully implemented [11]. Feasibility studies on
heroin prescribing were initiated in Australia [12,13].

The Swiss cohort study and the WHO expert report

Serious attempts to engage in new scientific research on the feasibility and effects of heroin prescribing started as a response to the challenge of unmanageable and intolerable open drug scenes (‘needle parks’) in major Swiss cities. The project of heroin-assisted treatment for addicts who failed in conventional treatments, including methadone maintenance, was one element in a new national drug policy, aiming at investing massively in prevention, treatment, harm reduction and law enforcement. Restoring public order, curbing drug-related delinquency and prostitution were as important as relieving the misery of addicts living in these public places. However, the idea was not only to engage in new initiatives, but also to gain solid scientific evidence, as a basis for future policy decisions. Evidence-based policy was asked for, in a context of controversial ideological debates.

The Swiss 3 year project was originally designed as a randomised controlled study comparing injectable heroin to injectable morphine and methadone. Because of frequent histamine-like side effects, patients could not be recruited for the morphine and methadone arms as planned. The design of the main study had to be adapted to a prospective cohort study, but including a number of randomised controlled sub-studies comparing i.v. (intravenous) heroin to i.v. morphine, comparing patients receiving i.v. heroin to patients on a waiting list, pilot studies on diverse diamorphine preparations for alternative routes of administration [14] and studies comparing self-report data on delinquency with police data [15,16]. The study results were first published as a monograph in 1999 [17]. A more recent study tested the safety and effectiveness of oral (slow release and instant release) diamorphine tablets, as a replacement of heroin reefer for patients unable or unwilling to inject [18].

The detailed positive results, acknowledged by an international expert committee set up by WHO [19], could nevertheless not separate the effects of heroin prescribing from the effects of concomitant care. This became the starting point for the randomised controlled trials, thereby adding essential new findings to the already established positive outcomes. In the UK a similar new approach has started, in contrast to the earlier practice of handing out prescriptions without an evaluation.

The randomised controlled trials

In the Netherlands, a randomised controlled study co-prescribing injectable or inhalable heroin in addition to oral methadone, in comparison with oral methadone alone, started in 1995. The inhalable application (‘chasing the dragon’) had to be considered because the majority of Dutch heroin users prefer it over injecting.

Trial participants were recruited from existing methadone maintenance programs, attending their program regularly and receiving at least 50 mg (inhaling trial) or 60 mg (injecting trial) methadone per day. The number of participants in the trials was 549, with 375 receiving inhalable heroin and 174 receiving injectable heroin. Altogether, 237 were randomised into the control groups and 119 into a comparison group starting out with oral methadone and transferred to inhalable heroin after 12 months [20].

The co-prescription of heroin in the two experimental groups lasted for 12 months. The dose of heroin was a maximum of 1000 mg per day, plus a maximum of 150 mg of oral methadone in the experimental groups, and a maximum of 150 mg of oral methadone per day in the control group. After termination of the co-prescription of heroin, all patients received oral methadone only. All groups were provided with ancillary standard psychosocial treatment [20,21].

Treatment response was significantly \((P=0.0001)\) higher in the experimental groups than in the control groups. Results from those who completed the study were similar to those from the intention-to-treat analysis. Treatment responders showed relevant improvements in all outcome domains [20]. The only patient characteristic predicting a positive outcome was past abstinence-oriented treatment [21].

Eighty-two per cent of the responders in the experimental groups deteriorated substantially during the 2 months following cessation of heroin co-prescription, and the mean outcome scores returned to those before entering the program [20].

The positive outcome of the study led to a parliamentary decision in 2004 to increase the number of treatment slots to 1000, to be situated in 11–15 cities. However, only about 300 treatment slots in six cities were actually set up, mainly because of financial problems. By 2008 there were eight specialist clinics prescribing heroin to approximately 350 patients. The centres have 25–70 treatment slots each. A further
increase is intended, mainly with smaller centres having 25–30 slots.

Injectable and inhalable heroin were registered as a substitution drug in the treatment of heroin dependence in December 2006 by the Dutch Medicines Evaluation Board. Heroin-assisted treatment is authorised for chronic, treatment-resistant heroin addicts who could not be stabilised satisfactorily in a methadone maintenance program. New patients can be admitted. The indication criteria are practically unchanged. In 2007 heroin-assisted treatment became acknowledged as a regular treatment under special conditions.

In Germany, the largest randomised study on heroin-assisted treatment started in 2002 and ended in 2005. Clinics were set up in seven cities and a total of 1032 patients were enrolled in the program (515 on heroin maintenance). All received an intensive psychosocial care program. The average daily dose of heroin was 442 mg; after the induction phase dosage was stable [22].

The design was a 4 × 2 randomised multicentre study with two target groups (methadone patients who continue to inject heroin, and heroin addicts out of treatment for at least 6 months) and four arms for each target group (heroin vs. methadone, psychoeducation vs. case management with motivational interviewing).

The study was divided into two phases:

Phase 1: in the first 12 months, a stratified 4 × 2 randomised controlled trial in order to examine the effects of heroin prescribing as compared with methadone prescribing under similar conditions.

Phase 2: follow-up study over 12 months in order to investigate the long-term effects in the experimental group; a randomly selected group of control patients receives heroin prescription, the rest leave the study and are offered regular treatment.

Special studies addressed criminological aspects, economic aspects, neuropsychological issues, psychosocial interventions, acceptability and implementation of the project.

The findings showed better results for the heroin group in regard to the criteria (improvement in somatic or mental health of at least 20%; a major reduction of street heroin use and no increase in cocaine consumption). The differences are statistically significant. The improvements from heroin-assisted treatment were equal for both target groups (refractory methadone patients, patients out of treatment) and for both types of psychosocial intervention (psychoeducation, case management) [22].

After 2 years, the heroin group showed highly significant improvements in physical and mental health, while illicit heroin and cocaine use also decreased significantly [23].

Based on the evaluation results, the Registration Authority (Bundesinstitut für Arzneimittel und Medizinprodukte BfArM) decided in favour of a continuation of heroin-assisted treatment on a routine basis, and Parliament agreed to provide the necessary new legal basis for a continuation in 2008.

In Spain, initiatives to set up trials with diamorphine were taken in two of the Autonomous Regions—in Andalusia and in Catalonia. During 2000–2001, these initiatives were discussed in the Central Agency for Drug Addiction. The authorities decided to allow the trials, with the expectation that they would generate new scientific insights, and to get approval of the Drug and Pharmaceutical Control Office for registration of diamorphine as a medicine. A clinical trial of heroin maintenance therapy was authorised in 2001 [24].

A randomised controlled trial started in 2003 in Granada and was completed in 2004. Sixty-two heroin addicts were recruited, 31 in each group. The average daily dose of heroin was 274.5 mg plus 42.7 mg methadone in the experimental group, while 105 mg methadone was prescribed in the control group. Both groups received comprehensive clinical, psychological, social and legal support.

The results showed significantly better results in the experimental group, in regard to physical health, reduction of risk behaviour, reduction of drug use and of involvement in crime [25].

The Council of Andalusia requested continued compassionate use for the 36 patients who participated in their clinical trial. The Spanish Agency for Medicine (an organisation under the Ministry of Health) gave its consent and authorised these patients to receive heroin for life.

In the UK, the Randomised Injecting Opioid Treatment Trial recruited 127 opiate addicts who continued to frequently inject illegal heroin despite being prescribed substitute oral opiate-type drugs. These 127 patients were randomly allocated either to injectable methadone or heroin for 6 months, or to continue on oral methadone. If necessary doses were individually adjusted to high levels (to 300 mg of oral methadone, to 200 mg of injectable methadone, to 900 mg of injectable heroin per day) to achieve maximal comfort and suppression of illicit opiate use. Patients received regular psychosocial support if needed. After the 6 months of the trial, patients were reassessed for the most appropriate treatment, including possible injectable prescribing for those previously allocated to oral methadone.

There was better retention in the groups receiving injectables (88% in the heroin group, 81% in the methadone group), in contrast to the group receiving
oral methadone (69%), and a significantly better reduc-
tion in illegal heroin use in the heroin group. After
adjusting for other factors, 66% of the heroin group had
a good response to treatment (vs. 30% in the i.v. metha-
done group and 19% in the oral methadone group).
These findings were based on urine analysis differenti-
ating illegal heroin use from prescribed heroin [26].

In Canada, 251 heroin injectors who had not prof-
ited from at least two previous treatments were ran-
domised to injectable heroin (n = 115), oral methadone
(n = 111) or injectable hydromorphone (n = 25), and
assessed after 12 months; main outcome criteria were
retention and use of illicit drugs or other illegal activity.
The intention-to-treat analysis resulted in a signifi-
cantly better retention in the heroin group (88% vs.
54% in the methadone group) and reduction in illegal
use or activity (67% vs. 48%). There were some adverse
events, but limited to non-fatal overdoses and seizures
after injections [27].

A summary of findings on feasibility, outcome
and impact

The results from all the studies have been published
extensively, including 2 year and 6 year follow-up
results from the Swiss cohort [28,29], 2 year follow-up
results from Germany [23] and 4 year follow-up results
from the Netherlands [30]. Recent reviews provide
details [31,32]. A monograph on heroin-assisted treat-
ment is in preparation at EMCDDA, the European
Centre on Drugs and Drug Addiction in Lisbon.

Feasibility

Heroin-assisted treatment can be implemented with
good acceptance by patients, by law enforcement
authorities and—in the case of Swiss national referenda—by
the general public. The target group of chronic, marginalised and treatment-resistant heroin
addicts could successfully be reached (for admission
criteria see Table 1).

Safety

Heroin-assisted treatment can be implemented without
undue risks for patients, staff and public order; under
the control conditions of the studies discussed here, no
diversion of prescribed substances to the illicit market
and no fatal overdose from prescribed heroin could be
found. Serious adverse effects occur, and can be well
managed. Cerebral undersaturation of oxygen, causing
convulsions and respiratory depression, was found
more frequently in heroin maintenance than in control
groups (in Switzerland, Germany, the UK and
Canada), but staff and patients learned to avoid this by
promoting physical activity after injections. Annual
mortality rates from all causes are below those of

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**Table 1. Admission criteria for heroin maintenance treatment**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Switzerland</th>
<th>Netherlands</th>
<th>Germany</th>
<th>Spain</th>
<th>UK</th>
<th>Canada</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal age (years)</td>
<td>18</td>
<td>25</td>
<td>25</td>
<td>18</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>Local residency required</td>
<td>Yes</td>
<td>&gt;3 years</td>
<td>&gt;5 years</td>
<td>—</td>
<td>Yes</td>
<td>&gt;1 year</td>
</tr>
<tr>
<td>Diagnostic assessment</td>
<td>ICD-10</td>
<td>DSM-IV</td>
<td>ICD-10</td>
<td>ICD-10</td>
<td>DSM-IVR</td>
<td>DSM-IV</td>
</tr>
<tr>
<td>Duration heroin dependence</td>
<td>&gt;2 years</td>
<td>&gt;5 years</td>
<td>&gt;5 years</td>
<td>—</td>
<td>&gt;3 years</td>
<td>&gt;5 years</td>
</tr>
<tr>
<td>Daily heroin use</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (last 30 days)</td>
<td>&gt;50% of days in last 3 months</td>
<td></td>
</tr>
<tr>
<td>Former treatments</td>
<td>Minimal</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>MMT</td>
<td>Min. 2 (incl. 1 MMT)</td>
</tr>
<tr>
<td>Health and/or social deficits</td>
<td>2 (any)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If in MMT</td>
<td>Yes</td>
<td>Min. 12 months (39–59 visits last 6 months), &gt;50 mg day⁻¹</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If out of treatment</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Informed consent</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Randomisation accepted</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

untreated heroin addicts and of those in other treatments [33].

Treatment effects
All treatment effects indicate an improvement in physical and mental health, a reduction of risk-taking behaviour (especially needle sharing), a reduction of crime involvement and some improvement in social integration (although the stigma of heroin dependence is a major obstacle). Significant positive effects are documented from all studies, at different time points (Table 2). Positive effects persist over time after leaving the program.

Patient satisfaction
Satisfaction is generally high; there were some complaints concerning organisational details, but not the treatment or the substance per se.

Impact on other treatment approaches
No negative effects on other treatment approaches could be observed. Where data are available, they show an overall increase in treatment availability, utilisation and quality for heroin addicts during the implementation of heroin-assisted treatment.

Impact on public health and public order
Heroin-assisted treatment reduces the risk of blood-borne infectious diseases and their transmission to others. It reduces the role of heroin addicts in recruiting new addicts, by a reduction of their involvement in drug trafficking. Heroin-assisted treatment reduces the crime involvement of patients, and the nuisance for the public in general caused by addicts not in treatment.

Cost–benefit
The Swiss, the Dutch and the German experiments have been evaluated economically; all with favourable cost–benefit ratios [34–36].

Implications for drug policy
All these scientific projects had and have some features in common: the model of maintaining heroin addicts on supervised injections (or inhalation or oral applications) of pharmaceutical diamorphine, in the framework of a comprehensive assessment and care program, targeting specifically heroin addicts who are out of treatment or who continued to use illicit heroin while being on other treatments, including methadone maintenance. The idea is not to reach out to heroin addicts in general, but to those otherwise not reachable, in a perspective of public health and public order priorities [37,38]. The treatment modality is not conceived as replacing other forms of treatment.

Heroin prescription has moved from idea to experimental project to routine treatment and is part of an overall treatment network for heroin addiction in Switzerland, the Netherlands, Germany and Denmark, without known negative effects on other approaches and on prevention. WHO made a cautious assessment of this approach, in view of the limited experience and the safety risks, especially when set up in less resourced and well-organised health systems [39,40]. An early Cochrane review came to similar conclusions [41], while a recent one is still under discussion [42].

References

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