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EMCDDA

INSIGHTS

New heroin-assisted treatment

Recent evidence and current
practices of supervised
injectable heroin treatment
in Europe and beyond





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Foreword

The prescription of substitution drugs, together with appropriate psychosocial support, is an integral part of today's mainstream approach to treating heroin dependence. This has come about because over the last two decades, an increasing body of high-quality research has demonstrated the efficacy of using drugs such as methadone and buprenorphine to help stabilise and improve the health status of those dependent on illicit 'street' heroin. The weight of evidence has been sufficient to counterbalance legitimate concerns about the value of replacing one opioid drug with another. Most importantly, the development of good clinical practice and safeguards has ensured that any possible unintended negative consequences have been largely avoided. This is important for the prescription of medicines that themselves have considerable abuse potential.

Today, methadone and buprenorphine are among the first-line responses to the treatment of opioid dependence. However, as with other pharmacologically-based treatments across the medical spectrum, some patients are poor responders. A small, but important, minority of chronic heroin-dependent individuals repeatedly fail to benefit from this kind of intervention. This group may be a small one, but it is also one in which the negative health and social implications of long-term drug dependence are pronounced. The effective treatment of these individuals thus has a high relative potential to impact on the health costs associated with drug dependence and this is the underlying theme that this Insights publication addresses.

History has taught us that the introduction of effective interventions in the drugs field can sometimes, at first, seem counter-intuitive and be viewed as controversial. This is true of the subject of this publication and this is also the reason why the clear-headed evaluation of evidence is so important. Internationally, a number of experimental projects using robust research designs have been beginning to suggest that for some of those failing to respond to other approaches, the use of diamorphine as a substitution medicine may be an effective way forward. This is not simply a case of giving heroin to heroin addicts. Rather, studies have looked at the use of heroin as part of a highly regulated treatment regime, targeting a particularly difficult-to-treat group of patients.

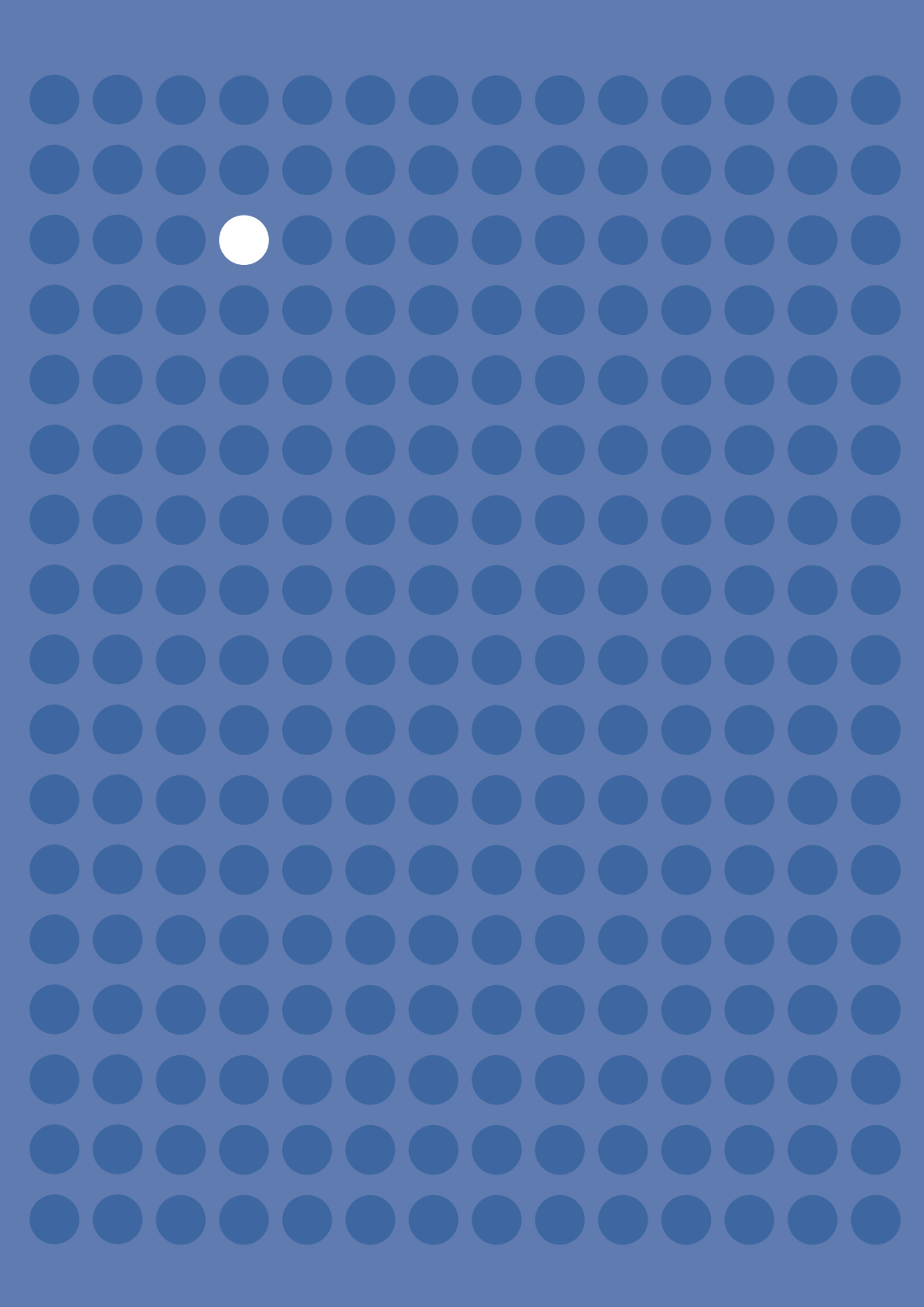
The EMCDDA is proud to have brought together here all the major contemporary studies on this topic, to address two key questions. Does the evidence available

now support the use of supervised injectable heroin treatment for those who have failed to respond adequately to other approaches? And if so, what are the clinical management issues necessary to ensure that this therapeutic option can be delivered in a manner that avoids the obvious risks associated with such an intervention?

When addressing a topic of this sensitivity and importance, maintaining a high degree of scientific rigour is paramount. To ensure this, the review of evidence that underpins this publication has been conducted in close collaboration with the Cochrane Group. But if this kind of approach is to become more widely adopted, then the evidence must also speak to the wider policy and practice community. This is the purpose of this report. I believe that it provides the reader with an easy to access, state-of-the-art overview of the current development of science in this area, together with a more practically orientated discussion on service-delivery issues. Our purpose in doing this is to inform — not to advocate. National drug situations across the European Union differ considerably, as do the relative costs and benefits of pursuing different therapeutic approaches. It remains, therefore, the readers' responsibility to draw their own conclusions about the appropriateness, or otherwise, of this kind of intervention for their use, within their own national context.

Wolfgang Götz

Director, EMCDDA





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Executive summary

Supervised injectable heroin (SIH) treatment has emerged over the last 15 years as a potentially important intensive second-line treatment for entrenched heroin addicts for whom previous orthodox treatments (i.e. oral methadone maintenance treatment (MMT) or residential rehabilitation) have produced little benefit. This treatment, by its very nature, attracts attention and controversy. Therefore, it is particularly important that there is a robust evidence base for its effectiveness and that the research evidence from international trials is brought together in one document and examined alongside the evidence from wider clinical experience in order to provide a complete picture of what we know about this treatment.

We now have the results from a series of well-designed randomised clinical trials, from Europe and Canada, which have been peer reviewed and published in high-impact scientific journals, as well as steadily accumulating clinical experience of the development and provision of supervised injectable heroin treatment.

All of the available findings from randomised controlled trials (RCTs) published in academic papers and project reports have been examined in order to gauge the efficacy (against a range of outcomes) as well as the cost and cost utility of SIH treatment. Thus, this Insights gives a historical overview of SIH, including the international policy and legislation regarding this treatment, before moving on to examine the research evidence and clinical and policy experience with this new treatment.

Context and history

Supervised injectable heroin treatment was developed and initially introduced in Switzerland during the 1990s after a century of prescribing heroin for the treatment of addiction without direct supervision, mostly in the United Kingdom. Since the 1990s, SIH treatment has been tested as a new clinical practice, sometimes in the context of clinical RCTs, in a number of European countries and in Canada.

Two common features characterise the new approach to heroin treatment. Firstly, SIH is not a first-line treatment, but rather is an option for patients who have not responded to standard treatments such as oral MMT or residential rehabilitation. Secondly, all injectable doses (typically, approximately 200 mg of diacetylmorphine per injection) are taken under direct medical or nursing supervision, thereby

ensuring compliance, monitoring, safety and prevention of any possible diversion of prescribed diacetylmorphine to the illicit market: this requires the clinics to be open for several sessions per day, every day of the year.

Scientific evidence base

Over the past 15 years, six RCTs have been conducted involving more than 1 500 patients, and they provide strong evidence, both individually and collectively, in support of the efficacy of treatment with fully supervised self-administered injectable heroin, when compared with oral MMT, for long-term refractory heroin-dependent individuals. These have been conducted in six countries: Switzerland (Perneger et al., 1998); the Netherlands (van den Brink et al., 2003); Spain (March et al., 2006); Germany (Haasen et al., 2007), Canada (Oviedo-Joekes et al., 2009) and England (Strang et al., 2010).

Across the trials, major reductions in the continued use of 'street' heroin occurred in those receiving SIH compared with control groups (most often receiving active MMT). These reductions occasionally included complete cessation of 'street' heroin use, although more frequently there was continued but reduced irregular use of 'street' heroin, at least through the trial period (ranging from 6 to 12 months). Reductions also occurred, but to a lesser extent, with the use of a range of other drugs, such as cocaine and alcohol. However, the difference between reductions in the SIH group and the various control groups was not as great (compared with major reductions in the use of 'street' heroin).

Patients receiving SIH treatment achieved gains in physical and mental health, as well as social functioning, although improvements in those receiving SIH were not consistently or significantly superior to the control group across all trials, particularly in relation to psychosocial functioning.

Reductions in the criminal activity of SIH patients were evident and were substantially greater when compared with patients under control conditions.

Retention in treatment varied substantially across the trials. The available evidence suggests added value of SIH alongside supplementary doses of methadone for long-term treatment-refractory opioid users.

Furthermore, efficacy of heroin provision as a treatment modality on several outcomes (retention, mortality) was corroborated by a systematic review conducted by the Cochrane Group. Although the inclusion criteria of studies in the latter

review were stricter from a methodological point of view, converging conclusions on the efficacy of SIH further strengthens the current evidence of this. However, it is important to note that more serious adverse events have been reported to occur in patients receiving SIH than oral methadone. This suggests that SIH may be less safe and therefore require more resources and clinical attention in order to manage greater safety issues.

Finally, countries that have conducted longer term (up to six years) follow-up studies have seen a high retention in SIH (55 % at two years and 40 % at six years), with patients sustaining gains in reduced 'street' heroin use and marked improvements in social functioning (e.g. stable housing, drug-free social contacts and increased rate of employment).

Cost and economic evaluations

The reported cost per patient per year of an SIH maintenance programme, across the different countries, was between EUR 12 700 and EUR 20 400. The lowest cost was reported by Switzerland at between EUR 12 700 and EUR 14 500, depending on the capacity of the injectable maintenance clinic; Germany reported a cost of EUR 19 000 and the Netherlands a cost of EUR 20 400. The costs reported by the trials were consistently and substantially higher than the cost of oral MMT provision at EUR 3 500 (Germany) and EUR 1 600 (Netherlands). This was largely due to a higher staffing requirement for the SIH treatment provision — at least two staff members must be present at all times and no 'take-home' injectable heroin doses are permitted, with clinics needing to be open daily and for extended hours — as well as the higher cost of diacetylmorphine (see also Chapter 5).

The higher cost of SIH compared with optimised oral methadone (OOM) treatment provision was compensated for by the significant savings to society. In particular, a greater reduction in the costs of criminal procedures and imprisonment as a result of associated criminal behaviour was seen with SIH than with OOM treatment. It should be noted that the provision of a more standard treatment to a patient who derives little benefit cannot be cost-effective, no matter how cheaply it may be delivered.

Impact, clinical practice and challenges

At the time of writing, the number of people receiving SIH treatment is changing, but there are approximately 1 000 SIH patients in the European Union (EU) and a further 1 400 in Switzerland.

In the United Kingdom, the medical use of heroin has been used in clinical practice since it was first synthesised — both for the relief of terminal pain and for the treatment of opioid dependence (even though it has rarely been used in recent years for the treatment of addiction (see Chapter 2)). In recent years, four other countries (Denmark, Germany, the Netherlands and Switzerland) have granted approval for diamorphine to be used as a medicinal product for the specific indication of treatment-refractory heroin addicts. In these countries, SIH clinics are now integrated into local addiction service networks and appear to successfully deliver important benefits to a small number of severely affected chronic heroin addicts. For these addicts, this new treatment delivers tangible benefit, for themselves, for their families and for society.

In Spain, one SIH clinic continues to provide treatment to participants enrolled in their trial, now operating under legal exemption, and Canada has approved diacetylmorphine for research trials only.

Supervised injectable heroin treatment inevitably stimulates public and political interest as well as clinical and scientific interest. As a result of the medicinal product being used in the treatment (diacetylmorphine, pharmaceutical heroin), there is bound to be special public and political interest. Consequently, precisely because of this, it is particularly important that science contributes evidence-based examination of evidence and objective analysis and critique.

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Chapter 1: Introduction to this EMCDDA Insights

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The size of the heroin problem in Europe has continued to grow (EMCDDA, 2010) and has prompted the introduction and expansion of various treatment responses, notably opiate substitution treatment (OST) (EMCDDA, 2010), as has occurred in many other countries across the world. However, for a minority of heroin-addicted patients, often with deeply entrenched addiction problems, the expected benefits of these treatment responses have not been seen.

Across Europe over the last 15 years, and more recently also in Canada, a novel approach of supervised injectable heroin (SIH) prescribing has been developed, introduced and tested in well-designed research studies — in most instances, specifically for this population of severe and previously refractory heroin addicts. This innovation has been particularly led by clinicians, researchers and policymakers in Europe. Therefore, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) asked a team of leading scientists in this area to produce a comprehensive and up-to-date overview that is relevant and accessible to a wide audience. Under the guidance of Professor John Strang, Dr Teodora Groshkova and Dr Nicola Metrebian, this publication was produced with the support of many national experts in the field. The evidence was described in close cooperation with the Cochrane Collaboration, the world's leading institution in promoting evidence-based healthcare by producing systematic reviews of evidence.

Diacetylmorphine, more commonly known as diamorphine or heroin, was first synthesised and used as a medicinal product in the late nineteenth century into the early twentieth century. After it was brought under international control, beginning with the Hague Convention in 1912, and its use was limited to 'legitimate' medical and scientific purposes, the drug continued to be abused by a small number of people in Europe. In the mid-1970s, use of the drug increased across Europe (Hartnoll, 1985), peaking during the 1980s and into the 1990s in western and southern European countries and more recently in the 1990s to early 2000s in eastern and central European countries, particularly after the political changes that took place in those parts of Europe (Hartnoll et al., 2010). Serious negative health consequences were linked to heroin use, in particular alarming increases in overdose deaths. Furthermore, the detection of large human immunodeficiency virus (HIV) epidemics among drug injectors, mostly heroin injectors, in many countries during the 1980s made heroin use a major public health concern. This led, among other

measures, to the adoption of OST, a treatment first developed in the 1960s in the United States, as a treatment modality in the European Union (EU) in the mid-1980s.

In many EU Member States, this modality has undergone a major scale-up since the mid-1990s. To date, OST constitutes the main modality for the treatment of opioid dependence in Europe and is part of a wider range of treatment options available to heroin users. It is estimated that more than half of the 1.3 million problem opioid users in Europe are receiving this treatment, a considerably high rate compared with most other world regions (EMCDDA, 2010). This achievement is supported by compelling scientific evidence accumulated over the last decades regarding the benefits of OST in treating opioid dependence and in improving its associated health and social consequences.

However, a certain percentage of problem opioid users turned out to be unresponsive to standard treatments, including OST. Furthermore, there was a strong belief that a considerable number of heroin users were not reached by the treatment services available. In order to address the needs of this target population, a few countries — nearly exclusively members of the EU — have taken steps to respond to these problems by developing a new clinical approach, namely SIH treatment.

This new approach was an adaptation from the concept of heroin prescription for the treatment of heroin dependence, provided unsupervised in the United States a century ago and most notably in the United Kingdom for more than a century. The new approach was developed during the mid-1990s and experimental trials started in order to gather evidence of its efficacy. Thus, 15 years of trials conducted first in Switzerland, followed by the Netherlands, Germany, Spain, the United Kingdom and outside Europe in Canada, yielded positive outcomes in a number of areas, which recently led Denmark, Germany and the Netherlands to officially adopt supervised heroin-assisted treatment (HAT) as a second-line treatment. Other Member States continue to offer it within the context of their research studies. While this treatment option has now gained acceptance in a number of EU Member States, it remains controversial in most other countries.

At European level and worldwide in general, today there is, however, a growing interest in this particular treatment option with ongoing discussions and pertinent questions on the evidence, the costs, the implementation or its legal basis. With Europe being at the forefront of implementing and investigating this clinical practice, the EMCDDA found it necessary and timely to provide a state-of-the-art overview on a number of relevant aspects of supervised heroin treatment for entrenched heroin

users. Besides an overview on the latest scientific evidence available, this publication aims to answer questions on SIH treatment implementation and service provision.

Thus, Chapter 2 of this publication introduces SIH treatment from a historical perspective and provides an overview of its development in Europe and beyond.

Chapter 3 provides a comprehensive review of the scientific evidence of SIH treatment that has been accumulated through clinical trials internationally over the last 15 years. The joint collaboration with the Cochrane Group on this chapter provides a high-quality systematic review of a number of relevant and informative outcomes of SIH treatment. Findings are presented study by study according to country of origin with a clear and user-friendly description of the methodologies applied. The evidence reviewed concerns retention in treatment, 'street' heroin use and other drug use, health and social functioning, criminal offence and safety of SIH treatment. It was also deemed necessary to provide a review of the long-term trajectories of patients receiving SIH, as well as their perspective on this treatment and the impact of supervised injectable maintenance clinics and service provision in local communities. It is worth mentioning that the joint work between the Cochrane Collaboration and the research team has also resulted in an update of the Cochrane Systematic Review on heroin maintenance for chronic heroin-dependent individuals (Ferri et al., 2011).

The high cost of implementing SIH may be considered as problematic, especially during the current economic turmoil in Europe. Chapter 4 deals with the economic evaluation of SIH treatment. It offers a detailed economic evaluation of heroin-prescribing treatment from the German, Dutch and Swiss studies. Also of interest is the actual medicinal product used in supervised SIH treatment to substitute for 'street' heroin, namely diacetylmorphine. Hence, the different commercial pharmaceutical diacetylmorphine products that are currently available and utilised in the countries are briefly described in Chapter 5, as well as a list of key features of each product.

Finally, Chapter 6 describes the implementation and delivery of SIH treatment in each country where it is available. For this chapter, the authors collaborated with national key informants who are lead clinicians, researchers who have pioneered SIH treatment trials and practice or others with a strategic overview of this type of treatment in each country. Thus, national experts contributed by describing the implementation, operational delivery and clinical practice of SIH treatment as practised in Belgium, Denmark, Germany, Spain, the Netherlands, United Kingdom, Switzerland and Canada, as well as identifying aspects which helped or

presented challenges to delivering SIH treatment in each of these countries. While the described conditions may be unique to each country, interested countries may identify similarities with their national situation, offering the opportunity to translate experiences of these countries into their national situation.

This EMCDDA Insights guides the reader through the concepts and the operational aspects of providing supervised heroin treatment and presents the reader with an overview of the research findings from the series of randomised clinical trials and associated analyses. With this publication to hand, we can now contribute more constructively to the clinical, public and political discussions that are required to establish the proper place of this new form of treatment in the wider provision of care to those with heroin addiction problems.

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Chapter 2: Development of supervised injectable heroin treatment in Europe and beyond

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Chapter 2: Development of supervised injectable heroin treatment in Europe and beyond

International policy and legislation regarding heroin treatment

Diacetylmorphine is derived from opium and was first synthesised at St Mary's Hospital in London in 1874. In 1898, it was produced as a new therapeutic drug and named 'heroin' by the German pharmaceutical company Bayer. Initially, heroin was principally used as a cough suppressant and for alleviating respiratory difficulties associated with such illnesses as bronchitis, pneumonia and tuberculosis. It was also used, and in some countries still is, as an analgesic to relieve the severe acute pain caused by injury, surgery or heart attacks and in palliative care for terminal illness. Moreover, heroin was believed to be non-addictive and was considered as an effective cure for morphine addiction. However, heroin was soon found to have addictive properties itself.

An international drug control policy was set in motion, beginning with the Shanghai Commission in 1909 and followed by a series of conferences at the Hague in 1911–12, 1913 and 1914. The movement towards international drug control was originally driven by American missionary concern about opiate use in the Far East, alongside the American government's strategic policy to extend its influence and economic opportunities in the Far East (Berridge, 1999; McAllister, 2000). The International Opium Convention of 1912 (the Hague Convention) aimed to reduce the use of opium, morphine, heroin and cocaine by restricting the manufacture, trade, distribution and use of these drugs to 'legitimate' scientific and medical purposes only and to make the possession of these drugs for anything other than medical purposes illegal. All preparations containing more than 0.1 % of heroin were also to be controlled. Although signed by countries at the conference and subsequently put into force by some of them, the convention obtained near-universal adherence in 1919 when countries, through signing the peace treaties following the First World War, also became party to the Hague Convention (Berridge, 1999; McAllister, 2000).

The Hague Convention did not create administrative machinery for the implementation of its principles. The League of Nations established after the First World War provided a centralised body for the administration of international drug control and it was under the League's auspices that the second Geneva Convention

of 1925 was signed. The Convention required parties to the treaty to provide annual statistics on drug stocks and consumption; the production of raw opium and coca; and the manufacture and distribution of heroin, morphine and cocaine. A limitation on the manufacture of opiates to amounts necessary for medical and scientific purposes was imposed by the Limitation Convention of 1931 (McAllister, 2000).

Further international drug control protocols followed, and eventually all the existing drug control treaties were consolidated in the United Nations 1961 Single Convention on Narcotic Drugs. Heroin is listed in Schedule I of the convention, and the principal objectives of the convention are to limit the possession, use, trade, distribution, import, export, manufacture and production of drugs exclusively to medical and scientific purposes and to address drug trafficking through international cooperation to deter and discourage drug use. The Single Convention confirms the importance of the medical use of controlled narcotics and notes that 'the medical use of narcotic drugs continues to be indispensable for the relief of pain and suffering and that adequate provision must be made to ensure the availability of narcotic drugs for such purposes'. Articles 1, 2, 4, 9, 12, 19 and 49 contain provisions relating to the 'medical and scientific' use of controlled substances. In almost all cases, parties are permitted to allow dispensation and use of controlled substances under a prescription, subject to record-keeping requirements and other restrictions.

Heroin can be legally prescribed in the United Kingdom and Belgium for pain relief. It is available for prescription to long-term opiate users in Denmark, Germany, the Netherlands, the United Kingdom and Switzerland.

Brief history of heroin prescribing

Heroin prescribing in the United States

For a brief period in the early 1900s, many cities throughout the United States had clinics providing legal supplies of opiates to addicts, with some providing maintenance treatment. Records suggest that there were clinics in 34 cities in 12 states, the largest number of clinics being in New York. Many kept records of the addicts they saw and some states required the addicts to be registered before receiving their prescriptions for opiates (Musto, 1987).

The 1912 Hague Convention did not indicate how the control over production and distribution of opiates was to be implemented in individual countries, but in 1914 the United States Congress passed the Harrison Narcotic Act, which restricted the

administration of opiates (including morphine, heroin and opium) to doctors and pharmacists, requiring them to register with the Department of the Treasury, pay tax at a moderate rate and keep records of the medicines they dispensed. Doctors (and dentists and veterinary surgeons) had a right to prescribe heroin for medical purposes. However, the act contained some ambiguities (Courtwright, 1982); the most important involved the provision that doctors in their professional practice might prescribe narcotics to their patients. It was left unclear whether prescribing narcotics to an addict for the treatment of addiction was for legitimate medical purposes. Addiction was not seen as a disease, nor was the addict seen as a patient and thus opiates prescribed for him or her by a doctor might not be supplied 'in the course of his professional practice'. This act was interpreted to mean that doctors could not prescribe for addiction and by 1919, doctors were prosecuted for prescribing opiates to drug users. Even those who escaped conviction had their careers ruined by the publicity (Courtwright, 1982). As a result, doctors discontinued prescribing heroin for this purpose for fear of being prosecuted. Furthermore, the medical use of heroin was withdrawn with the United States Narcotic Drug Control Act of 1956.

British heroin prescribing (without direct supervision)

The Dangerous Drugs Act 1920 enacted into United Kingdom domestic legislation the provisions of the Hague Convention, which came into force in 1919 when it was ratified under the Versailles Peace Treaty. The Dangerous Drugs Act also retained most of the provisions of the 1916 Defence of the Realm Act Regulation 40B (DORA 40B), wartime domestic legislation restricting cocaine and opium use. The Dangerous Drugs Act restricted the import, export, manufacture, sale, distribution and supply of morphine and heroin except by persons licensed by the Home Secretary or otherwise authorised. The supply of morphine and heroin was restricted to registered medical practitioners for the purpose of medical treatment (and dentists for dental treatment and veterinary surgeons for the treatment of animals). The act was intended to meet international obligations but to interfere as little as possible with medical use of these drugs. The act imposed no limitations on the circumstances under which doctors could prescribe heroin and morphine to their patients.

DORA 40B had given the British Home Office the central power over drug policy. The Home Office was uncertain whether prescribing heroin and morphine for the treatment of addiction fell legitimately under the 1920 Act. At the suggestion of the Home Office, the Ministry of Health convened an expert committee (Departmental Committee on Morphine and Heroin Addiction), chaired by Sir Humphrey Rolleston, the President of

the Royal College of Physicians, to consider and advise on the circumstances in which it was medically advisable to prescribe heroin or morphine to addicts. The report (Ministry of Health, 1926) produced by the committee (usually known as the Rolleston Report) recommended that these drugs could be prescribed in the following cases:

1. to persons suffering from addiction to morphine or heroin who are under treatment by the gradual reduction method; and
2. to two classes of persons, to whom the indefinitely prolonged administration of morphine or heroin may be necessary:
 - i. those in whom a complete withdrawal of morphine or heroin produces serious symptoms which cannot be treated satisfactorily under the ordinary conditions of private practice; and
 - ii. those who are capable of leading a fairly normal and useful life so long as they take a certain quantity, usually small, of their drug of addiction, but not otherwise (Ministry of Health, 1926).

The report suggested that opiate-dependent drug users receive a gradual withdrawal from heroin (or morphine), but recognised that there would be patients for whom abstinence was not possible. It recognised the need for doctors to maintain such opiate-dependent drug users on a prescription indefinitely while keeping the supply of the drug within the limits of what is necessary. The Rolleston Report reaffirmed the right of doctors to treat heroin dependence and established that this could be done by either long-term or maintenance prescribing of heroin.

Heroin prescription was the main medication used for the treatment of opiate addicts up until the 1960s. The number of addicts in treatment was small and most were middle class, addicted to morphine and in the medical and allied professions, or had become dependent in the course of medical treatment. However, largely prompted by concern about whether long-term prescribing was still appropriate more than 30 years after the Rolleston Report, the Home Office convened the Interdepartmental Committee on Drug Addiction chaired by Sir Russell Brain to review the advice given by the Rolleston Report. The committee's 1961 report concluded that the drug problem remained small and no changes in approach were needed. However, increasing evidence of a heroin epidemic in the United Kingdom involving younger heroin users led to the Second Interdepartmental Committee on Drug Addiction, again chaired by Brain. The committee concluded that the increase in heroin use had been fuelled by a small number of doctors who were overprescribing heroin. As a result, it was

recommended that restrictions should apply to the prescribing of heroin and cocaine and that new drug treatment centres should be set up (Ministry of Health and Scottish Home and Health Department, 1965). The recommendations were enacted in the Dangerous Drug Act 1967, which restricted the prescribing of heroin in the treatment of addiction to doctors licensed by the Home Office. The doctors who obtained licences were mostly psychiatrists in charge of drug treatment centres or clinics set up by the National Health Service (NHS) to meet the increase in heroin use. Prescribing heroin for the treatment of other medical conditions was unaffected.

The drug clinics took over the prescribing of heroin to patients previously prescribed by private doctors and NHS general practitioners. Heroin prescribing declined in the early 1970s as doctors at the drug clinics were uncomfortable doing so. Methadone had recently been developed in the United States as a new treatment specifically for opiate dependence, and oral methadone was considered by the clinic doctors to be a more suitable medication. The findings of a research trial conducted in the early 1970s comparing the effectiveness of heroin with oral methadone treatment showed there were advantages and disadvantages to both, and the authors were unable to conclude whether one treatment was more effective than the other (Hartnoll et al., 1980). This research was used as justification for the move away from prescribing heroin to oral methadone, which had already started (Stimson and Oppenheimer, 1982).

Nevertheless, heroin prescribing for the treatment of addiction continues to be a legal option for the treatment of heroin problems. The established method of heroin prescription in the United Kingdom has been as a 'takeaway' supply, which is then injected in an unsupervised context. In practice, since the early 1970s, few doctors have prescribed it and few patients have received it (Metrebian et al., 2002). Heroin prescribing has steadily decreased, owing to the potential for diversion on to the black market (with an increased risk of spread of abuse and addiction and the danger of overdose) and the lack of evidence for effectiveness, as well as the development of oral medications such as methadone (Metrebian et al., 2002, 2007; Mayet et al., 2010; Strang and Sheridan, 1997, 2003, 2006).

Interest in heroin prescribing treatment from Switzerland

In 1991, in light of increasing numbers of young addicts injecting heroin, emerging open drug scenes in Swiss cities and increasing human immunodeficiency virus (HIV) infection rates, a national drug policy was formulated, which contained a new element of harm reduction. Prescribing heroin was proposed as both a harm-

reduction measure and a means of targeting those addicts with severe health and social problems who were not benefiting from conventional treatment.

In the early 1990s, senior clinical and academic experts in addiction from Switzerland visited the United Kingdom to look for a treatment that might be applied to heroin addicts who were not succeeding with orthodox oral methadone maintenance. Among the sites they visited was a clinic in the north of England led by a psychiatrist, Dr John Marks, where both smokable and injectable heroin were prescribed. Following this visit, Professor Ambros Uchtenhagen and colleagues concluded that they could reconceptualise the delivery of heroin prescribing so as to secure the positive advantages while avoiding the disadvantages by delivering heroin prescribing on a strictly medically supervised on-site clinic basis specifically to treat the most entrenched, treatment-resistant heroin addicts in their communities (Uchtenhagen, 2010). Consequently, new clinics, which would be open 365 days a year and where injectable prescriptions were consumed under medical supervision with no take-home doses, were established in Swiss cities and towns.

A scientific study to evaluate supervised injectable heroin treatment was designed. Findings from the study showed positive benefits and the World Health Organization (WHO) convened an international expert committee to review the design, implementation and findings of the study. The international expert committee confirmed the positive findings but felt that the research had limitations of design as it had not used a control group. The WHO recommended further studies, in particular randomised controlled trials (RCTs).

Movement towards renewed interest in supervised injectable heroin and development of evidence for such treatment

The research trials in Switzerland prompted a renewed interest in heroin prescribing delivered within new supervised injecting clinics, which was seen as a potential way to solve the heroin problem and improve the health and social well-being of entrenched heroin users for whom conventional treatments have repeatedly failed. Trials of heroin treatment delivered in the new European-style supervised injecting clinic were undertaken in Germany, Spain, the Netherlands, the United Kingdom and Canada. All the trials showed that such programmes can reduce illicit heroin use and criminal activity and improve the health of entrenched heroin users for whom conventional treatments repeatedly fail (Perneger et al., 1998; van den Brink et al., 2003; March et al., 2006; Haasen et al., 2007; Oviedo-Joekes et al., 2009; Strang et al., 2010), providing a good evidence base for this treatment.

However, the development of new supervised heroin treatment has not been solely influenced by the evidence for its effectiveness. The historical context, pressure from medical professionals and political considerations have all helped to shape these responses. Germany, the Netherlands, the United Kingdom and Switzerland have all been able to continue to provide supervised injectable heroin (SIH) as part of regular treatment. A trial of SIH treatment has just started in Belgium and in 2009, Denmark introduced SIH as a medical treatment for addiction. However, Spain and Canada have not been able to provide SIH despite evidence for its effectiveness in these countries, and the Australian government stopped a well-prepared and scientifically sound SIH study for political reasons in the mid-1990s.

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Chapter 3: Scientific evidence base for supervised injectable heroin treatment

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Chapter 3: Scientific evidence base for supervised injectable heroin treatment

In this chapter, we present the scientific evidence for supervised injectable heroin (SIH) treatment that has been accumulated through randomised controlled trials (RCTs) internationally.

The methodology for this exercise was designed to collect evidence in a sequential and logical manner. It has a clear focus on evidence of SIH treatment efficacy and cost-effectiveness as well as allowing a broad scope for learning about current clinical practices of SIH treatment across Europe and Canada.

Comprehensive review of the scientific literature on supervised injectable heroin treatment trials

The following detailed database search strategies were used to identify studies for inclusion in the review: the Cochrane Central Register of Controlled Trials (CENTRAL) Issue 2, 2010; MEDLINE (1966–2010), EMBASE (1980–2010).

There were no language or publication year restrictions. The following terms or combinations of these terms were used in the search strategy: ‘addiction’, ‘assisted’, ‘supervised’, ‘dependence’, ‘diacetylmorphine’, ‘diamorphine’, ‘heroin’, ‘maintenance’, ‘prescription’, ‘programme’, ‘provision’, ‘therapy’. The citations were reviewed by the research team based on their relevance to SIH treatment and the domains of its outcomes, efficacy and cost-effectiveness. Thus, papers which were primarily assessing unsupervised heroin treatment provision, focused on policy aspects, reporting profile of trial participant or which had no measures that related to drug use, physical health, psychological or social functioning, cost-effectiveness or community impact were excluded. Table 1 shows the results of the search by topic area, and these articles provide the evidentiary base for the literature review.

| Table 1: Initial search yield | |
|--------------------------------------|---------------------------|
| Subject | Number of articles |
| SIH efficacy | 7 |
| SIH cost-effectiveness | 1 |
| Long-term SIH effects | 5 |
| Community impact | 2 |
| Patients' perspective | 2 |
| Total | 17 |

SIH: supervised injectable heroin.

In addition, we searched relevant categories of the United Kingdom's NTA publications database, UK's Drugscope Library, and the National Research Register, Meta-register of Controlled Trials, Clinical Trials and Trials Central registers to ensure that no trials that were under way were neglected, as well as including recently published or 'in press' academic research that may not have been picked up in the literature review. Also, we assembled a list of contacts and conducted a review of the full project reports, provided on a more confidential basis by the principal investigators of the SIH treatment trials conducted in the EU Member States (Germany, Spain, the Netherlands) and also in Switzerland and Canada. Finally, the Cochrane Review (Ferri et al., 2011) was consulted to ensure consistency of key data sources. No additional main trial papers were identified, and the evidence in the subsequent sections is thus based on papers summarised in Table 1.

Efficacy

This section sets out the findings of a review of the published papers and project reports from studies examining the efficacy of heroin treatment under conditions of supervised administration.

The RCT design is considered the 'gold standard' for the generation of scientific level-1 evidence (evidence obtained from at least one properly designed RCT) about the efficacy of treatments (Ashcroft et al., 1997; Glasziou et al., 2007). However, other study designs may enable other domains to be explored and other important questions to be answered. We therefore briefly outline the large cohort study conducted in Switzerland – a study that marks the beginning of the scientific interest in SIH treatment – but we then focus on the evidence derived from more rigorous

evaluations using the RCT design. Although the Hartnoll et al. (1980) study was the first RCT to examine heroin (diacetylmorphine) treatment versus oral methadone treatment, this study is not included in the evidence reported in this chapter because the study did not use heroin treatment for the same target group (i.e. 'chronic heroin-dependent individuals'), as has been used in all of the new generations of SIH treatment trials (i.e. from Perneger et al., 1998 onwards). Furthermore, the heroin treatment that was provided in this first trial was very different from the heroin treatment provided in all of the subsequent heroin trials (i.e. Hartnoll et al., 1980: take-home unsupervised consumption-based provision vs. from Perneger et al., 1998 onwards: strictly medically supervised, injectable clinic-based heroin provision) (for further details, see Chapter 2).

The Swiss cohort studies

A series of five linked studies (the Swiss studies) on medical prescriptions of injectable opiates were designed and conducted in Switzerland between 1994 and 1996 (Uchtenhagen et al., 1996, 1997). The Swiss studies were originally planned as RCTs to compare (i) intravenous heroin with intravenous morphine and intravenous methadone, (ii) intravenous heroin with intravenous morphine and (iii) intravenous heroin with a waiting list control. However, owing to difficulties in recruitment into the non-heroin component, among other issues, the studies evolved into an observational open-label-type study following a single-group pre-post design. A total of 800 treatment slots were set up for heroin treatment in three different clinical contexts: (i) newly established clinics, (ii) existing outpatient methadone programmes and (iii) a medium-security prison with an inmate-run farm.

Between January 1994 and June 1996, 1 035 heroin-dependent individuals over 18 years of age who were chronically dependent, suffering from health and social problems as a consequence of their heroin addiction and had, without success, engaged in other treatment programmes at least twice entered the programme at a number of treatment centres throughout Switzerland and were followed up at 12 and 18 months. The first layer of analysis showed that, according to the entry criteria, a group of long-time opiate addicts with severe social and health problems could be reached and 76 % of them could be retained in SIH treatment over a 12-month period (Uchtenhagen et al., 1999). In the SIH cohort, significant reductions were reported in illicit drug use and criminal behaviour, as well as improvements in physical health and psychosocial functioning. At entry, 81 % of the sample retained in treatment for at least 12 months were using heroin illicitly on a daily basis. Only 6 % reported almost daily illicit heroin use at 6 months, with that reduction being

maintained over the remaining months of treatment. Overall, statistically significant reductions in consumption of cocaine, cannabis and benzodiazepines were reported. Criminal behaviour declined, with the proportion reporting an income from illicit sources reducing from 69 % to 10 %, with self-reported criminal activity verified by police records and official crime statistics (Killias and Rabasa, 1998).

Although patients prescribed SIH (alone or in combination with methadone or other medication) improved significantly in all key domains of substance use and functioning, in the absence of data from an appropriate control group, it was not possible to conclude that these improvements were caused or enhanced by the prescription of supervised injectable heroin, the provision of ancillary services or by the combination of these interventions. In the face of this major weakness, from a design point of view, commentators such as Ali et al. (1999) have suggested that some of the findings of the Swiss studies have been somewhat over-interpreted as favourable to SIH treatment.

Supervised injectable heroin randomised controlled trials' overview of methods

To date, six RCTs have assessed the efficacy of SIH treatment. As Fischer et al. (2002) point out, each of the evaluations had a different profile and used different methodologies in terms of target population, nature of interventions and measures, often reflecting the different treatment systems and policy environments in the countries involved (see Chapter 6 of this publication). Nonetheless, the main underlying objective of the trials in Germany, Spain (Andalusia), the Netherlands, Switzerland, Canada and, most recently, the United Kingdom has been consistently similar — to determine the therapeutic value of medical heroin prescription as second-line treatment for high-risk heroin users for whom such benefits cannot be expected or achieved from existing treatment options (van den Brink et al., 1999; Fischer et al., 2002; Lintzeris et al., 2006).

Participants across the six trials were daily heroin users with a stipulated minimum history of opiate dependency ranging between two (Switzerland (!) and Spain) and five (the Netherlands, Germany, Canada) years, commonly between 18 and 65 years of age at enrolment, who were residents of the supervised injecting clinic area. Also, they had a history of at least two unsuccessful treatment attempts, although there was variation with regard to their current treatment status at the time of enrolment, with the differences across the trials described in more detail below. Exclusion criteria,

(!) In the Swiss trial, this criterion was defined as 'addiction to *intravenous* heroin'.

where specified, included the presence of active symptoms of a severe psychiatric disorder, a pending prison sentence, a recent (past 12 months) episode of abstinence, a severe physical disorder or pregnancy.

The setting for treatment provision in all RCTs was an outpatient in supervised injecting clinics of varied size.

The duration of follow-up in each trial ranged from six to 12 months. The Swiss and the English trials were the shortest, with outcome assessment compared six months after commencing treatment. The Spanish trial followed up participants over nine months, and the trials conducted in Germany, the Netherlands and Canada continued for 12 months after allocation to the randomised treatment.

Primary outcomes to measure patients' response to SIH varied across trials: four trials (Germany: Haasen et al., 2007; Spain: March et al., 2006; the Netherlands: van den Brink et al., 2003; and Canada: Oviedo-Joekes et al., 2009) used composite or multi-domain outcomes including:

1. physical health, mental health status, and social functioning evaluated using validated indicators (van den Brink et al., 2003);
2. (i) health improvement (physical or mental) and (ii) decline in 'street' heroin use and concurrent non-increase of cocaine use (Haasen et al., 2007);
3. improvement in general health or psychological or family adjustment without a significant deterioration in any of these dimensions (March et al., 2006);
4. (i) retention in SIH at 12 months and (ii) reduction in drug use or criminal activity (or both) (Oviedo-Joekes et al., 2009).

The primary outcome measures in the Swiss trial included a reduction of self-reported drug use, and improved health status and social functioning (Perneger et al., 1998); the United Kingdom's Randomised Controlled Opioid Treatment Trial (RIOTT) measured a reduction of 'street' heroin use as a primary outcome (Strang et al., 2010). *Secondary outcomes* across trials included, but were not limited to, SIH safety, criminal activity, other drug use, physical health, and psychological and social functioning. A range of variables that were regarded as secondary outcomes in one trial were included as primary outcomes of patient treatment response in other trials. In some countries (e.g. the United Kingdom and Canada), *community outcomes*, such as levels and types of crime occurring in the community linked with heroin use, public safety and sensitivity, were also considered.

Additionally, research teams in Germany, the Netherlands and Switzerland assessed the *cost-effectiveness* of SIH treatment. More detail, where reported by trials, on secondary and other outcomes and the outcome measures used is provided in subsequent sections of this chapter.

All trials were analysed on an intention-to-treat basis — a method of analysis for randomised trials in which all patients randomly assigned to one of the treatments are analysed together, regardless of whether or not they completed or received the treatment.

Overview of treatment investigated

Five trials (van den Brink et al., 2003; March et al., 2006; Haasen et al., 2007; Oviedo-Joekes et al., 2009; Strang et al., 2010) compared supervised injectable heroin (plus flexible doses of oral methadone) with oral methadone treatment only (i.e. without additional heroin). In the Swiss trial (Perneger et al., 1998), injectable heroin was compared with a waiting list where control patients were encouraged to select any drug treatment programme that was available in Geneva and were enrolled straight after a place became available. A Dutch trial (van den Brink et al., 2003) was conducted over the same time period and included a comparison between inhalable heroin (plus flexible doses of oral methadone) and oral methadone alone, and in the English trial (Lintzeris et al., 2006), injectable methadone (plus flexible doses of oral methadone) was included as a second experimental treatment to be studied and was evaluated separately against optimised oral methadone maintenance treatment (MMT).

Overview of treatment regimes

Across the trials, the mean daily dose of injectable heroin ranged between 275 mg (Spain) and 392 mg (Canada), 399 mg (United Kingdom) and 442 mg (Germany), up to 509 mg (Switzerland) and 548 mg (the Netherlands). In the control groups, the mean dose of oral methadone was lowest in the Dutch trials (60 mg), within the optimised range in the German (99 mg) and the Canadian (96 mg) trials, and highest in the Spanish (Andalusian) (105 mg) and the British RIOTT (107 mg) trials.

Supervised self-administration of heroin in the newly established injecting clinics was the key common feature of treatment provision in all countries. No take-away doses of injectable medication were available to patients and the clinics were open for supervised injecting in two (Spain and the United Kingdom) to three (Germany, the

Netherlands, Switzerland and Canada) sessions per day (for 365 days per year). In all six trials, supervised treatment was combined with some form of psychosocial support.

Methodology and interventions: review by country

Switzerland, 1998

The Swiss trial was conducted as part of the cohort studies in the national evaluation (Perneger et al., 1998). It recruited a total of 51 participants: 27 long-term dependent heroin injectors with two previous episodes of methadone treatment, but who were not in treatment at enrolment, were randomly allocated to receive diacetylmorphine prescription (with all at least occasionally also receiving methadone as a replacement drug) and 24 were put on a six-month waiting list for diacetylmorphine, during which time they received conventional treatment, with most ($n = 19$) receiving MMT. Participants were studied over a six-month period of randomisation.

Patients randomised to receive SIH attended a clinic for supervised injections up to three times daily and received an average daily dose of 509 mg, occasionally supplemented with oral methadone. All patients received psychological counselling, as well as social and legal support services.

Outcomes, compared at six months, included self-reported consumption of 'street' heroin and other drugs, frequency of overdoses, use of health services, health status, work status, living arrangements, quality of social relationships, monthly living and drug-related expenditures, sources of income and criminal behaviour.

Netherlands, 2003

Two separate RCTs were conducted — an injectable heroin trial and a parallel study examining inhalable heroin for heroin smokers; with each of the two forms of treatment compared with oral methadone substitution therapy. Participating patients have typically been prescribed 'effective daily dose methadone' — at least 60 mg (injectable trial) or 50 mg (inhalable trial) — for at least four consecutive weeks in the past five years and, despite being in regular contact with a methadone maintenance programme for at least six months prior to enrolment, were not well stabilised and were continuing to regularly use illicit heroin, had poor physical or mental health or poor social functioning, and had not voluntarily abstained from heroin for more than two months in the year prior to trial enrolment (van den Brink et al., 2003).

The injectable heroin trial recruited a total of 174 participants, and the study of inhalable heroin had 375 participants taking part in it. Participants in the RCT with injectable heroin were allocated to one of the following treatment groups: (i) oral methadone over 12 months in combination with a standard package of psychosocial interventions (Group A; $n = 98$) or (ii) injectable heroin and co-prescribed oral methadone, plus equivalent package of psychosocial interventions for 12 months (Group B; $n = 76$).

Within the inhalable trial, 139 participants in Group A were allocated to receive oral methadone supplemented with psychosocial care for 12 months, and 117 participants in Group B were receiving inhalable heroin plus methadone plus psychosocial interventions for 12 months. Group C ($n = 119$), involving six months of methadone followed by six months of inhalable heroin with co-prescribed oral methadone, plus psychosocial interventions, was included to test whether six months would be long enough to result in stable positive outcomes. Group C is not reported in the present review and the focus is kept on SIH treatment.

Patients in Group B for 12 months and Group C for the last six months were attending for supervised heroin injections seven days a week, three times a day, and were receiving an average daily dose of 548 mg (a maximum of 1 000 mg per day and 400 mg, at the most, per visit). A daily dose of inhalable heroin averaged 502 mg. Oral methadone was delivered once a day (with a mean dose of 60 mg).

Primary outcomes included self-reported illicit drug use, physical health, mental status and social functioning. Treatment response in these areas was measured after 12 months in treatment, using a dichotomous, multi-domain outcome index. Response to treatment was considered as an improvement of at least 40 % in month 12 of outcome assessment compared with patients' situation at baseline in at least one of the areas in which they functioned poorly: physical health, psychiatric status, social functioning and substance use, with no substantial deterioration (> 40 %) in any of the domains compared with baseline and no increase (> 20 %) in the use of cocaine or amphetamines.

Secondary outcomes included (i) treatment completion, defined as the proportion of patients still in the index treatment at the end of the trial and (ii) sustained treatment response, where participants who had become responders before assessment in month 12 remained as responders during the course of the trial.

Spain, 2006

The experimental drug-prescription programme in Andalusia (PEPSA) (March et al., 2006) examined the efficacy of injectable heroin (in combination with methadone) compared with oral MMT alone in a study sample of 62 patients (31 per study group) with a history of, or current, unsuccessful addiction treatment attempts.

Oral methadone (at a mean daily dose of 105 mg) was dispensed to patients once a day. Patients in the SIH group attended twice a day and received a mean dose of 275 mg per day supplemented with oral methadone (at a mean daily dose of 43 mg).

Outcomes were assessed at four stages in the trial — at baseline and at three-, six- and nine-month follow-up — using a composite score of measures of general health, self-reported 'street' heroin use, quality of life, drug addiction-related problems, risk behaviour for human immunodeficiency virus (HIV) and hepatitis C virus, psychological functioning, and social and family status as based on ASI (Addiction Severity Index; McLellan et al., 1992), OTI (Opiate Treatment Index; Darke et al., 1992), SCL-90 (Symptom Checklist-90; Derogatis and Cleary, 1997) and SF-12 (Short Form-12; Gandek et al., 1998).

Germany, 2007

The German SIH RCT consisted of several stratified components and was based on a sample of 1 032 participants — both regular injecting heroin users presently in treatment but not sufficiently responding to MMT ($n_1 = 492$) and individuals who were currently not in substance misuse treatment but had a treatment history ($n_2 = 540$). In order to separately assess the benefit and impact of psychosocial treatment, a 4×2 design was adopted, whereby participants in each group were randomised to one of two types of psychosocial care. Thus, participants from each target group were randomly allocated to receive 12-month treatment in one of four treatment groups: (i) heroin plus education ($n_1 = 127$; $n_2 = 131$), (ii) heroin plus case management ($n_1 = 119$; $n_2 = 138$), (iii) methadone plus education ($n_1 = 125$; $n_2 = 130$) and (iv) methadone plus case management ($n_1 = 116$; $n_2 = 129$).

Doses of injectable heroin ranged up to 1 000 mg per day (at a mean daily dose of 442 mg) administered up to three times a day under supervision in the injecting clinic, and could be supplemented with oral methadone doses (at a mean daily dose of 8 mg) for 'take-home' night use. Methadone (at a mean daily dose of 99 mg) was administered once a day.

Outcomes were assessed at 12 months using two response criteria: (i) improvement in physical and/or mental health and (ii) decrease in illicit drug use. For the primary outcome measure on health, participants were considered to be responders if they had shown at least a 20 % improvement, based on the OTI Health Scale (physical health) and/or at least 20 % improvement, based on the Global Severity Index (GSI) (mental health), either of which occurring in tandem with no deterioration of more than 20 % in other domains of health. For the second primary measure, participants were identified as responders if a reduction in 'street' heroin use was evidenced in at least three of five urine samples negative for the drug in the month prior to the 12-month assessment, in tandem with no increase in cocaine use, evidenced and confirmed by hair analysis.

Canada, 2009

The North American Opiate Medication Initiative (NAOMI; Oviedo-Joekes et al., 2008, 2009) evaluated the feasibility and effectiveness of SIH in the Canadian context. The trial recruited a total of 251 entrenched opioid injectors, aged 25 years or older, who had used opioids for at least five years with at least two previous unsuccessful opiate addiction treatment attempts (including one oral methadone maintenance in which they received 60 mg or more of methadone daily), but who were not enrolled in treatment at the time of recruitment to the study (Schechter, 2002, 2006). A total of 251 participants were randomly allocated to receive one of three treatments: SIH ($n = 115$), MMT ($n = 111$) or injectable hydromorphone ($n = 25$), all supplemented with psychosocial interventions, with hydromorphone used to validate the self-reported use of illicit heroin by means of urine testing.

The injectable medications could be received up to three times daily, with a maximum daily dose of 1 000 mg of heroin (at a mean daily dose of 392 mg) plus oral methadone (at a mean daily dose of 34 mg). Oral methadone (at a mean daily dose of 96 mg) was dispensed on a daily basis.

Participants were followed up for 12 months. Retention in treatment was adopted as the first primary outcome and defined as receipt of the study medication on at least 10 of the 14 days before the 12-month assessment, or confirmation of retention in any other treatment programme or abstinence from opioids during this interval. The second primary outcome measure of patient response was a reduction in illicit drug use or criminal activity as based on the composite score of the European Addiction Severity Index (EUROP-ASI). Patients were considered responders at 12 months in treatment if they had an improvement of at least 20 % from the baseline score for

illicit drug use or legal status, or both, in tandem with a maximum of one of the remaining ASI composite scores (e.g. physical, mental health or social functioning) where there was a deterioration of 10 % or more.

United Kingdom, 2010

In the United Kingdom, RIOTT (Strang et al., 2010) recruited individuals who were currently in oral substitution treatment but were nevertheless still injecting illicit heroin on a regular basis. A total of 127 patients were randomised to one of three conditions: (i) optimised oral methadone treatment (control group, $n = 42$); (ii) injected methadone treatment ($n = 42$); or (iii) injected heroin treatment ($n = 43$) (with access to oral methadone doses).

Daily dose of injectable heroin (at a maximum daily dose of 900 mg) was divided into two (450 mg per injection). Patients in both injectable treatment groups were encouraged to take additional doses of oral methadone on a regular basis and instead of injectable medication if unable to attend the clinic. Supervised injectable methadone (at a mean daily dose of 31 mg) was administered once a day. Optimised oral methadone treatment involved once-daily doses of ≥ 80 mg (with a mean dose of 107 mg) consumed under direct nurse supervision at clinic sites ≥ 5 days per week for at least 3 months, with 'take-home' doses for weekends, and a reduced frequency thereafter if clinically appropriate.

Participants were followed up within the randomised trial for six months, with between-group comparisons on an intention-to-treat basis across a range of outcome measures. The primary outcome was the reduction in regular use of 'street' heroin, defined as 50 % or more of urine drug screens testing negative for markers of illicit heroin during trial weeks 14–26. For the first time, the primary outcome was measured using objective measures rather than self-reported illicit heroin use. Secondary outcomes included measures of other drug use, injecting practices, health and psychosocial functioning, criminal activity, patient satisfaction and incremental cost-effectiveness (Lintzeris et al., 2006).

Overall international evidence on individual and community outcomes

Retention

In the Swiss RCT, the retention rates at six-month follow-up in the SIH and methadone groups were high and not distinctively different — 93 % and 92 %, respectively (Perneger et al., 1998).

Although completion rates in the Dutch trials were high in all treatment groups, at 12 months, patients who were randomly assigned to receive methadone alone were marginally more likely to be retained in treatment at 12 months than those receiving injectable heroin (oral methadone: 85 % vs. injectable heroin: 72 %; difference: 12.3 %; 95 % confidence interval (CI) 0.2–24.5 %). Similarly, after 12 months in the inhalable trial, 87 % of the oral methadone patients were still in treatment compared with 68 % of the group allocated to inhalable heroin plus methadone (difference: 18.7 %; 95 % CI 8.8–28.6 %) (van den Brink et al., 2003). However, it was acknowledged by the authors that 7 % of the intention-to-treat population in the experimental groups never started the heroin treatment and a further 6 % were expelled from heroin treatment because of repeated violation of the clinic rules.

March and colleagues (2006) reported a 74 % retention rate in the SIH group at nine months, which was higher, although not significantly so, than the retention of 68 % achieved in the oral methadone group for the same time period.

In the German model project, retention at 12 months, too, was higher in the SIH group than in the methadone group (67 % vs. 40 %). However, when only those patients initiating trial treatment were considered in the calculation, 68 % of the heroin group and 56 % of the methadone group completed study treatment, and these proportions did not differ between treatment groups (Haasen et al., 2007).

In the Canadian trial (Oviedo-Joekes et al., 2009), the retention rate at 12 months in the SIH group was significantly higher than in the methadone group (87.8 % vs. 54.1 %; $P < 0.001$).

Finally, the RIOTT group reported that 88 % of SIH patients and 69 % of optimised oral methadone patients had remained in the assigned treatment at six months. Patients on oral methadone were found to be significantly more likely not to start treatment than those on injectable heroin ($P = 0.03$). After the exclusion of those who had not started treatment, the proportions of participants retained at six months did not differ significantly between treatment groups.

Retention in treatment appears to be similar or greater for patients in SIH than those engaging in oral methadone substitution therapy. Although this effect varied significantly across the trials, trials consistently reported good retention in the SIH group. Retention in the control groups was more varied.

'Street' heroin and other drug use

A measure of reduction of 'street' heroin and/or other drug use, rather than abstinence, was consistently used across the trials.

All trials gathered self-reported data on 'street' heroin use (these data from the UK RIOTT trial are not yet published in peer-reviewed journal form). Within the RIOTT, reduction in 'street' heroin use was measured by weekly urinalysis during weeks 14–26. Urine samples were obtained from patients at random once a week for 26 weeks and analysed with laboratory urinalysis using liquid chromatography mass spectrometry to detect opioid impurities (e.g. noscopine, papaverine), and thus it was possible to differentiate between the prescribed pharmaceutical diacetylmorphine and 'street' heroin. The German and Canadian trials also included objective laboratory test results for illicit heroin. These were, however, incorporated into the composite scores and were not reported separately.

In the Swiss trial (Perneger et al., 1998), compared with the control group, those in the diacetylmorphine group showed significant reductions in 'street' heroin use — only 4 % compared with 48 % in the control group were still using 'street' heroin daily at the six-month follow-up point ($P = 0.002$; difference 44 %; 95 % CI 16–72 %). Although the use of other substances (e.g. alcohol, cannabis, cocaine, barbiturates, opiates other than heroin) was described as differential between the two groups at baseline and at the end of the follow-up period, no significant differences between the two groups were observed, with the exception of benzodiazepines, for which 33 % in the control group still used at the time of follow-up compared with 0 % in the experimental group ($P = 0.049$).

For the Dutch trials, van den Brink et al. (2003) reported that at 12 months, SIH was significantly more effective than treatment with methadone alone — in relation to the pre-defined outcome parameter, that is a self-reported 40 % improvement in at least one domain (physical, mental, social) — both in the trial with injectable heroin (55.5 % vs. 31.2 %; difference 24.3 %; 95 % CI 9.6–39.0 %) and in the trial with inhalable heroin (response rate 49.7 % vs. 26.9 %; difference 22.8 %; 95 % CI 11.0–34.6 %). Disaggregated data on changes in 'street' heroin and other drug use were, however, not available.

In the Spanish project, both the SIH and the control group were found to have achieved considerable improvements in relation to their 'street' heroin and other drug use. At follow-up, SIH patients reported significantly less use of non-prescribed

heroin and were engaging in lower-risk injecting behaviour, as measured by OTI (Darke et al., 1991) (baseline: 8.90; 9 months: 0.59; $P = 0.001$). In a between-group analysis, the rate of improvement, measured by EURO-ASI (McLellan et al., 1992) was higher in the SIH group than in the control group, with better EURO-ASI drug score indicators for heroin use (15.3 vs. 6.5; $P = 0.020$) and OTI HIV risk behaviour (general: 8.3 vs. 5.1; $P = 0.012$; drug-use related: 7.8 vs. 4.2; $P = 0.004$).

Haasen and colleagues (2007) reported significantly greater reductions over 12 months in illicit drug use (reduction in illicit heroin use and no increase in cocaine use) in the SIH group compared with the methadone group (69.1 % vs. 55.2 %; odds ratio (OR) 1.85; 95 % CI 1.43–2.40; $P < 0.001$). The German research group also reported the results of a more conservative analysis strategy that it had used, whereby only patients responding on both primary outcome measures — illicit drug use and health — had been defined as responders. Using this strategy, both their intention-to-treat (ITT) and per protocol analysis showed a significantly better response rate for the heroin than the methadone group (ITT: 57.3 % vs. 44.8 %; OR 1.67; 95 % CI 1.30–2.14; $P < 0.001$; per-protocol analysis: 63.6 % vs. 39.5 %; OR 2.73; 95 % CI 1.88–3.97; $P < 0.001$).

In the Canadian trial (Oviedo-Joekes et al., 2009), self-reported illicit heroin use in the past 30 days (mean days) had reduced from 27 at baseline to 5 days at 12-month follow-up (SIH group) versus 27 days at baseline to 12 days at follow-up (methadone group) ($P < 0.001$). Reduction in illicit drug use or other illegal activity was reported at 67.0 % (SIH) versus 47.7 % (MMT), with a relative risk of 1.40 (95 % CI 1.11–1.77; $P = 0.004$). The reduction in illicit drug use alone was 22.6 % (SIH) versus 13.5 % (MMT), and reduction in both illicit drug use and other illegal activity was reported at 43.5 % (SIH) versus 28.8 % (MMT). No change in cocaine use was reported in either group.

Strang et al. (2010) reported that after adjustment for treatment centre, regular crack use at baseline and other variables, 66 % of the injectable heroin versus 19 % of the optimised oral methadone patients were responders ($P < 0.0001$) at the six-month follow-up. Responders in this trial were patients achieving a reduction in regular use of 'street' heroin and providing 50 % or more negative specimens on urinalysis during weeks 14–26.

Conclusion

Compared with oral methadone substitution, treatment with heroin brings about additional reductions in illicit heroin use, although in both treatments this is markedly reduced. Cocaine use, where it was reported, had either not changed or reduced at a comparable rate across the two treatment types.

Health, health-related quality of life and social functioning (integration at work, family relationship)

In the Swiss cohort, mental health, role-emotional and social functioning, measured by means of an SF-36 health survey, significantly improved between baseline and the six-month follow-up in the SIH group (mean for mental health: 54.4; role-emotional: 63.0; social functioning: 64.4) in comparison with the oral methadone group (mean mental health: 49.3; $P = 0.025$; role emotional: 43.9; $P = 0.027$; social functioning: 61.9; $P = 0.041$). There were, however, no statistically significant differences between the groups on a number of other health and social functioning variables, such as being employed and having a stable partner, although the SIH group consistently showed improvements when compared with baseline data (Perneger et al., 1998).

For the Dutch trials (injected and inhaled heroin), no disaggregated data were available on health and social functioning outcomes.

For patients recruited to treatment in the Spanish trial, March and colleagues (2006) reported health and social functioning outcomes as mean scores in the ASI (Kokkevi and Hartgers, 1995) and the OTI (Darke et al., 1991, 1992). SIH patients showed an improvement in physical health (OTI: from 16.5 to 9.8; $P = 0.001$) and in respect to their psychological status and adjustment (composite ASI: from 0.5 to 0.3; $P = 0.009$). In the control group, similar improvements were observed in the mental health domain (composite ASI: from 0.5 to 0.4; $P = 0.017$). These improvements occurred in tandem with significant gains in the social and family areas: for the SIH group (ASI: from 0.4 to 0.3; $P = 0.007$; OTI: from 21.9 to 19.0; $P = 0.009$) and for the control group (ASI: from 0.5 to 0.3; $P = 0.002$; OTI: from 25.1 to 20.7; $P = 0.002$). In between-group comparison at nine months, however, only the general health status was significantly better in the SIH group when compared with the methadone group (OTI: 7.8 vs. 3.2; $P = 0.034$).

Unlike the other trials, where health was typically a secondary outcome measure, in the German model project, improvement in health was adopted, along with reduction in illicit drug use, as a primary outcome measure. Consistent with illicit drug-use results, the SIH group demonstrated a significantly greater response on the health outcome measure. The difference between the SIH and the methadone group in health improvement rate was significant, in both ITT (80.0 vs. 74.0; OR: 1.41; 95 % CI 1.05–1.89; $P = 0.023$) and per-protocol (87.0 vs. 77.0; OR 2.05; 95 % CI 1.28–3.27; $P = 0.003$) analyses (Haasen et al., 2007). An in-depth analysis of physical (e.g. nutritional status, cardiac function, infectious diseases) and mental

health functioning and quality of life, using a range of measures: OTI (Darke et al., 1991, 1992); the body mass index (BMI); a 12-lead electroencephalogram (ECG); an echocardiogram; hepatitis B virus, hepatitis C virus and HIV serology; a tuberculin test (Mendel–Mantoux method); GAF (the Global Assessment of Functioning Scale; Jones et al., 1995) and Symptom Checklist 90-R (SCL-90-R).

Although improvements were observed and reported in patients receiving both the heroin and methadone treatment regarding OTI, BMI and SCL-90-R, these changes were greater in the heroin group (analysis of variance (ANOVA), all $P < 0.0001$). While there were significantly fewer pathological echocardiograms in the heroin group than in the methadone treatment group (χ^2 test, $P < 0.05$), the occurrence rate of markers of pathological diseases and frequencies of pathological ECGs did not differ between the two treatment groups, or between baseline and the 12-month follow-up (Reimer et al., 2011). An increase was reported in the average quality of life scores, as measured by the MSQoL (Modular System for Quality of Life; Pukrop et al., 1999), from 3.3 to 4.1 in the heroin group and to 3.9 in the methadone group, but these differences were not statistically significant.

Regarding outcomes in the social functioning domain, Haasen and colleagues (2007) reported improved family relationships, with a baseline of around 30 % of patients having a stable relationship and a slight increase in both SIH (SIH plus education or case management) groups at month 12. In terms of housing, approximately 69 % of patients in either the SIH group or the oral methadone group had stable housing (e.g. own apartment, partner's apartment, parents/relatives or flat sharing) at baseline, with these percentages increasing to 72.2 % and 67.7 % in the SIH and the methadone group, respectively.

For the Canadian trial, Oviedo-Joekes and colleagues (2008) reported the health and social outcome as a mean score change in the EuropASI (European Addiction Severity Index; Kokkevi and Hartgers, 1995). Mental health status was significantly improved at the 12-month follow-up in the SIH group in comparison with the methadone group (ASI score psychiatric status: SIH: 0.16 vs. methadone: 0.20; $P < 0.01$), and in the social domain, employment satisfaction and social reintegration showed significant improvement (employment satisfaction: SIH: 0.10 vs. methadone: 0.11; $P = 0.02$; social reintegration: SIH: 0.09 vs. methadone: 0.08; $P = 0.05$).

The impact of SIH treatment on health and social functioning is yet to be reported by some of the trials.

Conclusion

Patients undergoing SIH treatment have experienced significant physical and mental health improvements compared with patients receiving conventional oral substitution prescribing. However, heroin treatment has not been consistently or substantially superior across all studies and outcomes, particularly the health and psychosocial functioning domains.

Criminal offences

Across the trials, criminal activity was commonly measured by self-report, although the German trial conducted an ambitious objective crime activity data collection, corroborating self-report data with data extracted from state criminal police records.

The Swiss SIH group showed significant reductions in criminal charges, including charges for drug use and/or possession (11 %) in comparison with the oral methadone group (38 %; $P = 0.008$), property theft (4 % vs. 24 %; $P = 0.015$), other offence/charge in the past six months (19 % vs. 57 %; $P = 0.0004$) and in income from drug dealing (passing from CHF 3 372 to CHF 331 in the SIH group at follow-up) versus CHF 3 123 to CHF 4 931 in the oral methadone group ($P = 0.053$) (Perneger et al., 1998). The trial did not report on incarceration or imprisonment.

For the Dutch trials (injected and inhaled heroin), no disaggregated data were available. Based on a subgroup of 430 patients (heroin plus methadone: $n = 193$; methadone only: $n = 237$) who were receiving their treatment for a 12-month follow-up period, Dijkgraaf et al. (2005) reported that participants in the heroin group engaged in criminal activities less often than those in the oral methadone group, with fewer reported days of crime against property (10.3 vs. 37.5), less frequent arrests (2.1 vs. 2.8 times a year) and less frequent convictions (0.25 vs. 0.54 times).

In the Spanish trial, although there were significant reductions in the number of days of involvement in illegal activities in both the SIH (11.5–0.6 days; $n = 27$; $P = 0.001$) and the control group (from 8.0 to 4.1 days; $n = 23$; $P = 0.015$) at nine months, there were no significant between-group differences in this outcome measure (March et al., 2006).

Importantly, in the largest RCT thus far — the German model project ($n = 1015$) — the investigation of SIH treatment's contribution to a reduced criminal activity, relative to oral MMT, was undertaken based on both self-reported criminal behaviour and police data collected for a subsample ($n = 825$) from the Landeskriminalämter (state

criminal police offices) of the federal states participating in the trial (Löbmann and Verthein, 2009). Although improvements were reported in both the SIH and the oral methadone group, the heroin group fared significantly better. The percentage of individuals who had committed at least one offence in the respective year dropped from 79 % to 45 % in the heroin group and from 79 % to 63 % in the methadone group (McNemar tests: heroin, $\chi^2 = 129.36$; $P < 0.0001$; methadone, $\chi^2 = 42.95$; $P < 0.0001$). The average number of offences also declined in the heroin group from 76.7 to 26.8; this drop was greater than the drop in the methadone group, where it declined from 79.7 to 49.9 (treatment effect, $F = 9.83$; $P = 0.002$; effect of time, $F = 179.40$; $P < 0.0001$; and an interaction between the two factors, $F = 11.53$; $P = 0.001$). Although a similar trend, indicating the superiority of the SIH group, was evidenced by the analysis of police data on alleged criminals, the primary aim of the study was not validation of self-reported criminal data, because the crime categories built for the self-reported data did not correspond exactly to the categories for the police data.

Within the Canadian trial, the reduction in illegal activities was reported at 0.9 % (SIH) versus 5.4 % (MMT). The British research team is yet to report on crime outcomes of SIH treatment delivered within RIOTT.

Conclusion

Trials that have reported findings in the crime domain stated that crime — self-reported or reported by official databases — had reduced, compared with levels at entry to SIH treatment and where available to controls (with the exception of the Spanish and the Canadian trials).

Safety

Across all trials, overdoses were registered as serious adverse events (SAEs) ⁽²⁾ when treatment with opioid antagonists was required, even when patients recuperated in a short space of time.

⁽²⁾ An SAE is an unanticipated problem involving 'risk' to participants that ultimately results in harm to the participant (impacts on the participant's morbidity and mortality) (e.g. unanticipated 'risk' requiring hospitalisation or prolongation of existing hospital stay) or to others.

No deaths occurred in the Swiss trial and data on other SAEs were not available. In 2005, Rehm and colleagues published data on mortality in SIH in Switzerland over a 6-year time period (1994–2000) (Rehm et al., 2005). Data in their study were sourced from two doctoral dissertations (Ryser, 1999; Gacond, 2004) and records monitoring SIH treatment in this country. The authors reported death occurrence during SIH treatment episode, that is from admission to discharge, plus a timeframe of 30 days post-SIH treatment discharge. Their analysis yielded a total of 49 deaths in more than 4 600 person-years over the period 1994 and 2000 (Rehm et al., 2005).

In the Dutch trials, the incidence of SAEs over the 12-month study period was similar across the treatment groups (van den Brink et al., 2003). Two SAEs were reported as probably or definitely related to the study medication — one non-fatal heroin overdose and one non-fatal car crash in a polydrug (heroin and cocaine)-using patient. One death was reported in each group (A, B and C). In the SIH group, the patient's death had occurred several hours after discharge from hospitalisation for an epileptic seizure treated with the opioid antagonist naloxone.

In the Spanish trial, 14 SAEs were reported in 14 patients, equally distributed between the two study groups (March et al., 2006). In the SIH group, none of the seven SAEs were definitely related to trial medication, two were not related to it and five were probably related to heroin (two occurring in one patient). One death, due to speedball overdose, was registered in the control group, which was confirmed by a forensic analysis and report.

Over the 12-month follow-up period of the German SIH RCT, a total of 315 SAEs were reported. Of these, 177 were among 124 patients in SIH and 138 among 88 patients in oral MMT (Haasen et al., 2007). In 58 instances in the SIH group, the adverse event was possibly, probably or definitely related to the study medication (of which 41 occurred within minutes after injection, and the majority ($n = 31$) were related to respiratory depression and a lesser number ($n = 10$) to an epileptic seizure). In the oral methadone group, SAEs that were classed as possibly, probably or definitely related to the study medication were just under four times less ($n = 15$) than those in the SIH group.

In the SIH group, SAEs that were possibly, probably or definitely related to the study medication were reported to occur 2.5 times more often than in the methadone group (every 2 572 vs. 6 501 treatment days in the SIH and methadone groups, respectively).

From a total of 12 deaths over the 12-month study period, five were registered in the SIH and seven in the methadone group. Of these, five were reported to have occurred while the participant was using study medication and none was reported to be possibly, probably or definitely related to the trial medication (three in the SIH group: one spleen rupture after falling, one intoxication with illicit methadone and one due to pneumonia and myocarditis; two in the methadone group: one ruptured aneurysm and one unknown reason but no methadone implicated) (Haasen et al., 2007).

Oviedo-Joekes and colleagues (2009) reported a total of 79 SAEs in 54 patients: 51 in the SIH group, 18 in the methadone group and 10 in the hydromorphone group. One death — unrelated to the study drug (methadone) — was reported for the NAOMI study period. Commonly related to injectable heroin were overdoses and seizures, with 7 out of 10 patients who had required naloxone subsequently reporting use of other drugs, such as benzodiazepines or cocaine, prior to the overdose.

Strang et al. (2010) reported seven SAEs in the injectable heroin group and nine in the oral methadone group. Of three events judged to be related to trial treatments, two had occurred in injectable heroin patients (and one of injectable methadone) — one at 17 days into treatment after the patient's regular dose of 200 mg of intramuscular heroin, and the other at 42 days into treatment after the patient's regular dose of 200 mg of intravenous heroin. The rate of SAEs was reported as one in every 6 613 injections for injectable heroin. For oral methadone, none of the SAEs had been judged to be related to the treatment received.

Conclusion

More SAEs have been reported to occur in patients receiving SIH than in those receiving oral methadone. This suggests that SIH may be less safe and therefore requires more resources and clinical attention in order to manage greater safety issues.

Table 2: International supervised injectable heroin (SIH) (plus flexible supplementary doses of oral methadone) trials' key features and outcomes

| Main paper | Country | Simple size; groups studied | Time to Follow-up | Outcomes |
|----------------------------|-------------|--|-------------------|---|
| Perneger et al., 1998 | Switzerland | N=51 SIH (+OM): n=27 OM, detox, rehab: n=24 | 6 months | <ul style="list-style-type: none"> Retention: SIH 93 %, OM 92 %. Self-reported illicit heroin use: SIH 22 %, OM 67 % (p=0.002). Serious adverse events data not reported |
| Van den Brink et al., 2003 | Netherlands | Injectable trial: N=174 SIH (+OM): n=76 OM: n=98 (also SinHH trial, N=75) | 12 months | <ul style="list-style-type: none"> Retention: SIH 72 %, OM 85 %. Self-reported 40 % improvement in at least one domain (physical, mental, social): SIH 56 % vs. OM 31 % (p=0.002). Serious adverse events: reported data limited to 11 SAEs (two definitely or probably, and nine possibly related to injectable heroin) |
| March et al., 2006 | Spain | N=62 SIH (+OM): n=31 OM: n=31 | 9 months | <ul style="list-style-type: none"> Retention: SIH 74 %, OM 68 %. Self-reported illicit heroin use in past 30 days (mean days): SIH=8.3 vs. OM=16.9 (p=0.02). Serious adverse events: SIH=seven (two unrelated and five probably, or definitely related to study drug) vs. OM=seven |
| Haasen et al., 2007 | Germany | N=1015 SIH (+OM): n=515 OM: n=500 | 12 months | <ul style="list-style-type: none"> Retention: SIH 67 %, OM 40 %. Improvement in drug use (measured by either UDS and self-report): SIH 69 %, OM 55 % (p<0.001). Improvement in physical/mental health: SIH 80 %, OM 74 % (p=0.023). Combined reduced drug use and improved physical/mental health (responder): SIH 57 %, OM 45 % (p<0.001). Serious adverse events: SIH=177 (58 possibly, probably, or definitely related to study drug) vs. OM=15 |
| Oviedo-Joekes et al., 2009 | Canada | N=251 SIH (+OM): n=115 OM: n=111 (also SIHM +OM, n=25) | 12 months | <ul style="list-style-type: none"> Retention: SIH 88 %, OM 54 % (p<0.001). Self-reported reduction in illicit drug use or other illegal activities (improvement of 20 % for either domain): SIH=67 %, OM=48 % (p=0.004). Serious adverse events: SIH=51 vs. OM=18 |
| Strang et al., 2010 | England | N=127 SIH (+OM): n=43 OOM: n=42 (also SIM +OM, n=42) | 6 months | <ul style="list-style-type: none"> Retention: SIH 88 % vs. OOM 69 %. Reduction in 'street' heroin – 50 % or more negative UDS during weeks 14–26 (responder): SIH 66 % vs. OOM 19 % (p<0.0001) Serious adverse events: SIH=7 (2 likely related to study drug) vs. OOM=9 |

Note: SAE, serious adverse event; OM, oral methadone; OOM, optimised oral methadone; SIM, supervised injectable methadone; SinHH, supervised inhalable heroin; SIHM, supervised injectable hydromorphone.

Cochrane systematic review of SIH treatment trials

The authors are grateful to colleagues from the Cochrane Drugs and Alcohol Group who prepared and produced the following summary (pp. 55–66) of the results from a systematic review of SIH treatment trials, and thus complementing the material reported in the previous section and providing additional detail.

Who produces the Cochrane systematic reviews on drugs and alcohol?

The Cochrane Drugs and Alcohol Group

The Cochrane Drugs and Alcohol Group (CDAG) is part of the Cochrane Collaboration and produces, updates and disseminates systematic reviews of trials on the prevention, treatment and rehabilitation of problematic drug and alcohol use. It was founded in 1998 in Rome, which is home to the editorial base office. Since then, around 200 authors have published with the CDAG: the majority come from the European Union, but many are also from Australia, Asia, North America, South America, South Africa and the Middle East.

The systematic reviews published by CDAG are based mainly on randomised controlled trials (RCTs) and controlled clinical trials, testing active interventions aimed at reducing the potential for harm or the actual harm directly related to the use of different dependence-producing substances, but other study designs also are included, in limited circumstances.

The publication of Cochrane reviews follows an editorial peer-reviewed process from the protocol stage onwards, with regular updates every two years or when new study results become available, according to the criteria of the Cochrane Collaboration (Higgins and Green, 2008).

As of January 2010, CDAG published 52 reviews covering pharmacological and psychosocial treatments of opioid (20 reviews), alcohol (10 reviews), cocaine and other psychostimulant (11 reviews), polydrug (four reviews), and cannabis, benzodiazepine and methaqualone (one review each) abuse or dependence. The effectiveness of preventive interventions across different substances was considered in four reviews.

For more information about CDAG activities, it is possible to consult the relevant website (<http://www.cdag.cochrane.org>); more general information about the Cochrane Collaboration can be found at <http://www.cochrane.org/>

The contribution from systematic reviews of randomised controlled studies to the evidence of effectiveness

Systematic reviews are aimed at collating all available evidence that fits pre-specified inclusion criteria in order to address a specific question (Higgins and Green, 2008). In practice, to develop a systematic review, all the studies (published and unpublished) that meet a set of pre-specified inclusion criteria should be identified, appraised and synthesised in an accessible format (Mulrow, 1994).

What are the meta-analyses?

Many systematic reviews include meta-analyses to summarise the results of independent studies (Glass, 1976). Meta-analyses can provide more precise estimates of the effects of healthcare and can facilitate investigations of the consistency of evidence across different studies. However, it should be noted that meta-analysis refers to the statistical technique of pooling the results of single studies, which can be carried out only in the absence of relevant heterogeneity (either statistical or clinical) across studies.

In the review of effectiveness, the suggested measure of effect for dichotomous outcomes is the risk ratio (based on the comparison among the proportion of events in the experimental groups and the control groups) and the 95 % confidence interval (CI), which is calculated for each individual study and then, when possible, pooled in a meta-analysis. The width of the CI for an individual study depends, to a large extent, on the sample size. Larger studies tend to give more precise estimates of effects (and hence have narrower CIs) than smaller studies.

To contribute to a pooled result, each study is weighted according to the number of participants and number of events (larger studies, which have smaller standard errors, are given more weight than smaller studies, which have larger standard errors). Eventually, a 95 % CI is also reported for the pooled results.

Why are study inclusion criteria pre-specified?

Cochrane systematic reviews are the result of a complex process that includes formulating a proper question, comprehensively searching studies, objectively selecting and extracting data, critically evaluating primary studies, and synthesising and updating results. In the last few years, grading the quality of the evidence has been added to this process. Several studies have evaluated the quality of systematic reviews and consistently found a better quality for Cochrane versus non-Cochrane

reviews (Jadad et al., 2000; Olsen et al., 2001; Moja et al., 2005; Delaney et al., 2007; Moher et al., 2007; Tricco et al., 2009).

The main feature of Cochrane reviews is the publication of a protocol of the review beforehand; peer review of protocols is carried out before the results of the studies that are to be included are analysed, and this avoids biases. Prior knowledge of the results of a potentially eligible study, for example, might influence the definition of a review question, the subsequent criteria for eligibility and the choice of intervention comparisons to analyse or the outcomes to be reported in the review.

On the other hand, systematic reviews are often (but not always) retrospective, and for this reason it is important that the methods used are established and documented in advance (Light and Pillemer, 1984).

The protocol of a review should specify the inclusion criteria of studies to answer the review question, and in particular the types of population (participants), types of interventions (and comparisons) and the types of outcomes that are of interest. The outcomes, in particular, should be pre-specified and not listed only on the basis of their presence in the studies considered.

The subsequent review should adhere to the pre-published protocol, although changes may sometimes be introduced if necessary. Nonetheless, every effort should be made to adhere to the pre-determined protocol without undue changes.

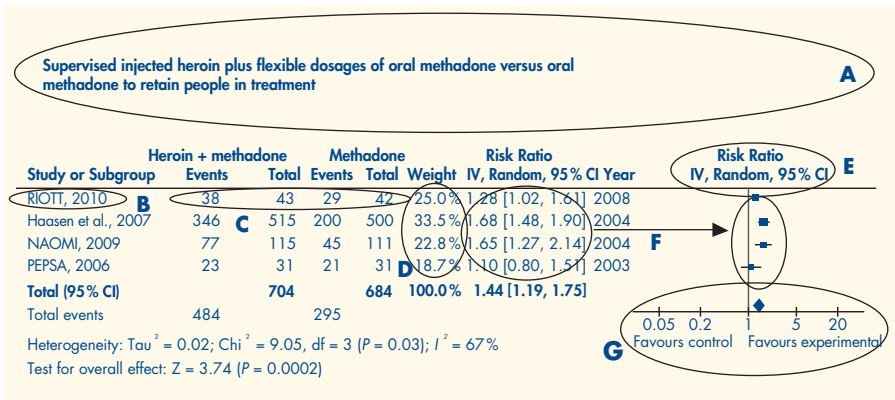
Post hoc decisions made when the impact on the results of the research is known, such as excluding selected studies from a systematic review, are highly susceptible to bias and should be avoided (Higgins and Green, 2008).

How to read and interpret a 'funnel plot'?

Funnel plots are the typical graph representing the meta-analysis results. They are useful as they allow a visual interpretation of the many elements that contribute to the final results.

Taking as an example the funnel plot in Figure 1, we illustrate the main components below:

Figure 1: An example funnel plot and its components



- A.** A title indicates what interventions are compared to obtain what outcome.
- B.** Each study has a reference with the date of publication (if published).
- C.** The number of patients with the event (related to the outcome) and the total number of patients randomised to each arm is indicated for each study.
- D.** The relative weight attributed to each study is indicated. As explained earlier, the weight is attributed taking into account the number of participants and events (larger studies, with smaller standard errors, are given more weight than smaller studies with larger standard errors).
- E.** A label indicates the measure of effect that has been calculated for each study.
- F.** Each risk ratio is represented graphically by a square and a horizontal line whose extension indicates the confidence interval (CI) (the estimate of variation due to chance). The last diamond represents the pooled analysis which, in this example, favours the experimental intervention.
- G.** A horizontal line indicates the position of effect in relation to the null hypothesis. The null hypothesis is the number 1 (the perfect symmetry of proportions of events between the interventions and the comparisons arms).

Two labels ('favours experimental' and 'favours control') indicate which parts of the line represent the experimental superiority and which part the control superiority.

When the representation of a risk ratio or its confidence intervals crosses the vertical line, this indicates that the results of the individual study are not statistically significant.

In the specific case, the experimental intervention gave better results and the risk ratio of 1.44 means that people in the heroin groups have 44 % more probability of being retained in treatment at the end of the study period.

- H.** The test for heterogeneity describes the percentage of variability in effect estimates that is due to heterogeneity rather than chance. Statistical heterogeneity is considered when confidence intervals for the results of individual studies have a poor overlap. In the case of the above-represented meta-analysis, the result of I² = 67 % may be interpreted as moderate to substantial heterogeneity.

The Cochrane systematic review on heroin-assisted treatment

Main results

Published as a protocol in 2001, the Cochrane systematic review on heroin maintenance for chronic heroin-dependent individuals (2010) was initiated to include prospectively the results from the existing, ongoing or planned randomised controlled studies about maintenance treatment with pharmaceutical heroin versus any other treatments.

At the time of first publication (2003), the review included four randomised controlled studies (with 577 participants) by Hartnoll et al. (1980), Perneger et al. (1998) and the two Dutch studies (Central Committee for the Treatment of Heroin Addicts CCBH (A) and CCBH (B)) by van den Brink et al. (2003). The studies conducted in Switzerland by Uchtenhagen (1999) were not included because they were not randomised controlled studies.

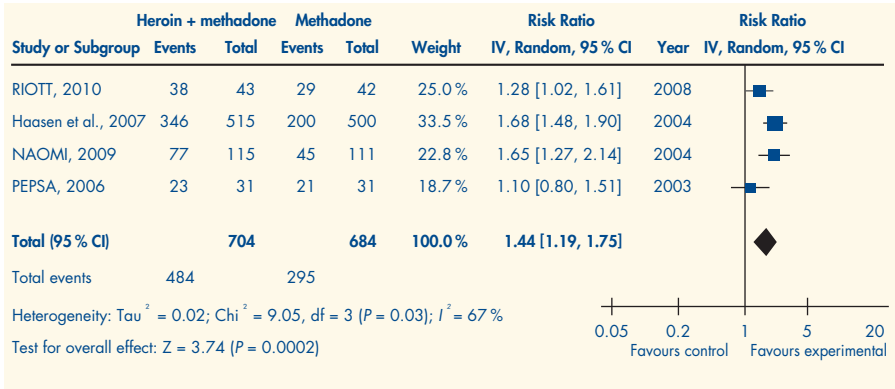
The studies included in the review were not comparable in terms of interventions and outcomes, and even though the heroin arms gave better end point measures, no overall conclusive results were possible.

When the results from a large new study by Haasen (2007) (of 1 032 patients) and the Spanish experimental drug prescription programme in Andalusia (PEPSA) (March et al., 2006; Perea-Milla et al., 2009), as well as from Canadian (Oviedo-Joekes et al., 2009) and, most recently, British (Strang et al., 2010) studies became available, the review was updated and the conclusions revised accordingly.

The updated version of the review encompassed eight studies and 2 007 patients, analysed in two steps. The first step compared the differences between SIH as the experimental intervention and oral methadone as the control intervention and included four recent studies (March et al., 2006; Haasen et al., 2007; Oviedo-Joekes et al., 2009; Strang et al., 2010). The study by Perneger et al. (1998) was not included in this comparison because the control intervention was on a waiting list for treatment as usual, and it was therefore included in a second step comparison. This second step compared the differences between heroin provision (all route of administrations) plus flexible doses of methadone versus any other interventions, and it included the valid data from all eight studies.

The pooled results of four of the most recent studies comparing SIH plus flexible dosages of methadone treatment with oral methadone showed that heroin helps patients to remain in treatment (valid data from four studies, $n = 1388$; risk ratio 1.44 (95 % CI 1.19–1.75) heterogeneity; $P = 0.03$) (see Figure 2).

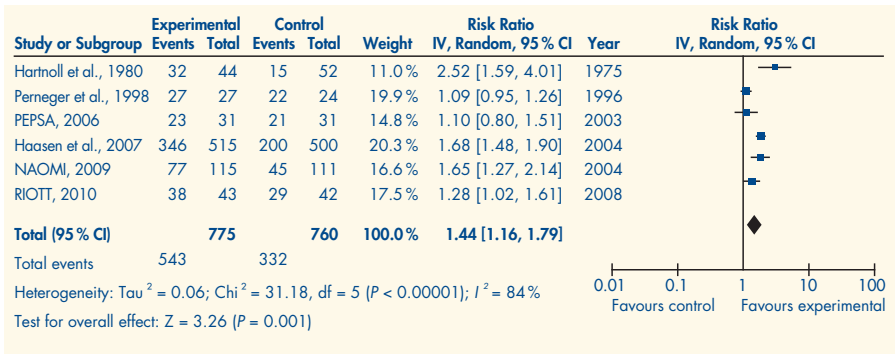
Figure 2: Supervised injectable heroin plus flexible dosages of oral methadone versus oral methadone to retain people in treatment



The results from the Dutch studies (van den Brink et al., 2003) could not be included in the meta-analysis for this outcome as the authors declared the non-comparability of the groups owing to differences in the discharge rules.

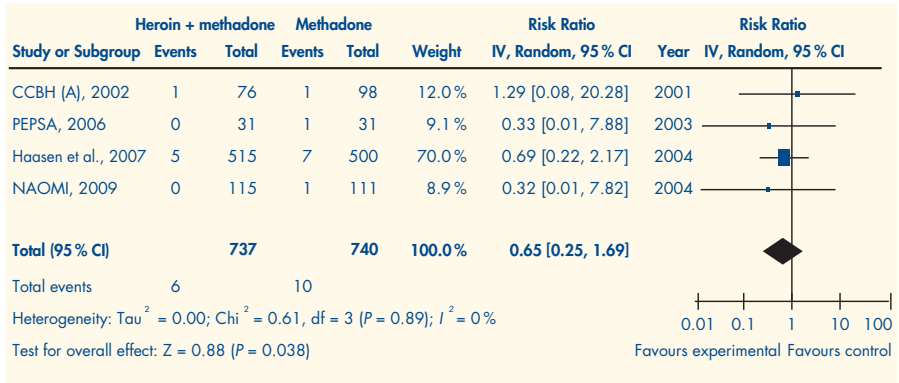
The results for the meta-analysis including all the studies, which consider unsupervised provision of heroin and/or compared SIH with waiting list or standard treatment, remain in favour of heroin provision (see Figure 3).

Figure 3: Heroin plus flexible dosages of oral methadone versus other interventions to retain people in treatment



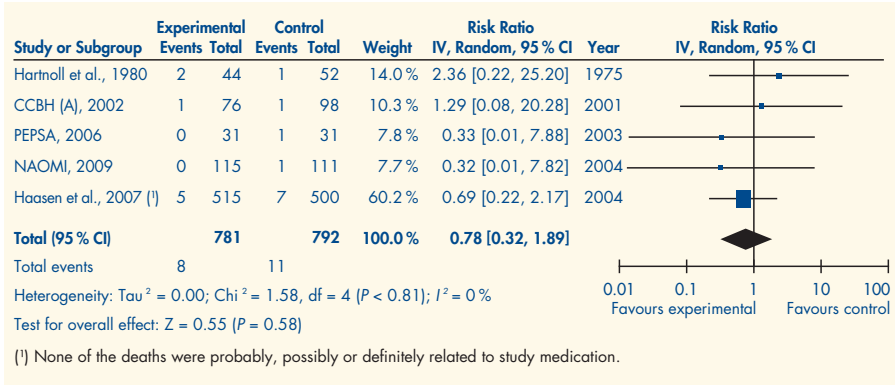
Heroin provision appears also to have a protective effect on mortality even though it is known that randomised controlled studies, owing to their short period of observation, are not appropriate for measuring this outcome (Figures 4 and 5).

Figure 4: Supervised injectable heroin plus methadone versus oral methadone – Outcome: mortality



For the mortality outcome among the patients provided with SIH or oral methadone, it can be noted that the British trial was not included in the meta-analysis because the original trial protocol did not declare that it would measure this outcome. Personal communication with the principal investigator (John Strang) informed us that no lethal events occurred in the two study arms during the trial phase, confirming that the study should not be added to the meta-analysis. In fact, if studies with zero events in both comparison arms are pooled in the meta-analysis, the pooled total become less precise in terms of statistical significance, and they do not contribute to cumulative knowledge (Higgins and Green, 2008).

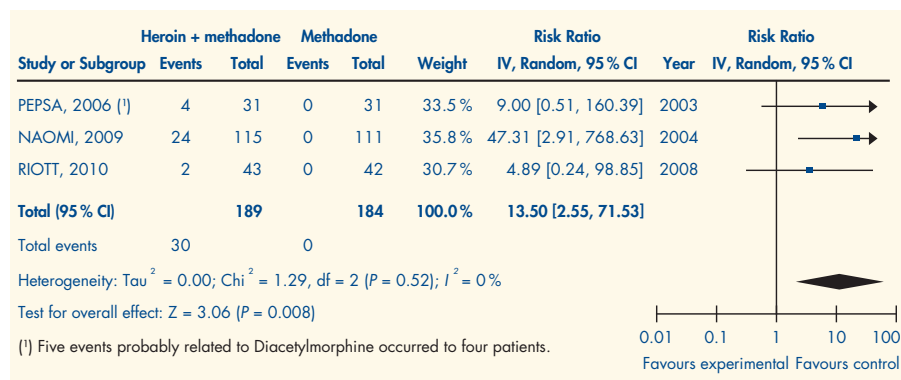
Figure 5: Heroin provision (various modalities and routes of administration) versus methadone in different modalities – Outcome: mortality



Only five studies were eligible for inclusion in the meta-analysis of the mortality outcome among the patients provided with heroin (any modality and route of administration) versus methadone in different modalities. The studies by Perneger et al. (1998) and Strang et al. (2010) did not measure the outcome, and there were no deaths in any of the compared groups in the Dutch study on inhaled heroin (van den Brink et al., 2003).

The studies also show a protective effect for criminal activities and the risk of being incarcerated; while the positive effect on social functioning is not different between the study groups, an equal achievement confirms the beneficial effect of being in treatment.

On the negative side of heroin provision, there is a higher risk of adverse events that, despite being rare, are more frequent among heroin-treated patients in all the studies reporting it. The Cochrane reviewers, in agreement with the conclusions of the trials (Haasen et al., 2007; Oviedo-Joekes et al., 2009; Strang et al., 2010), recommend that the treatment should be provided in settings where emergencies can be readily treated (see Figure 6).

Figure 6: Supervised injectable heroin plus methadone versus oral methadone — Outcome: adverse events related to intervention medications

Heroin prescription is shown to help to reduce illicit drug use, a domain that is considered as a primary outcome in each study (see Table 3).

Table 3: Definition of responders at study level, measures of effect and number of patients that is needed to treat (NNT) in order to have one patient responding to treatment

| Study name | Definition of 'responder' | Measure of effect as published and ARR (1) | Number needed to treat (2) |
|---------------------|--|---|--------------------------------|
| Strang et al., 2010 | Reduction of regular use of 'street' heroin $\leq 50\%$ negative urinalysis specimens during weeks 14–26 | Injectable heroin: (72% [n=31]) Oral methadone (27% [n=11]), OR (3) = 7.42, (95% CI 2.69–20.46), P<0.0001 ARR=0.46 (95% CI 0.27–0.65) | NNT=2.17 (95% CI 1.60–3.97) |

(1) Absolute risk reduction (ARR) = difference between the proportion of events in the experimental arm and the control arm.

(2) Number needed to treat (NNT) = 1/ARR or the number of patients that are needed to be treated in order to obtain one success. The 'ideal' NNT is one.

(3) Odds ratio (OR) = ratio of the odds of an event occurring in the experimental group to the odds of it occurring in the comparison group.

Table 3 (continued)

| | | | |
|----------------------------|---|---|--------------------------------|
| Oviedo-Joekes et al., 2009 | Retention in addiction treatment at 12 months (defined as receipt of the study medication on at least 10 of the 14 days before the 12-month assessment, or confirmation of retention in any other treatment program or abstinence from opioids during this interval). Improvement of at least 20 % from the baseline score (measured by the European ASI) ⁽⁴⁾ for illicit-drug use or legal status (or both). In addition, to rule out deterioration in other variables, a patient with a response could have a decrease of 10 % or more on at most one of the remaining composite scores. | Retention in treatment: 87.8 % in the diacetylmorphine group, 54.1 % in the methadone group (rate ratio=1.62; 95 % CI 1.35–1.95; $P<0.001$). ARR=0.34 (95 % CI 0.23–0.45) | NNT=2.9 (95 % CI 2.22–4.35) |
| | | Reduction in illicit-drug use or other illegal activities: 67.0 % diacetylmorphine group 47.7 % methadone group (rate ratio=1.40; 95 % CI 1.11–1.77; $P=0.004$) ARR=0.19 (95 % CI 0.07–0.32) | NNT=5.3 (95 % CI 3.1–14.3) |
| Haasen et al., 2007 | Health: at least a 20 % improvement and at least 4 points on the OTI ⁽⁵⁾ Health Scale (physical health) and/or at least a 20 % improvement in the GSI ⁽⁶⁾ (mental health), without a deterioration of more than 20 % in the other area of health. Reduction in Illicit drug use: reduction in the use of 'street' heroin with at least 3 of 5 urine samples negative for the drug in the month prior to the 12-month assessment and no increase in cocaine use (hair analysis). If less than 3 urine samples or no hair was available at 12 months, data from urine or hair testing at 6 months were used. | Health Improvement (adjusted OR=1.54, 95 % CI 1.02–2.34, $P=0.042$). ARR=0.06 (95 % CI 0.01–0.11) | NNT=16.7 (95 % CI 9.09–100) |
| | | 'Illicit drug use' (adjusted OR=1.91, 95 % CI 1.30–2.79, $P=0.001$). ARR=0.14 (95 % CI 0.08–0.20) | NNT=7.1 (95 % CI 5–12.5) |

⁽⁴⁾ ASI: Addiction Severity Index.

⁽⁵⁾ OTI: Opiate Treatment Index.

⁽⁶⁾ GSI: Global Severity Index.

Table 3 (continued)

| | | | |
|-------------------------------------|--|---|----------------------------|
| March et al., 2006 | At least 20 % improvement at 9 months, compared with the baseline values, in general health or psychological or family adjustment, without a deterioration superior to 20 % in any of these dimensions evaluated with the respective ASI composite scores. | MDO (?) index 70.4 % experimental group; 60.9 % control group, difference not statistically significant. ARR=0.10 | NNT=10 (8) |
| Van den Brink et al., 2003 (CCBH A) | Responders: at least 40 % improvement in at least one of the 3 domains of inclusion (physical, mental, social) at the end of the treatment compared with baseline; if this improvement was not at the expense of a serious ($\geq 40\%$) deterioration in functioning in any of the other outcome domains; and if the improvement was not accompanied by a substantial ($\geq 20\%$) increase in use of cocaine or amphetamines. | risk difference=24.3 %, (95 % CI 9.6–39) | NNT=4.1 (95 % CI 2.6–10.4) |
| Van den Brink et al., 2003 (CCBH B) | see above | risk difference 22.3 %, (95 % CI 11.0–34.6) | NNT=4.4 (95 % CI 2.9–9.1) |

(?) MDO: Dichotomous Multidimension Outcome Index.

(8) Not statistically significant.

Number needed to treat

The number needed to treat (NNT) has been calculated for each study (Table 3) and it indicates the number of patients that needs to be treated to obtain one respondent patient. Numerically, the NNT is the reciprocal of the difference between the proportion of events in the experimental and the comparison group (absolute risk reduction).

It is important to highlight that the NNT cannot be compared across the included studies as the criteria for being ‘responders’ were different. Nonetheless, the results show that providing heroin can be quite effective in obtaining pre-specified effects on patients. Taking into consideration that the ideal NNT would be one (the unreal situation in which every single patient succeeded), it is easily understood that an NNT close to three or four would be very good results, especially considering the nature of the patients studied. These patients are, by definition, long-term treatment

refractory and dependent on heroin, and therefore are very likely to fail to respond to treatment.

Long-term trajectories

The findings of extended (2- to 6-year) follow-up studies are an important addition to the shorter (6- to 12-month) data available about treating this most difficult group of heroin users.

Switzerland, 2001, 2003

Rehm and colleagues (2001) demonstrated the safety and long-term benefits of SIH in different outcome categories based on a cohort of 237 patients seen between January 1994 and December 2000 in 21 outpatient treatment centres in Switzerland.

A total of 1 693 (86 %) patients have remained in the heroin treatment programmes across the country for at least 3 months, 1 378 (70 %) for at least a year, 985 (50 %) for at least 2.5 years and 669 (34 %) for 5 years or longer. Among those who have dropped out, a clear relationship has been established between length of stay and reasons for discharge ($P < 0.001$), with discharges related to lack of patient cooperation occurring early on (< 4 months) rather than later on (> 3 years) in SIH (30 % vs. 4 %, respectively). On the other hand, transfer onto abstinence-based treatment or treatments other than methadone tended to be more common late in treatment, and while only 9 % of the discharges during the first four months switched to abstinence treatment, this proportion accumulated to 29 % for patients discharged after three years of treatment.

A sharp reduction was reported in illicit 'addictive behaviour'. For example, daily use of 'street' heroin declined from 82 % (baseline) to 6 % (18 months) and similar reductions were observed with cocaine and benzodiazepine use, which decreased from 29 % to 5 % and from 19 % to 9 %, respectively. These considerable reductions in drug use occurred in tandem with significant improvements in all measures of health and social behaviour. The health of those with severe somatic (baseline: 22 % vs. 18 months: 13 %; $P = 0.001$) or mental (baseline: 37 % vs. 18 months: 19 %; $P < 0.0001$) problems at the start of treatment improved, and those with a low BMI were observed to put on weight (baseline: 35 % vs. 18 months: 24 %; $P < 0.0001$). Also, long-term improvement was evident in reduced proportions of patients with an unstable housing situation (baseline: 43 % vs. 18 months: 21 %; $P < 0.0001$), homelessness (baseline: 18 % vs. 18 months: 1 %; $P < 0.0001$), unemployment

(baseline: 73 % vs. 18 months: 45 %; $P < 0.0001$) and those receiving welfare payments (baseline: 63 % vs. 18 months: 54 %; $P = 0.035$).

Increased proportions of patients reported no debts (baseline: 26 % vs. 18 months: 33 %; $P = 0.026$) and no visits to illegal drug scenes in the last month (baseline: 14 % vs. 18 months: 59 %; $P < 0.0001$). Finally, a smaller proportion of patients reported illegal income (baseline: 69 % vs. 18 months: 11 %; $P < 0.0001$) and these reductions in criminality were corroborated by objective judicial data in an independent investigation (Kiliyas and Rabasa, 1998).

A subsequent six-year follow-up study (Güttinger et al., 2003) focused on two groups of SIH patients in Switzerland: (i) those who have continuously been in SIH treatment since entry into the initial Swiss SIH treatment study or those who have re-entered this treatment and (ii) ex-patients who have discontinued SIH at the time of the follow-up. The study found that of all patients examined ($n = 366$), 332 (88.3 %) were alive at the six-year follow-up point, and of these patients, 40 % were still in SIH. Compared with baseline status, in relation to use of illicit drugs, illegal income and other social functioning variables, the results at follow-up showed significant improvements, which were evident in patients remaining in SIH for a minimum average period of 2.4 years. Of those still in treatment at the six-year mark, a significantly smaller proportion (4 %) were still using illicit heroin daily or almost daily compared with 19 % in the group of SIH-terminators ($\chi = 14.3$; $P < 0.001$). A less positive result indicated that both patient groups — those still in SIH treatment as well as those who had terminated treatment — were showing an increase in unemployment and reliance on social benefits.

Seven-year mortality data from the Swiss studies (Rehm et al., 2005) showed a 1 % death rate per year of patients in SIH treatment, which was lower than the 2.5–3 % mortality rate of Swiss heroin users in 1990s (Rehm, 1995), and lower compared with the mortality rates of opioid users in other maintenance treatments in other countries.

Germany, 2008

All patients of the SIH group were included in the long-term follow-up study, plus a random sample of patients whose initial randomised treatment was oral methadone, but who, after the initial 12-month period, were offered to take vacated SIH places.

In 2008, Verthein and colleagues (Verthein et al., 2008) published the findings of a prospective cohort study of 515 heroin patients initially recruited into the German SIH RCT. At two years, 55 % were still in SIH, with an average treatment duration

of 527 (\pm 276) days. Most drop-outs ($n = 225$) had switched to another addiction treatment, predominantly MMT (27 %), or were imprisoned in the meantime (16 %).

With respect to illicit drug use, the reduction of 'street' heroin use achieved during the first six months of the RCT (less than one day of use within the last month) (Haasen et al., 2007) has been sustained throughout the two-year follow-up. Earlier gains of reduced cocaine use were also present at the two-year point when patients were using cocaine on an average of three days (compared with a mean of nine days at baseline). Similarly, the greatest changes in the symptoms related to both physical and mental health had occurred during the first six months after treatment initiation (Haasen et al., 2007) and were thereafter stabilised at satisfactory levels.

In the social domain, marked improvements were observed during the two-year treatment period, with a significantly higher proportion of patients in stable housing at 24 months compared with 12 months and baseline (24 months: 91 % vs. 12 months: 82 % vs. baseline: 76 %; $P < 0.001$) and a significant increase in the drug-free social contacts, for example leisure activities in the company of people without drug or alcohol problems (24 months: 30 % vs. 12 months: 22 % vs. baseline: 15 %; $P < 0.001$), and involvement in leisure behaviour (24 months: 74 % vs. 12 months: 71 % vs. baseline: 59 %; $P < 0.001$). The rate of employment among SIH patients had increased in the first year of treatment, but no further gains were reported in that domain (24 months: 26 % vs. 12 months: 26 % vs. baseline: 15 %; $P < 0.001$).

Similarly, last month, prior to assessment, illegal activities, according to EuropASI (Kokkevi and Hartgers, 1995) had decreased in the first year of treatment, although this was not followed by substantial further decline during the second year (24 months: 25 % vs. 12 months: 23 % vs. baseline: 70 %; $P < 0.001$).

On safety, the study reported that the main SAEs associated with SIH — respiratory depression and epileptic seizures, both occurring within minutes after injection — occurred in 6 % (respiratory depression) and 8 % (epileptic seizures) of the two-year sample. Within the study period, eight patients treated initially with diacetylmorphine had died: five while in treatment and three after discontinuation of SIH. No death was reported to be causally related to the study medication (Verthein et al., 2008).

Spain, 2010

The Andalusian research group reported that 44.4 % of the original SIH treatment patients were still in receipt of SIH treatment at two-year follow-up, and, while all

study participants were reported to have achieved significant reductions in 'street' heroin use (measured as self-reported mean number of days used in last month) from baseline to two years post trial, those continuously engaging in SIH treatment were the only group that had, at two years, sustained the health-related improvements made over the nine-month trial period (Oviedo-Joekes et al., 2010).

The Netherlands, 2010

Completers of SIH (both injectable and inhalable) in the Dutch trials and those who were eligible to be brought back into supervised heroin treatment (i.e. were showing positive response to SIH or had deteriorated seriously after the planned discontinuation of SIH treatment) were followed in an observational cohort study for 3 years (Blanken et al., 2010). Assessment was carried out at the end of the second, third and fourth years of SIH treatment.

The study used two dichotomous outcome indicators of recovery: (i) 'health recovery', defined as the absence of problems in physical and mental health, social functioning and involvement in illegal activity and (ii) 'complete recovery', defined as the absence of any problems in tandem with lack of any non-prescribed drug and excessive alcohol use.

Four-year retention was 56 % (95 % CI: 47.6–63.8 %), with the main reasons for terminating SIH being violation of house rules (23 %) and unsatisfactory treatment response (21 %). Of the 66 patients who were not in SIH treatment at the end follow-up point, the majority (85 %) were in substitution treatment; although seven patients had progressed to abstinence-based treatment, nine were no longer in treatment and one had died, 7 months after leaving SIH treatment.

Patients in receipt of SIH treatment at the 4-year follow-up point showed significantly higher response rates than those who had terminated SIH (90 % vs. 21 %; 69 % difference; OR 48 %; 95 % CI: 17.6–159.1; $P < 0.0001$). Continued SIH treatment was also associated with an increasing proportion of patients without health problems who had stopped illicit drug use and excessive alcohol use (that is complete recoverers) – from 12 % after the first year to 25 % after 4 years of SIH (OR 1.24; 95 % CI 1.04–1.48; $P = 0.02$).

Four-year data on the safety of SIH treatment reported by the Dutch group included 11 SAEs, two of which probably related to the prescribed heroin (inpatient drug detoxification and pneumonia). No deaths had occurred in the study group, and

the SAEs among the patients who had discontinued SIH before the final follow-up assessment were not related to the termination of treatment.

Conclusion

Retention in SIH treatment is still high at 2- (44 %; Oviedo-Joekes et al., 2010), 2.5- (50 %; Rehm et al., 2001), 4- (56 %; Blanken et al., 2010) and 6-year (40 %; Güttinger et al., 2003) follow-up. There is consistency in the finding of sustained and additional benefit in terms of reduced drug use and improved health status and social functioning. Different studies, however, have used different outcome measures, making direct comparisons difficult and presenting challenges for sought-after firm conclusions about the long-term benefit of SIH treatment. It is imperative that the collection of comparable data is continued as we begin to develop an evidence base, capturing any remission to illicit drug use, elimination of related problems and, more importantly, enhanced quality of life and social functioning of patients in long-term SIH treatment.

Patients' perspectives

A qualitative study (Romo et al., 2009) involving 21 patients receiving SIH treatment was conducted in the final phase of the RCT of injectable treatment in Spain. The findings of this study recognised that SIH treatment not only offered patients 'legal medicine', that is pharmaceutical-grade heroin, but also fundamentally changed the situation in which heroin was acquired and administered by patients. In addition, the contextual change was associated with improvements in a range of areas of patients' lives, such as physical and mental health, family relationships and work. Blanken et al. (2010b), based on the qualitative accounts of 24 patients receiving heroin in the Dutch trials, provided further evidence for the consistency in patients' appreciation of the quality of prescribed heroin and the positive experience of the structure provided by the injectable maintenance clinics, as well as the availability of a secure supply of pharmaceutical heroin.

Conclusion

There is a dearth of research into the treatment expectations and satisfaction of patients in SIH treatment, reflecting the lack of research in general in these topics in relation to addiction treatment. Future studies will need to address these areas, together with research examining families' perceptions of treatment, including the impact it has on family relationships.

Impact of supervised injectable heroin clinics and service provision on local communities

A critical issue that SIH clinics, akin to other substance misuse services, are facing is the resistance that the local community may have towards a supervised injectable maintenance clinic and the patients it is looking after.

Driven by the need to evaluate whether the establishment and operation of SIH clinics generates an impact (e.g. changes in street public nuisance, amount of criminal offences) for those residing and working in surrounding areas, two community impact studies have been conducted, and their findings are outlined below.

Lasnier et al. (2010) looked at the impact of SIH clinics on public safety, assessing changes in the amount of criminal offences (violent crimes, property crimes and drug-related crimes) and acts of public disorder in the Vancouver and Montreal sites before and during the Canadian trial (2002–06). A primary hypothesis that was tested by the research group related to the general concern that SIH clinics may induce a ‘honeypot’ effect, leading to increases in crime and/or disorder problems in the clinic locality. A competing suggestion that was also tested in this study was around a possible reduction, rather than an increase, in the occurrence of crime in the local communities. Data on crime (assault, robbery, theft, breaking and entering, vehicle theft, illegal possession of property, possession of a prohibited substance and trafficking in a prohibited substance) and disorder (disorderly conduct, public nuisance, misbehaviour, drifting and panhandling) were collected from the Montreal and Vancouver police departments. The study found that most indicators remained stable during the pre- and post-implementation phase of the Canadian trial at both sites. For example, no impact was detected of either the introduction of the SIH clinics or the increase in the number of attending patients on the number of violent or property crimes committed in the clinic vicinity (Montreal and Vancouver downtown eastside). In fact, the SIH clinic’s presence in Montreal appeared to be correlated with a significant (although negligibly small) reduction in the number of property offences (t -ratio = -2.041 ; $P < 0.05$). Similarly, no relationship was detected between acts of disorder inside the two areas under study and the operational status of the SIH clinics and the monthly increase of the number of SIH clinic attendees. It was concluded that the SIH clinics operating at both localities had had no clearly observable impact on crime and disorder in the local communities. However, as the number of participants enrolled at each site of the Canadian trial was too small

(Vancouver: $n = 158$; Montreal: $n = 52$), the study might have been underpowered to detect significant effects had they existed.

Another study that took a similar focus was carried out in London, United Kingdom. Miller et al. (2010; 2011) evaluated the impact on the local community of the supervised injectable clinic that was set up to provide SIH within the RIOTT, London, and documented the expectations, fears and experiences of the local community members.

Based on 21 key informants who were interviewed before the trial, the study reported concern and, in some instances, clear opposition, stemming from a fear over an increase in the street drug user population ($n = 11$), crime ($n = 6$) and drug dealing ($n = 1$). After two years, during which time 35 individuals had participated in the trial and had attended the local supervised injecting clinic, 40 community members, including everybody who had taken part in the initial wave of interviews, were approached and asked about their current perception of the trial and any current concerns. Although some key concerns were expressed, relating to street drinking and antisocial behaviour, alcohol licensing, and young people and violence, there were no particular major issues about the trial specifically. In fact, a third of the key informants had not previously been aware of the trial. None of the participants reported a perceived change in the level of crimes committed locally, nor in drug use and dealing, street drinking, public intoxication, street cleanliness or local trade since the start of the trial.

Corroboration with Metropolitan Police figures carried out by the same research team revealed no significant changes in monthly or average annual crime levels in the local area (Boroughs of Southwark and Lambeth) over the two-year trial period. Similarly, antisocial street behaviour data collected from the Camberwell Street Population Forum (CSPF) ⁽³⁾ between 12 November 2004 and 8 September 2006 showed that all study individuals ($n = 7$) identified on this register had dropped off the CSPF list while undergoing injectables treatment, and no injectables treatment participants were subsequently noted in this record. Furthermore, the study found that, on average, trial participants were spending 20 weeks less on the CSPF register than the general street population. The study concluded that the trial has had limited

⁽³⁾ The CSPF is the operations forum, with enforcement and police surveillance powers, of the Camberwell Street Drinking Initiative (CSDI), established to facilitate discussion of possible solutions for street users with local agencies and local groups.

impact, either positive or negative, on the local community. It identified a sensitive instrument (CSPF) for measuring local impact to illuminate treatment effect for patients who were originally identified as violators of local community order.

Conclusion

While a definite conclusion is difficult, owing to the small study samples and the fact that many extrinsic factors may be involved in shaping the process around observed local crime and disorder trends, available data consistently suggest no positive or negative effects of SIH clinics on public safety. Future research attention will also need to address the perceived public nuisance, security and potential for diversion where SIH unfolds outside of the research context.

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Chapter 4: Economic evaluation of supervised injectable heroin treatment

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Chapter 4: Economic evaluation of supervised injectable heroin treatment

This chapter covers the evidence detailed in the published papers and project reports from the German, Dutch and Swiss studies examining heroin-prescribing treatment, both in a public domain and on a confidential basis, to identify reports of any existing findings of previous economic evaluation of heroin-prescribing treatment.

Two publications and unpublished economic analysis from Germany were identified, and their findings are summarised here. The three countries that have evaluated the costs and outcomes of heroin treatment have chosen different approaches to economic evaluation (see Glossary). The selection of one or another approach for economic analysis, that is cost–benefit (in the Swiss experiment) or cost–utility (within the German and Dutch trials), determines which cost categories are included in the analyses. Therefore, inclusion or not of different cost categories is likely to differ between the different studies. More importantly, however, the aim and outcome measures of the evaluation differ between the types of evaluation, and thus prevents comparison between the findings of the different research groups.

To allow for more direct comparison between the unit costs, these have been recalculated and adjusted for 2009 using country-specific consumer price indices (CPIs) (OECD, 2010). Original unit cost figures, along with original price years, are kept and reported in brackets following adjusted figures.

The Swiss experiment

A study by Gutzwiller and Steffen (2000) aimed to (i) determine the costs for various services and the therapeutic results of six pilot injectable heroin maintenance treatment projects and a total of 452 participants and (ii) compare the results according to project size of large-scale (> 98 patients), medium-scale (60 patients) and small-scale (19–40 patients) heroin maintenance treatment projects (price year 1995).

Description of clinic

The six supervised injectable maintenance clinics in Switzerland are stand-alone clinics that are purpose built with varied capacity — large-scale (Basel, Project Janus, $n = 134$; Berne, Project KODA-1, $n = 98$), medium-scale (Zürich, Project Lifeline,

$n = 60$; Zürich, Project ZOKL-2, $n = 90$) and small-scale clinics (Olten, Project HEROL, $n = 30$; Thun, Project H, $n = 40$).

In all six clinics, heroin is dispensed during set opening hours in the morning, afternoon and evening (8–10 a.m., 1–3 p.m., 6–9 p.m.) 7 days a week. The staff-client ratio is one staff member for every 10–15 patients, with at least two staff members present at all times.

Multi-dose 10-g diacetylmorphine ampoules (Diaphin®) manufactured by DiaMo Narcotics GmbH, Switzerland, are used. The multi-dose Diaphin ampoules are reconstituted in accordance with the manufacturer's recommendation — on a cleaned surface within the clinic conforming to Swiss 'aseptic conditions'. Multiple syringes are drawn up from the reconstituted solution for multiple patients' use and could be stored for up to 72 hours.

Direct costs of the projects

The costs of the six projects were measured, using a purpose-designed timesheet, over a period of one month. For a range of reasons (holidays, work overload, etc.), the time expenditure data could not be collected during the same period in all projects; the four-week periods were thus extended and the survey was carried out between September and December 1995.

The following types of costs were assessed:

- direct costs — including the opiates dispensed (heroin, methadone, morphine, substitution drugs), medical material and external medical services;
- fees for third-party services — fees paid for services not regulated by an employment contract and for which no social benefits accrue;
- labour costs — wages and extra allowances of the entire workforce involved in the project, including social services, further costs for personnel and services provided free of charge by the canton, commune or other institutions. These costs were broken down for each project per person per day according to the following tasks: research; social insurance; medical attendance; opiate dispensing; and project management/administration; and
- other operating costs — rent, interests, maintenance, depreciation, material insurances, energy and heating and administrative costs.

All costs in this study were calculated for large-, medium- and small-scale projects. The total costs per participant and day classified according to cost category and capacity of the projects are grouped in Table 4.

Table 4: Costs (EUR; mean values) classified according to cost category and clinic capacity

| Projects | Number of participants | Direct costs | Personnel costs | Other operational costs | Total costs per patient/day | Total costs per patient/year |
|--------------|------------------------|--------------|-----------------|-------------------------|-----------------------------|------------------------------|
| Large scale | 232 | 6.0 (5.3) | 24.8 (21.7) | 3.3 (3.0) | 34.8 (31.0) | 12 702 (11 315) |
| Medium scale | 150 | 9.3 (8.6) | 26.1 (23.1) | 4.0 (3.4) | 39.4 (35.1) | 14 381 (12 812) |
| Small scale | 70 | 5.6 (4.9) | 29.8 (26.8) | 4.3 (3.6) | 39.7 (35.3) | 14 491 (12 885) |
| All projects | 452 | 7.0 (6.3) | 26.9 (23.9) | 3.9 (3.3) | 38.0 (33.8) | 13 870 (12 337) |

Note: Unit cost figures are recalculated and adjusted for 2009 (with original cost figures from price year 1995 reported in brackets).

The costs for personnel in this study were further divided into a number of sectors, including care, medical assistance, dispensing of drugs, and administrative work and research. Of the EUR 26.9 spent on the average for personnel expenditures, 4.8 % were for research expenses, 21.3 % for social assistance, 7.5 % for medical care, 28.8 % for drug dispensation and 40.2 % for general administration.

Without the costs for research, the average total costs per participant and day incurred by the study were reduced from EUR 38.0 to EUR 36.5 when all projects were considered.

Overall benefit per participant per day

This evaluation focused on and covered four key domains of benefit (listed below), which were valued, based on procedures and rates applicable for Switzerland and expressed also in terms of benefits per participant and per day. The partial benefits in the four domains were then added and directly compared with the costs.

These were as follows:

1. Housing — reduced housing costs and costs for services such as accompanied forms of housing, treatment and care (in institutional forms of housing such as night shelters, treatment centres, psychiatric wards).
2. Work and professional status (productivity) — increased productivity defined as the amount which salaried and self-employed persons contribute per year to the GDP, including housework.

3. Legal behaviour — reduced costs to victims; police investigations and prosecution; pre-trial detention; legal proceedings (trial); and imprisonment.
4. Health — reduced frequency of diseases associated with drug abuse, exposure and neglect; a decrease in medical expenditure for ambulatory and inpatient treatment.

The benefits calculated per participant and day in the different sectors were EUR 1.3 (EUR 1.17, price year 1995) for housing, EUR 2.0 (EUR 1.8, price year 1995) for work, and EUR 59.0 (EUR 52.5, price year 1995) and EUR 14.0 (EUR 12.5, price year 1995) for legal behaviour and health, respectively. The overall benefit was obtained by adding the partial benefits as ascertained in this study, and this amounted to EUR 78.2 (EUR 69.6, price year 1995) per participant per day. The highest benefit was obtained in the sector of 'legal behaviour', which accounted for 75 % of the total benefit. The improvement in the domain of 'health' was also substantial, accounting for almost 18 % of the total benefit, whereas the benefit in the domains of 'housing' and 'work' were less important from an economic point of view.

Costs and benefits

The cost-benefit analysis of this study determined the economic relationship between the costs of the treatment intervention to its socio-economic benefits. This analysis was based on the fundamental assumption that illicit drug opiate use and addiction results in a wide variety of direct and indirect costs, and cost was determined from a societal perspective. The perceived socio-economic benefits of injectable heroin maintenance treatment in the four domains outlined above were compared with the individual economic costs. Results showed that the costs of treatment were compensated by the overall revenue achieved — EUR 26 470 (EUR 23 563, price year 1995) per year, leading to an annual socio-economic benefit of EUR 13 096 (EUR 11 658, price year 1995).

The Dutch trial

Dijkgraaf et al. (2005) have determined the cost utility of medically supervised injectable heroin (SIH) compared with methadone maintenance treatment for chronic treatment-resistant heroin addicts. The economic analysis was performed with pooled data from 430 patients enrolled in inhalable or injectable heroin treatment within the two Dutch heroin trials (price year 2001).

Description of clinic

Eight outpatient treatment units in six cities in the Netherlands (Amsterdam, the Hague, Groningen, Heerlen, Rotterdam, Utrecht) were established. Heroin was dispensed up to three times a day during the opening hours of these treatment units — in the morning, at noon and in the evening, seven days a week. Heroin was prescribed in the Dutch clinics in an injectable and an inhalable form.

The main outcome measures included one year costs estimated from a societal perspective and quality-adjusted life years (QALYs) based on responses to the EuroQol questionnaire (EQ-5D, EuroQol Group, 1990; 2005) at baseline and at 6, 10 and 12 months during SIH treatment.

In this study, the following cost data were collected:

1. Direct medical care within the programme — healthcare staff; security personnel; materials, overheads and depreciations over 30 years of initial rebuilding costs of the heroin dispensation clinic.
2. Use of external healthcare resources — out-of-institution consultations; institutional outpatient consultations; institutional inpatient stays/week.
3. Travel related to the programme.
4. Illegal activities — law enforcement (police investigations, prosecution, adjudication, imprisonment, resettlement) and damage to victims.

Production loss due to sick leave or lowered efficiency at work was not measured because unemployment or disability rates were expected to be high in the target population. Neither were financial consequences of changes in patients' housing arrangements in the community or changes in the public's perception of safety.

Use of resources, programme-related travel and crime data were collected using clinical report forms and the European version of the Addiction Severity Index (EuropASI). The EuropASI was completed at the same intervals as the EQ-5D.

Direct cost of heroin treatment and oral methadone maintenance treatment

The costs, averaged per person and grouped by type (as described above), were as follows: for the heroin and methadone maintenance treatment group: EUR 20 410

(EUR 17 634, price year 2001); for the methadone-only group, the average annual costs per participant amounted to EUR 1 634 (EUR 1 412, price year 2001).

Heroin:

- other healthcare costs — EUR 1 343 (EUR 1 160, price year 2001);
- health-related travel — EUR 695 (EUR 600, price year 2001);
- damage to victims — EUR 11 131 (EUR 9 617, price year 2001); and
- law enforcement costs — EUR 10 135 (EUR 8 756, price year 2001).

With cost of clinic, these amounted to a total of EUR 43 713 (EUR 37 767, price year 2001) per heroin patient per year.

Oral methadone:

- other healthcare costs — EUR 1 303 (EUR 1 126, price year 2001);
- health-related travel — EUR 169 (EUR 146, price year 2001);
- damage to victims — EUR 40 500 (EUR 34 991, price year 2001); and
- law enforcement costs — EUR 14 914 (EUR 12 885, price year 2001).

The total annual costs, including cost of clinic averaged per person in the methadone group, thus reached EUR 58 520 (EUR 50 560, price year 2001).

Cost utility

Significant mean cost differences between the two groups was observed where the heroin treatment group had significantly higher treatment costs compared with the oral methadone group. The costs of law enforcement and of damage to victims from criminal activities were, however, higher for the oral methadone group than in the heroin treatment group, resulting in mean total net savings to society from the provision of heroin treatment of EUR 14 807 (95 % confidence interval (CI) EUR 1 254–29 201; EUR 12 793 (95 % CI EUR 1 083–25 229), price year 2001), higher than that from the provision of oral methadone maintenance treatment. Heroin treatment was also associated with higher QALYs than oral methadone — 0.058 more QALYs per patient per year (95 % CI 0.016–0.099).

The German trial

The abridged economic evaluation report (Haasen, 2009) of SIH and methadone maintenance treatment in Germany was performed on 1 015 trial participants (price year 2006).

Description of clinic

In the German trial, heroin was dispensed up to three times a day during the opening hours of outpatient units hosting the supervised injecting clinics — in the morning, at noon and in the evening, seven days a week.

Costs

In the context of the German model project, the average annual costs amounted to EUR 19 020 (EUR 18 060, price year 2006) per study participant in the SIH treatment and to EUR 3 490 (EUR 3 314, price year 2006) per participant in the methadone treatment group. The methadone treatment plus psychosocial support had additional average annual costs of EUR 2 031 (EUR 1 928, price year 2006) per study participant per annum. The main part of the expenditures was personnel related. The higher expenditures of SIH treatment in comparison with methadone treatment were mainly a result of the longer operating clinic times and higher safety measures, such as injecting under medical supervision.

Savings from improved health

Compared with the previous year, there were no significant changes in the use of other prescribed medication for both groups. However, there were changes in the use of health services (acute/inpatient and community psychiatric care units). Reduction in mental health service use, in relation to the previous year, resulted in savings to the health system of EUR 3 978 (EUR 3 777, price year 2006) over a 12-month period for the heroin group. For the methadone group, the health/treatment cost reduction reached approximately EUR 1 194 (EUR 1 134, price year 2006) for the same period of time.

Savings from reduced offending and regained productivity

Reductions in offending behaviour, court appearance and regained productivity were greater in the heroin group in comparison with the methadone group. When valued for the heroin group, the harm due to risk and offending had decreased by

EUR -3 424 (EUR 3 251, price year 2006) over the first 12 months in treatment. For the same period, the damage related to criminal behaviour and risk taking had risen by EUR 792 (EUR 752, price year 2006) in the methadone treatment group. Similarly, the savings related to custody and prison stays were significantly greater for the SIH group than for the methadone group (SIH: EUR -1 273 (EUR -1 209, price year 2006); MMT: EUR -870 (EUR -826, price year 2006)).

Also, during the study, a small increase in gainful employment was observed. This amounted, in the SIH treatment group, to EUR 172 (EUR 163, price year 2006) and in the methadone group to EUR 197 (EUR 187, price year 2006) per study participant per year.

In summary, SIH generated savings of about EUR 6 301 (EUR 5 985, price year 2006) per patient per year from improved health, reduced offending and regained productivity, while the costs of methadone treatment remained greater than its calculated savings (EUR -2 179 (EUR -2 069, price year 2006)).

Cost utility

This analysis showed that with additional medical costs, SIH could achieve a higher level of quality of life than that achieved with methadone treatment. It was less expensive to reach a QALY by SIH than it was by methadone treatment (SIH: EUR 163 140 (EUR 154 907, price year 2006) for each QALY; methadone: EUR 179 934 (EUR 170 853, price year 2006) for each QALY).

Only when consideration is made to the numbers of participants completing and terminating treatment and the additional costs associated with increased retention is methadone treatment clearly superior over heroin treatment. However, an examination of the costs generated by participants following their drop-out from treatment suggests that methadone treatment is less favourable in economic terms for this group of patients.

Conclusion

The reported cost per patient per year in an SIH maintenance programme was between EUR 12 700 and EUR 20 400. The lowest cost was reported by Switzerland at between EUR 12 700 and EUR 14 500, depending on the capacity of the outpatient treatment programme; EUR 19 000 was reported for Germany and EUR 20 400 for the Netherlands. SIH cost was substantially higher than the cost of

oral methadone maintenance treatment provision at EUR 1 600 (the Netherlands) and at EUR 3 500 (Germany). This was largely because of higher staffing requirements for SIH provision — at least two staff members must be present at all times and it is necessary to supervise all injecting of heroin medication at the clinic. Therefore, clinics had to be open daily, and for extended hours. In addition, all programmes had employed therapists, social workers and other staff members to help clients deal with drug-related health and social problems.

Studies consistently demonstrated a considerable economic benefit of SIH, particularly from the reduction in the cost of criminal procedures and imprisonment. Based on the results of the studies from Germany and the Netherlands, which directly compared the cost and cost utility of heroin and oral methadone maintenance treatment, methadone maintenance appeared to be the less costly programme to provide. However, when costs of crime are included, heroin maintenance appeared to be more cost-effective.

The Swiss study reported an annual socio-economic benefit of EUR 13 000 for each patient in heroin treatment, which was comparable to the finding of the Dutch group for a societal saving of EUR 15 000 per year for every patient maintained on heroin treatment. In the German cohort, SIH treatment generated savings of about EUR 6 000 per year from improved health, reduced offending and regained productivity. The German and Dutch studies reported a significant improvement in the quality of life in the heroin-maintained patients.

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Chapter 5: Pharmaceutical diacetylmorphine products

Chapter 5: Pharmaceutical diacetylmorphine products

This chapter describes the different commercial pharmaceutical diacetylmorphine products that are currently available, as well as listing key features of each product, including the amount per ampoule or vial, whether it was with or without a reusable membrane and whether it was licensed or safety-tested for multi-dose use (see Table 5). It was felt that such a review of the products was necessary for unveiling differences in national approaches as well as differences in the degree of availability and access to pharmaceutical heroin.

Presently, three countries produce pharmaceutical heroin that is available to the supervised heroin maintenance clinics. The greatest availability of products is in the United Kingdom, where several medicinal diacetylmorphine products are licensed for pain relief and also used for the treatment of addiction:

- (i) Auralis diamorphine hydrochloride BP, available in five strengths (5 mg, 10 mg, 30 mg, 100 mg, 500 mg), with two of them typically used in addiction treatment: 100 mg and 500 mg of lyophilisate (powder for solution for injection).

The existing product is not licensed for addiction treatment. However, the company plans to submit a licence application with the UK Medicines and Healthcare Products Regulatory Agency (MHRA) in early 2012 for the 100-mg and 500-mg variants of diacetylmorphine hydrochloride injection BP. This product is expected to be branded with the trade name 'Addimorph', and the proposed indication is for addiction use. Auralis has also developed a 3-g multi-dose presentation in a vial that will be submitted to the MHRA for licensure in 2012.

The shelf life of the product is 36 months.

The final pack design for all strengths of Addimorph is being developed. However, the current container for both the 100-mg and 500-mg diacetylmorphine packs are 5-ml clear Ph. Eur. Class I glass ampoules containing either 100 mg or 500 mg of diacetylmorphine hydrochloride BP lyophilisate each.

The 100-mg and 500-mg variants⁽⁴⁾ and the 3-g product has been tested and shown to meet the requirements for multi-dose use.

The price of the products is dependent upon the current drug tariff price, and so it is subject to change.

⁽⁴⁾ The licenses for Auralis diamorphine (100-mg and 500-mg variants) do not restrict the product to single use. If the product is not used immediately, it can be stored for up to 24 hours, or longer if it has been reconstituted under aseptic conditions. This would allow for both multi-use and multi-dose handling.

- (ii) TEVA diacetylmorphine hydrochloride powder solution for injection is available in 2-ml clear glass vials (5 mg, 10 mg and 30 mg strengths) and 5-ml clear glass vials (100 mg and 500 mg strengths).
At present, the product is indicated for the relief of severe pain and holds no licence approval for addiction treatment. Tests of the sterility and chemical stability of the product indicate and recommend its use for up to 24 hours from opening after dilution and storage between 20 °C and 25 °C.
- (iii) Wockhardt UK Ltd diacetylmorphine (5 mg, 10 mg, 30 mg, 100 mg and 500 mg) — ampoules with freeze-dried diacetylmorphine for reconstitution and injection. The products are usually supplied in National Health Service (NHS) tenders, and therefore the price is highly variable.

The Netherlands and Switzerland also have their own medicinal diacetylmorphine products:

- (iv) Diacetylmorphine hydrochloride monohydrate 10-g vials (Diaphin®), manufactured by DiaMo Narcotics GmbH, Switzerland (DiaMo), licensed and safety-tested for multi-dose use with approval in Denmark, Germany and Switzerland. The price differs between the countries because of different levels of distribution and other infrastructure and safety requirements set by different governments, as well as the variable extent of the level of service. In addition, DiaMo is also producing Diaphin tablets — Diaphin IR 200® immediate release (fast onset) and Diaphin SR 200® slow release, both containing 200 mg of diacetylmorphine hydrochloride — with marketing authorisation in Switzerland since December 2010.
- (v) In the Netherlands, two products have been developed — diacetylmorphine hydrochloride for injection and diacetylmorphine base for inhalation. A private company (Diacetyl-M BV) holds the pharmaceutical market licences for both products, while being under strict contractual terms with the Ministry of Health in the Netherlands regarding production, distribution and price settings.
There are no ampoules available owing to the low flexibility in dosing. Diacetylmorphine hydrochloride is available as a multi-dose vial containing 3 g of lyophilised diacetylmorphine hydrochloride. The chemical stability and antimicrobial properties of the solution for injection allow a vial prepared for use in the morning (dissolving the lyophilised powder in water) to be used for 12 hours (Klous et al., 2004a; Blanken et al., 2010). Vials for heroin

hydrochloride have a membrane that can be repeatedly used within 12 hours from opening and after first use. In practice, local nurses use a spike (with a lid), enabling multiple doses to be extracted without continuously inserting a needle through the membrane.

Diacetylmorphine base is available as a powder, containing a 3:1 mixture of diacetylmorphine base and caffeine anhydrate developed in four dosages: 75-, 100-, 150- and 200-mg sachets (Klous et al., 2004b; Blanken et al., 2010).

There is no publicly available price for either of the Diacetyl-M BV products.

Table 5: Summary of currently available commercial pharmaceutical diacetylmorphine products used in addiction treatment

| Company and country of origin | Product | Amount per ampoule/vial | Re-usable membrane | Licensed or safety-tested for multi-dose use |
|-----------------------------------|---|--|--------------------|--|
| Auralis, UK | Diamorphine hydrochloride powder for solution for injection | 100 mg and 500 mg | N/A | Yes |
| TEVA, UK | Diamorphine hydrochloride (for injection) | 2 ml clear glass vial (5 mg, 10 mg and 30 mg strengths) 5 ml clear glass vial (100 mg and 500 mg strengths) | Yes | Yes |
| Wockhardt UK Ltd, UK | Diamorphine hydrochloride powder for solution for injection | 30 mg, 100 mg, 500 mg ampoules BP | N/A (single-use) | No |
| DiaMo, Switzerland | Diamorphine hydrochloride monohydrate (Diaphin®) | 10 g vial | Yes | Yes |
| Diacetyl-M BV, Netherlands | Diamorphine hydrochloride solution for injection | 3 g multi-dose vial | Yes | Yes |
| | Diamorphine base (for inhalation) | 75 mg, 100 mg, 150 mg, 200 mg sachets | N/A | N/A |

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Chapter 6: Implementation and clinical practice of supervised injectable heroin treatment in Europe and beyond

Chapter 6: Implementation and clinical practice of supervised injectable heroin treatment in Europe and beyond

In this chapter, we describe the implementation and delivery of supervised injectable heroin (SIH) treatment, based on initial analysis and synthesis with a key national stakeholder and other expert sources, and the operational policies and other relevant documentation and data sources.

At this phase, the research team switched from collation and analysis of original data source materials to national key informants (lead clinicians and/or researchers who have pioneered SIH trials and practice or others with a strategic overview of SIH treatment) and alternative data sources. The aims were: (i) to test the implementation, operational delivery and clinical practice of SIH as practised within European countries (Belgium, Denmark, Germany, Spain, the Netherlands, the United Kingdom and Switzerland) and Canada; and (ii) to identify aspects of implementation, organisational delivery and clinical practice which helped or presented challenges to delivering SIH. These other key sources included:

- recently published national/local SIH clinical guidance reports (e.g. injectable heroin (and injectable methadone), National Treatment Agency (NTA), 2003; prescription of injectable diacetylmorphine (heroin) in case of opioid dependence, 2009);
- ‘grey literature’ sources; and
- the identification of wider sources by national key informants.

National key informants were accessed and asked to contribute to the report using the following format and guiding list of topics:

- (a) Historical background:
 - i. National policy/drug strategy/legal framework for substitution treatment/ existing service provision.
 - ii. Drug and related health/social problems and rationale for SIH treatment.
- (b) Description of implementation:
 - i. National policy/legislation concerning SIH treatment.
 - ii. Supply of diacetylmorphine.
 - iii. Government/local direction/involvement.

- (c) Description of operational delivery:
 - i. Types of clinic models, setting and capacity.
 - ii. Accessibility.
 - iii. Service provision and logistics.
 - iv. Cost.
 - v. Supply, storage, preparation and administration of diacetylmorphine.
 - vi. Laboratory methods to differentiate between pharmaceutical and 'street' heroin use.
- (d) Description of clinical practice and operational issues:
 - i. Use of clinical guidelines.
 - ii. Inter-agency partnerships between SIH clinics and other health and social services.
 - iii. Social reintegration intervention.
 - iv. Admission and discharge criteria (particularly for disciplinary discharge).
 - v. Clients' experience/perspective.
- (e) What worked and challenges for the implementation of this treatment.

Switzerland

Historical background

National policy/drug strategy/legal framework for substitution treatment/existing service provision

Drug-free therapeutic communities were set up in 1970 in all regions of the country, mostly run by not-for-profit non-governmental organisations, some as commercial institutions and, only exceptionally, as public institutions. After the revision of National Narcotic Law in 1975, methadone maintenance treatment (MMT) was systematically introduced under the control of Cantonal Health Authorities (BetMG, 1975, Article 15a). Consequently, an extended and diversified treatment system for heroin addicts was available in all cities where SIH started, with outpatient and inpatient detoxification services, long-term residential rehabilitation centres (therapeutic communities) and outpatient clinics providing psychosocial treatment and/or agonist maintenance treatment (mainly methadone, but also buprenorphine) (BAG, 1991). Maintenance treatment was also provided in private practice through family doctors (60 % of all methadone maintenance; Hosek, 2006). By 1994, when

the first SIH clinics were opened, the treatment system included 12 000 treatment slots for methadone maintenance and 1 250 places in residential rehabilitation.

The Federal Law on Narcotics in its revised version of 1975 allowed the use of narcotic drugs for scientific research and for limited medical use, with a special authorisation by the Federal Office of Public Health (BetMG, 1975, Article 8). The national cohort study with medical prescription of heroin, 1994–96, was based on a Federal Decree of 1991. After the positive evaluation of the study (Uchtenhagen et al., 1999), endorsed by a World Health Organization (WHO) international expert committee (Ali et al., 1999) and a randomised substudy (Perneger et al., 1998), federal decrees allowed the continuation of this practice (Bundesrat, 1999). Follow-up studies confirmed its feasibility and safety (Rehm et al., 2001) so that it could be adopted as regular treatment and prolonged by national parliament in 2003.

The introduction of SIH was made in accordance with United Nations (UN) conventions. The Single Convention of 1961 allowed the use of scheduled substances for scientific research, including clinical trials, if in line with national legislation, and the 1971 Convention on Psychotropic Drugs allowed the use of schedule I drugs for 'scientific and very limited medical purposes' (Article 7). The ratification of this convention in 1996 reserved the option to set up research on the medical prescription of diacetylmorphine in the treatment of heroin dependence. This was not changed when ratifying the 1988 Convention, by 1998.

Drug and related health/social problems and rationale for SIH treatment

The decision to set up a research project with the medical prescribing of heroin was part of a new national drug policy issued in 1991 by the Swiss federal government (Bundesrat, 1991) and included in the revised Federal Law on Narcotics by 2009 (BetMG, 2010). This policy is based on prevention, treatment, harm reduction and law enforcement, and innovative approaches were encouraged in all four pillars. All innovations had to be documented and evaluated. Supervised heroin prescribing was one of the innovations in treatment.

The main reasons for this new policy were:

- high and increasing prevalence rates of human immunodeficiency virus (HIV) among drug injectors (the highest rates in Europe);
- high and increasing prevalence rates of heroin users (over fourfold increase within 10 years);
- high and increasing rates of overdose mortality (fourfold increase within 10 years);

- open drug scenes in major cities, with intolerable consequences for the safety and public order;
- incapacity of city administrations and cantonal authorities to cope with the problems; and
- non-governmental organisation initiatives with harm-reduction approaches proved to be useful.

The specific rationale for SIH treatment was the growing number of patients in MMT who continued to inject illegal drugs, as well as the large number of injectors in the open drug scenes who were out of treatment. The public health aim was to reach out to these individuals, to cover as many injectors as possible and engage them in the treatment system (Uchtenhagen et al., 1999, 2010).

Description of implementation

National policy/legislation concerning SIH treatment

A revision of the Federal Narcotic Law was necessary to provide a definite legal basis for SIH provision. The revision passed parliament in 2008 and obtained an overall approving vote at a national referendum held a year later (BetMG, 2010, Chapter 1a). This allowed for SIH treatment to become a regular treatment option provided in authorised clinics only and with the permission of the Federal Office of Public Health (BetMG, 2010).

Procurement, supply and distribution of diacetylmorphine

The various preparations (ampoules and slow-release and immediate-release tablets) are produced in a specialised commercial production site in Switzerland under the auspices of the Federal Office of Public Health (DiaMo Narcotics GmbH, Switzerland). This site was part of the federal administration during the cohort study, and was then outsourced when SIH became a regular treatment modality.

Government/local direction/involvement

The national government has set out detailed regulations for the local implementation of clinics, especially for the safety of patients and for preventing medication diversion. Thus, federal decrees have provided the regulations for SIH treatment and these regulations are laid out in a comprehensive handbook on SIH treatment (BAG, 2000).

Description of operational delivery

Types of clinic models, setting and capacity

There are 23 heroin clinics, two of which are in prisons.

Only four clinics are exclusively providing SIH treatment, and the rest are providing all forms of agonist maintenance treatment or a comprehensive programme for substance misuse treatment (Infodrog, 2010).

The overall capacity of the injectable heroin maintenance clinics is 1 454 treatment slots. This number is authorised by the Federal Office of Public Health. The capacity of the individual clinics varies between 15 slots and 210 slots (Infodrog, 2010).

If needed, patients from the injectable maintenance clinics can receive oral diacetylmorphine while in residential care during crisis situations, or in somatic hospitals while being hospitalised (with special authorisation, and under the responsibility of the prescribing doctor at the SIH clinic where the patient is enrolled (Infodrog, 2010).

Geographical coverage/accessibility

All but one of the supervised injectable maintenance clinics are located in the German-speaking region of the country. There is one clinic in the French-speaking region (Geneva) and none in the Italian-speaking region. No SIH clinic can be opened against the will of the competent cantonal authorities.

Clinic opening hours and number of clinics per day

The typical opening hours of the supervised injecting clinics guarantee adequate accessibility. All clinics have two or three blocks of opening hours, one in the morning, one in the afternoon and/or one in the early evening. The number of hours per block depends on the number of patients and varies from 2 to 4 hours. All clinics are opened on Saturdays and Sundays, some with reduced opening hours. In a few clinics, the daily consultations are made on appointment (Infodrog, 2010).

The capacity of the injectable maintenance clinics ($n = 1\,454$) is greater than the number of patients involved ($n = 1\,356$ by July 2011) and there are no waiting lists at any of the clinics. This is a strong indicator for a good coverage of those in need for this treatment approach.

The overall coverage of the estimated number of heroin-dependent individuals with agonist maintenance therapies is 67 %; SIH alone provides 8 % of the maintenance therapies (Hosek, 2006).

Service provision and logistics

The SIH maintenance clinics respect full safety conditions, particularly ones relating to the visually controlled intake of injectables and the logistical controls, in order to prevent any leakage of pharmaceutical heroin into the illicit market. These conditions are part of a comprehensive handbook on SIH, which can be consulted at all times by any staff member (especially junior/new staff), and which serves as a reference tool in the staff supervision process (BAG, 2000).

Visually supervised self-administration of the medication does not include the oral preparations that can be taken out for home consumption for a few days, under certain conditions, such as stabilised daily dosage, no polydrug use, and a stabilised social and health situation. A recent cohort study found this application to be safe and effective (Frick et al., 2006a, 2010).

Logistic controls include book-keeping of incoming amounts of pharmaceutical heroin, stored and daily dispensed individual dosages. Compliance with these regulations is ensured by Swissmedic staff via regular inspections. During the last years, no infraction of rules could be found during the control visits (BAG, 2009).

Storage, preparation and administration of diacetylmorphine

The procedures are centrally regulated by the Federal Office of Public Health and the Federal Office for Pharmaceutics Swissmedic.

Heroin clinics inform the production company on the quantities needed, which are sent by safety transport to the clinic and stored in special safes. Book-keeping records include delivered and stored amounts of heroin and the individual daily doses used.

Daily doses are individually determined by the doctor and prepared for administration. All doses are self-administered under supervision by a medic or a nurse (BAG, 2000). A missed dose leads to a reduction of the next dose in order to avoid over-sedation. The average daily dose per patient has varied in the last five years (533–467 mg) (BAG, 2009).

The average time spent for supervising injecting is five minutes per patient. In addition, 20 more minutes are spent per patient per day. Psychosocial interventions are available to all patients, and sessions to provide these are scheduled individually.

Laboratory methods to differentiate between pharmaceutical and 'street' heroin use

In a few clinics, urines are analysed for 6-mono-acetylmorphine, which is considered to be a likely indicator of 'street' heroin use; in the majority of clinics, the funds for this analysis are not available.

Description of clinical practice and related issues

Use of clinical guidelines

The detailed guidelines are set up in the handbook for SIH treatment; it contains all regulations, recommendations and necessary additional information to guarantee good practice. The handbook was produced by experts under the guidance and responsibility of the Federal Office for Public Health (BAG, 2000).

The main responsibility for supervising daily practice is with the clinical directors. In addition, the Federal Office of Public Health and Swissmedic make regular controls of the practice, including site visits. A checklist is in use for these controls.

At entry, a comprehensive assessment of the health, social condition and needs of the individual is made by the respective professionals. The prescribing physician determines the dosages and the regime and all changes of those. Social support needs are dealt with by social workers, and individual and family counselling is provided by psychotherapists. Preparation and supervision of injections is the task of nurses.

Staff and staffing structure

Staffing structure and staff/patient ratios differ between the stand-alone supervised injectable maintenance clinics and integrated specialised substance abuse services, depending on the various target groups served and the range of services provided.

The stand-alone clinics typically have multi-disciplinary teams, including medical doctors, nurses, psychologists and social workers. A minimum of 0.7 % of a physician's post and 0.7 % of a psychosocial professional's post per patient is conditional for an SIH clinic. By the end of 2008, a total of 363 staff worked in the 23 heroin clinics (BAG, 2009).

The stand-alone clinics have organised themselves for continued training according to needs, for discussing upcoming problems and for administrative matters. There is an e-mail network of doctors working in the clinics, and an administrator responsible for all the clinics. Whenever needed, a regional or national workshop is organised for exchanging good practice and experience and for additional training.

In integrated services, training and support for SIH treatment-specific issues is part of an overall training and support scheme, mainly directed at staff working with maintenance patients.

The clinical teams have been stable over the years; the average staff turnover is about 17 % per year (BAG, 2009). This is about the same as for other medical staff at the front line.

Inter-agency partnerships between SIH treatment clinics and other health and social services

In line with the diverse functions and structural models, the supervised injectable maintenance clinics have also diversified links and partnerships with other services. The guiding principle is to respond to the wider needs of patients, including their health and social needs. The degree of providing, for example, somatic, psychiatric or social assistance varies considerably within the different clinics and is contingent upon the extent of partnerships with external services. The costs of some of the external services are covered by patients' health insurance; others are free of charge.

Social reintegration intervention

All clinics have social workers with the aim of improving patients' living conditions and, to the extent possible, resocialisation of patients. Networking with other services for housing, job opportunities, sheltered living and so on are part of their responsibility.

Operational costs

A survey carried out in 1995 on the costs of heroin clinics (stand-alone and integrated) per patient/day reported costs of between CHF 47 and 54 in larger and smaller clinics, respectively (Gutzwiller and Steffen, 2000). In 2008, the average costs per patient/day were CHF 57. The total cost for 1 300 SIH patients amounts to CHF 27 million per year; of which 80 % is paid by health insurance and the rest is covered by welfare (psychosocial care) and patients themselves (BAG, 2009).

Admission and discharge criteria (particularly for disciplinary discharge)

The entry criteria to the supervised injectable maintenance clinics are a minimum age of 18 years, a minimum of two years of opiate dependence, a minimum of two past failed treatment episodes, deposition of driver licence while engaging in SIH and informed consent with regulations and rules (BAG, 2000).

Reasons for disciplinary discharge involve severe violence, carrying weapons, repeatedly bringing illegal drugs into the premises, taking injectables out from the premises and breaking into the premises. Exclusion is the most severe sanction; other sanctions are loss of privileged regimes, cautioning and temporarily replacing heroin with methadone. The competence for exclusion is with the chief physician. All patients and staff members are aware of the house rules and the consequences from non-compliance with those (BAG, 2000).

An overview of exits in the years 2005–09 showed 40–55 % transfers back to MMT, 9–20 % transfers back to drug-free treatment, 5–15 % deaths, 2–10 % arrests and 3–7 % involuntary discharges. Smaller proportions of patients were reported as hospitalised, moved away or exited for an unknown reason (Hiltebrand et al., 2010).

The criteria for moving to another treatment are mainly the patients' preference; staff have the task of discussing with the patient the possible consequences of such a change and, if a decision is made, to help find the appropriate institution where treatment can be continued. HIV seropositivity and delinquency are found to increase the risk for dropping out of SIH treatment (Frick et al., 2008).

Approximately 50 % of patients stay in treatment for at least two years and around 20 % for 15 years or longer. The average stay is three years. Only a small minority drops out without changing to another treatment (BAG, 2008).

Description of patient characteristics

The typical patient's characteristics mirror the entry criteria, which are strictly followed and controlled centrally. In the course of years, the average age of patients has increased and is approximately 40 years (range 20–71 years). The average age at entry increased from 31 years in 1994 to 41 years in 2009 (Hiltebrand et al., 2010).

On average, 77 % of patients are male and 23 % are female. Over 80 % of new entries come on their own initiative, and approximately 8.5 % have a court order (Hiltebrand et al., 2010).

The rate of HIV seropositivity at entry has shown a decline over the last five years, from 20 % to 11 %; the rate of hepatitis C seropositivity has fallen, from 77 % to 63 %. The risk of seroconversion was also reduced during enrolment in the SIH treatment programme (Steffen et al., 1999).

During 2005–10, approximately 14–21 % of new entries had full-time or part-time employment, but only 11–15 % could live from their working income, while 24–27 % lived on disability or unemployment payments and over 50 % on welfare. Only a small minority lives on income from illegal activities (0–0.9 %) or prostitution (0–0.6 %) (BAC, 2011). After one year or longer in treatment, 42 % are integrated into the labour market (BAC, 2009).

Approximately 76 % of new entries have a stable living situation and 41.2 % are living alone (Hiltebrand et al., 2010); after a year in treatment, the respective rates are 96 % and 58 % (BAG, 2009).

Over 90 % had previously been in maintenance treatment, over 70 % had tried to detoxify and live drug-free and about half had tried outpatient care and residential treatment. On average, the duration of previous treatments was 73 months for agonist maintenance, 19 months for residential rehabilitation and 7 months for detoxification and aftercare (Hiltebrand et al., 2010).

More than half of SIH patients were dually diagnosed; the most frequent psychiatric conditions were personality disorders, behavioural disorders and/or affective disorders (Frei and Rehm, 2002). The rate of dual diagnosis has been relatively stable over the last years.

What works and what are the challenges for the implementation of SIH treatment in Switzerland?

SIH treatment is well accepted and has received a majority of votes in a number of local and national referenda. Only one of the major political parties is against SIH prescribing. Practical problems have mostly been resolved, the implementation no longer presents difficulties, and within the treatment system and the target population it is an accepted therapeutic modality.

Conclusion

All requirements to continue SIH treatment as a regular treatment under special conditions are in place: a definite legal basis, funding by health insurance and additional local sources, a well-established clinical practice and a monitoring system.

The policy is to continue this therapeutic approach as one element in a comprehensive treatment system. Ten years after the introduction of SIH, the treatment system had developed from 11 000 to 18 000 treatment slots in MMT, and 1 300 in therapeutic communities. SIH had completed the system, increasing to the present capacity of 1 454, but it has not replaced any of the other therapeutic approaches. This continues to be the main strategy (Uchtenhagen, 2010).

A monitoring system and a quality assurance system document procedures any unintended events and effects, such as overdoses and seizures. The comprehensive handbook on heroin-assisted treatment, which provides all the rules, recommendations and basic information for a professional working style in the clinics, will be revised in the light of accumulated experience and of changes in the characteristics of heroin users. A working group is mandated to adapt the regulations and recommendations accordingly.

The safety conditions will not be changed; preventing a leakage into an illicit market is still a political priority. So far, according to police information, such leakage has not been detected. Also, SIH treatment will remain restricted for authorised outpatient clinics and prisons; it will not be allowed in private practice, in contrast to other agonist maintenance treatments.

The Netherlands

Historical background

National policy/drug strategy/legal framework for substitution treatment/existing service provision

Notable illicit heroin use began in the Netherlands in the autumn of 1972. At first, heroin use was largely limited to the native Dutch population and the route of administration was mainly through intravenous injection. A rapid upsurge in the number of heroin users was recorded around 1975 when Surinam, a former colony of the Netherlands, became independent. Young Surinamese men started to play a major role in the street trade of heroin, and many of them became users themselves. They adhered to their own way of administering the drug; that is, not injecting but inhaling. Since then, the estimated number of heroin users increased from 10 000 in 1977 to 20 000 in 1979 and 30 000 between 1988 and 1996. The general picture was one of a relatively stable population of problematic heroin users with

a low incidence of new cases and a low mortality rate. However, the percentage of injectors among heroin users dropped from 60 % in the 1980s to 10–15 % in the late 1990s. Currently, the vast majority is using heroin mainly or exclusively by inhalation ('chasing the dragon').

Methadone maintenance treatment was introduced in 1968 in the Netherlands for the treatment of morphine-dependent patients. Following the introduction of heroin in the Netherlands in 1972, treatments with methadone were primarily directed towards achieving abstinence from heroin dependence. Generally, these methadone reduction programmes suffered from high drop-out rates, and there was a serious threat that they would lose contact with many of the addicts. As a response to the rapid increase in the number of problematic heroin users during the late 1970s, and the introduction of HIV/acquired immune deficiency syndrome (AIDS) in the mid-1980s, the aim of oral methadone prescription in the Netherlands shifted from achieving abstinence towards achieving stabilisation and reducing harm. At the time that the heroin trials started, most of the methadone programmes in the Netherlands were so called 'low-threshold' maintenance programmes, characterised by the absence of mandatory counselling, the absence of sanctions in case of drug positive urines and relatively low doses of methadone. According to the treatment staff at the MMT centres in 1990, 36 % of methadone patients were functioning well, 40 % were frequently using illegal drugs and were not socially integrated and 24 % were extremely problematic, with daily use of various illegal substances and committing frequent criminal acts (Driessen FMHM, 1990). Taken together, these findings suggest that in 1995 (just before the start of the Dutch heroin trials), MMT was widely available in the Netherlands. At least 50 % of all problematic heroin users were enrolled in one of these programmes and, of these, about 40 % did very well. However, a substantial number of the patients failed to benefit from MMT (using illegal substances and often involved in criminal acts) and supervised injectable (and inhalable) heroin maintenance was thought to be a suitable and promising additional treatment option for these treatment-refractory patients.

By the late 1980s in the Netherlands, the stable and ageing population of problematic heroin users was served by a comprehensive treatment and healthcare system that provided services free of charge, including various kinds of abstinence-orientated treatment facilities (e.g. inpatient and outpatient detoxification, methadone reduction, residential treatment, therapeutic communities) and a wide range of facilities directed at stabilisation and harm reduction (e.g. methadone maintenance, needle and syringe

exchange, sheltered housing, user rooms). Depending on the local circumstances, 65–85 % of problematic heroin users were in contact with the formal treatment system: 50–60 % in MMT and 15–25 % in abstinence-orientated treatment. All methadone maintenance programmes in the Netherlands had at least some medical, psychotherapeutic and psychosocial treatment offered to their patients, but the nature, intensity and structure of this treatment offer varied considerably. Medical prescription of heroin was seen as a final treatment option intended only for chronic heroin-dependent patients who had repeatedly failed in other available treatments, including a state-of-the-art methadone maintenance programme (van den Brink et al., 1999).

Drug and related health/social problems and rationale for SIH treatment

In 1995, approximately 70 % of the heroin addicts in the Netherlands were in contact with the treatment system, including 15–20 % in drug-free treatment settings and 50–60 % in one of the methadone maintenance programmes. Around 40 % of the patients in MMT did very well, but a substantial number of patients failed to benefit from this treatment (using illegal substances and often involved in criminal acts). In order to improve the situation of these patients, a number of small non-controlled experiments were conducted between 1983 and 1995, including experiments with intravenous morphine in 1983 ($n = 37$), intravenous methadone ($n = 30$) in 1990 and oral dextromoramide ($n = 53$) in 1995. In 1994, the Swiss had started the medical prescription of SIH to treatment-resistant heroin-dependent patients. The first positive results from the Swiss heroin experiment (Uchtenhagen et al., 1996) led the Netherlands Minister of Health in 1996 to ask the Netherlands Health Council to formulate conditions for the prescription of heroin in the Netherlands. The Health Council advised the minister to conduct two randomised controlled trials (RCTs), one for treatment-refractory heroin-dependent patients injecting heroin and one for similar patients inhaling heroin. Both trials were in full agreement with the Dutch narcotic law, which at the time (1998) allowed the use of diacetylmorphine (heroin) for scientific purposes, but not for routine clinical practice.

Description of implementation

National policy/legislation concerning SIH treatment

The national drug policy of the Netherlands is an integrated mix of prevention, treatment, harm reduction and law enforcement. Within the treatment domain, both drug-free and harm-reduction approaches are actively supported at the national,

regional and local level. MMT is the core treatment for heroin addiction and is freely available for an indefinite period for all treatment-seeking heroin addicts. Since the registration of diacetylmorphine (heroin) as a medicinal product (Medicines Evaluation Board, 2006) and the change of the national narcotic law (Staatsblad, 2009), SIH is available free of charge for all treatment-resistant heroin-dependent patients.

After the positive evolution of the Dutch heroin trials in February 2002 (van den Brink et al., 2003) and the registration of diacetylmorphine as a medicinal product for the treatment of treatment-resistant heroin-dependent patients by the Netherlands Medicines Evaluation Board in December 2006, the national narcotic law was changed in July 2009 to allow the use of diacetylmorphine for both scientific research and regular medical treatments in specially authorised clinics (Blanken et al., 2010a).

Procurement, supply and distribution of diacetylmorphine

The different preparations (diacetylmorphine hydrochloride for injection and diacetylmorphine base/caffeine for inhalation) were developed in the Netherlands (Klous, 2004c; Rook, 2004; Blanken et al., 2010a). Both products are currently produced by a special firm that has a long-term agreement with the Netherlands Ministry of Health to supply pharmaceutical-grade heroin to all authorised SIH clinics in the Netherlands. The medication is delivered by armoured cars at the SIH clinics, where it is stored in a special safe from where it is distributed to individual patients during their visits to the clinic. Special drug accountability procedures and monthly controls by a pharmacist are required in order to prevent diversion. It should be noted that SIH in the Netherlands means the co-prescription of methadone plus heroin; a situation referred to by others as a heroin-augmented methadone treatment.

Government/local direction/involvement

The national government has an exclusive agreement with the producers of pharmaceutical-grade diacetylmorphine and has the exclusive right to appoint heroin clinics. According to the adapted narcotic law, heroin can be prescribed only in these specially appointed and authorised clinics. Moreover, these clinics have to comply with a series of minimum requirements in terms of staffing, training, architectural layout and the maximum number of patients that is allowed to be treated in that clinic. In addition, these clinics have to comply with the special direction of the National Health Inspectorate and with annual external audits. Finally,

all clinics have to submit an annual progress report on all individual patients to the National Health Inspectorate.

Description of operational delivery

Nature of the clinics, settings and capacity

Currently (July 2011), there are 17 heroin clinics in 15 cities in the Netherlands, treating a total of about 650 patients on any given day. Amsterdam and Rotterdam each host two clinics. The maximum number of treatment slots is set by the national government. The capacity of the individual clinics varies between 20 and 75 slots.

All clinics are part of addiction treatment services that provide a comprehensive programme for substance-use disorder treatment, including crisis intervention, abstinence-orientated interventions (residential and outpatient treatment) and harm-reduction treatments (methadone, buprenorphine, needle exchange, user rooms, social services). In many instances, the heroin clinic is located at the same location or is very close to the other addiction and mental health services of the city.

Geographical coverage/accessibility

At least one clinic is present in all big cities (with a population of more than 300 000) and in most of the larger cities (with a population of more than 100 000–300 000). Smaller cities are not yet served and it is not very likely that such clinics will be opened in the near future. No clinic can be opened against the will of the local authorities. SIH treatment is freely available for an indefinite time for all patients who meet the entry criteria and are willing to comply with the house rules of the treatment centre. In all centres, heroin can be either injected or inhaled, and heroin is generally prescribed in combination with a daily dose of oral methadone.

All clinics have three blocks of opening hours: one in the morning, one in the afternoon and one in the early evening. The number of hours per block depends on the number of patients and varies from 2 to 4 hours. All clinics are open 7 days a week, including all Saturdays and all Sundays. Currently, the capacity of the heroin clinics ($n = 745$) is slightly greater than the number of patients treated ($n = 650$ in July 2011). There are no waiting lists at any of the clinics. This is a strong indicator for a good coverage of those in need of this treatment approach. Currently, SIH serves approximately 5 % of all heroin-dependent patients in substitution treatment in the Netherlands.

Service provision and logistics

Treatment conditions are described in detail in a comprehensive manual, which can be consulted by all staff at any time and serves as a reference tool for staff supervision. In addition, the clinics have to respect detailed safety conditions, especially the visually supervised intake of inhalable and injectable heroin, and the logistical controls in order to prevent any diversion to the illicit market. Logistic controls include detailed drug accountability, including book-keeping of incoming amounts and storage amounts and registration of daily dispensed dosages per patient. An annual progress report, including a standardised assessment of the physical and mental condition and social function of patients, has to be sent to and approved by the Netherlands Health Inspectorate in order to continue heroin treatment.

Storage, preparation and administration of diacetylmorphine

Almost all procedures relating to the production, distribution and storage of diacetylmorphine are centrally regulated by the Netherlands Health Inspectorate. SIH clinics inform the production company on the quantities needed, which are then sent by armoured cars to the clinic and stored in special safes. Book-keeping includes arrivals, stores and daily dosage for each patient. A pharmacist performs a monthly edit on the quality of the execution of the procedures and the actual amount of diacetylmorphine in stock. Compliance with the regulations is controlled by the Netherlands Health Inspectorate.

Daily doses are individually determined by the doctor and prepared for administration on site. Staff assist injecting patients if needed. Inhaling patients generally do not need assistance. Missed doses lead to a reduction of the next dose in order to avoid overdosing. There are no take-home doses and the use of alcohol, cannabis or other illicit drugs in the treatment unit is strictly forbidden.

The average time spent for supervised injecting is 5–10 minutes per patient. For safety reasons, injecting patients are required to stay in the treatment unit at least 15 minutes after they have taken the prescribed heroin. Additional special psychosocial interventions are scheduled individually. The average time spent for supervised inhaling is about 20–30 minutes and these patients are not required to stay in the treatment unit after they have taken their prescribed heroin.

Laboratory methods to differentiate pharmaceutical from 'street' heroin

No attempts are made to verify self-reported use of 'street' heroin because it is assumed that patients in SIH can generally use as much diacetylmorphine as they wish (average dose about 500 mg/day with a maximum dose of 1 000 mg/day) and because urines positive for 'street heroin' would not be sanctioned and would not automatically result in expulsion from the treatment programme.

Description of clinical practice and related issues

Use of clinical guidelines

Detailed guidelines are available in the Manual for Heroin Treatment. This manual contains all regulations, recommendations and necessary additional information to guarantee good clinical practice. The handbook was produced by experts under the guidance and responsibility of the Central Committee for the Treatment of Heroin Addicts (CCBH, 2002). The main responsibility for supervising daily practice is with the clinic coordinator. In addition, the CCBH makes monthly visits to check the quality of the execution of the treatment and compliance to the guidelines. If needed, the Netherlands Health Inspectorate can do an official inspection. Finally, an annual external audit is performed by a contract research organisation following a fixed list of checks.

At entry, a comprehensive assessment of the treatment history, health, social condition and needs is made by the physician and nurse. The prescribing physician determines the doses and the regime and all changes of those. Counselling and social support needs are dealt with by the social worker. Preparation and supervision of injections are the tasks of nurses.

Staff and staffing structure

Staffing structure is similar in all SIH clinics, but staff/patient ratios differ depending on the size of the centre, that is the number of patients in treatment at the centre. All clinics have a multi-disciplinary team, including a physician, nurses and a social worker. In addition, all centres have their own security staff and a supervising pharmacist. Teams are quite stable, with an average staff turnover of 10–20 % per year.

Interagency partnerships between heroin clinics and other health and social services

All SIH clinics are part of an addiction treatment service with a comprehensive treatment offer for substance-use disorders and generally also for other mental

health and social problems. The guiding principle is to cover as much as possible all the health and social needs of the patients within the SIH clinic. However, if needed, patients can be referred within the addiction treatment service or to some external healthcare organisation or social services provider. Generally, these external services are covered by the health insurance of the patient or by the local government in cases of non-insured patients.

Social reintegration intervention

All SIH clinics have their own social worker who aims to improve the living conditions and, to the extent possible, the resocialisation of patients. Networking with other services for housing, job finding, sheltered living and so on are part of their responsibility.

Operational costs

Costs per patient per year are dependent on the size of the treatment unit, the housing costs in a specific city and the percentage of inhalers within the treatment group, as inhaling takes approximately 20–30 minutes whereas injecting heroin generally takes no more than 10 minutes.

The main costs were those of personnel, including a project coordinator (0.5 full-time equivalent (fte) for 25 patients, 0.75 fte for 50 patients and 1.0 fte for 75 patients), a physician (0.4 fte for 25 patients, 0.6 fte for 50 patients and 0.8 fte for 75 patients unit), nurses (7 fte for 25 patients, 9 fte for 50 patients and 10.5 fte for 75 patients), security personnel during opening hours (1.0 fte for 25 patients, 1.2 fte for 50 patients and 1.4 fte for 75 patients) and a pharmacist (0.1 fte independent of the size of the clinic). The second highest costs were general material expenses, including adaptations to existing buildings, depreciations, rent, cleaning, energy and maintenance (all dependent on the size of the treatment centre). Patient-related material costs were relatively modest and included the costs for pharmaceutical-grade heroin and other medical supplies. Depending on the number of patients per treatment unit, the costs for SIH treatment range between EUR 15 000 and EUR 27 000 per patient per year.

Admission and discharge criteria (particularly for disciplinary discharge)

The entry criteria are a minimum age of 25 years, a minimum duration of five years of opiate dependence, failure to benefit from adequately dosed MMT as indicated by (nearly) daily use of illicit heroin, and serious impairments in physical or mental health or social function (including lack of contacts outside the drug scene and

criminal involvement). In addition, participants have to agree with regulations and rules. Reasons for disciplinary discharge can be severe violence, carrying weapons, bringing illegal drugs into the premises repeatedly, stealing heroin from the premises and breaking into the premises. Permanent exclusion is the most severe sanction; other sanctions are tightening the regimen and temporary exclusion (replacing heroin with methadone). The competence for exclusion is a team decision, except when medical reasons prevail, in which case the physician decides. All patients and all staff know the house rules and the consequences of non-compliance.

Naturalistic long-term follow-up studies indicate that for most patients, SIH treatment is just a phase in their illness and treatment career, and with time many patients leave SIH treatment, as shown by the following retention rates: 1 year, 70 %; 2 years, 60 %; 3 years, 46 %; 4 years, 39 %; and 6 years, 25 %. Most of the patients who leave SIH treatment within this period return to MMT, generally with a higher dose of methadone and in a much better condition (60–80 %), and relatively small proportions move to abstinence treatment (5–10 %), drop out of treatment altogether (10 %) or die (10 %) (Blanken et al., 2010b). The criteria for moving to another treatment are mainly patient preference or expulsion owing to repeated rule violation. Staff have the responsibility to inform the patient, to discuss the possible consequences of the various changes and — if a decision is made — to help find the appropriate service to continue treatment.

Description of patient characteristics

In a naturalistic study (2003–05; $n = 345$) examining the effectiveness of SIH treatment under routine clinical circumstances, the effects and the patient characteristics were very similar to those in the RCTs (Blanken et al., 2010a): 86 % male, mean age 41.6 years, 75 % with low education, 13 % homeless, 91 % unemployed, 8 % HIV positive, 34 % with a lifetime suicide attempt, duration of regular heroin use of 19.8 years, duration of cocaine use of 13.0 years, and 26 days of heroin use and 15 days of cocaine use in last month before heroin treatment. Of all patients in routine SIH, 22 % were injecting and 78 % were inhaling diacetylmorphine.

What works and what are the challenges for the implementation of SIH treatment in the Netherlands?

Although MMT has been an undisputed treatment for opioid addiction since 1968 in the Netherlands and harm-reduction programmes such as needle exchanges were implemented without much opposition, heroin treatment has been a highly debated

issue with highly polarised positions taken by the various national political parties. On the other hand, heroin treatment has been received with little political opposition at the local level, although neighbourhood representatives were rather sceptical at the beginning of the trials. Currently, there seems to be a national consensus that heroin treatment is a useful addition to the existing treatments for heroin addicts, and the programme is fully financed by the Ministry of Health together with the municipalities with one or more heroin clinics. The presence of an independent research organisation (CCBH), the ongoing care about possible public nuisance due to the presence of a heroin clinic in a certain neighbourhood, the publications of the results in prestigious scientific journals (e.g. *BMJ*, *Addiction*), the results of the cost-effectiveness study and the approval of diacetylmorphine as a regular medicinal product for the treatment of chronic, treatment-resistant heroin addicts by the Netherlands Medicines Evaluation Board (MEB) have been instrumental in the current acceptance of SIH by almost all political parties, cities and neighbourhoods. With the exception of some practical problems, the implementation of heroin treatment no longer presents difficulties within or outside the treatment system. Currently, the most important issue is to preserve the high quality of heroin provision as a routine intervention. Regular internal and external audits are needed to check and — if needed — restore the formal requirements in terms of staff ratio and quality and in terms of adherence to the treatment guidelines.

Conclusion

All requirements to continue SIH as a routine medical treatment under special conditions are in place: a registered medication, a definite legal basis, funding by health insurance and additional local sources, a well-established clinical practice, and a monitoring and audit system. The plan is to continue this therapeutic approach as one useful element in a comprehensive treatment system. After 12 years of experience with SIH, MMT is still the main treatment modality for heroin-dependent patients, and abstinence-orientated treatments are still available for those patients choosing this treatment option (including some newly started Minnesota clinics). In general, the high-quality services of the SIH centres have resulted in new quality requirements and quality improvements in existing methadone and abstinence-orientated treatment programmes. Twelve years after the introduction of SIH, it is recognised that SIH is not the final answer for all patients. Therefore, new treatments have to be developed for those who do not benefit from the currently available treatments. Consequently, an RCT with contingency management added to SIH has

been initiated in order to further reduce cocaine use in heroin-dependent patients in SIH and to improve their prognosis. In addition, a study has been initiated to treat SIH-refractory patients with a new type of neuromodulation: deep brain stimulation (e.g. Mantione et al., 2010). Other approaches being explored for those who do not seem to benefit from SIH include the support and improvement of existing social support systems and of user rooms.

Finally, explicit clinical guidelines for supervised injectable and inhalable heroin treatment, along with an ongoing interest in the needs of the patients, are mandatory in a treatment system that seeks to be of optimal service to the patients, their family and society as a whole.

Spain

Historical background

National policy/drug strategy/legal framework for substitution treatment/existing service provision/rationale for SIH treatment

The basic structure and organisation of addiction services in Spain is guided by the National Drug Strategy and the National Drug Plan. However, each autonomous community also develops its own drug plan. Addiction services are structured around different treatment phases, sequential and parallel – from harm reduction to social integration, including detoxification, oral substitution therapy and abstinence-orientated interventions, services and programmes. These services are provided by public and private (contracted) centres, and are free at the level of the individual patient.

Despite the broad array of services provided and the wide availability of MMT programmes, there was still an important subgroup of heroin users not reached by the healthcare system and, therefore, not benefiting from those services. In addition, as a consequence of the HIV epidemic in the 1980s, there was a high prevalence/incidence of HIV among opioid-using injecting drug users, despite the wide implementation of MMT and harm-reduction strategies (Rinken and Romero, 2002). The success of the Swiss experience in the 1990s in the provision of medically prescribed injectable heroin under supervision showed that SIH treatment was a safe and feasible treatment alternative (Uchtenhagen et al., 1999). The critical HIV situation and the lack of alternatives for those not being reached by the addiction treatment system were the main factors that drove the introduction of SIH in Spain.

Spain approves and ratifies the UN Single Conventions, and therefore heroin is considered a Schedule I drug. Following extensive negotiations with the federal authorities, an RCT was approved in 2002 that aimed to test the feasibility of the introduction of SIH prescribing in Spain, as well as its efficacy in the treatment of long-term opioid-dependent users (March et al., 2006). While it was intended that several provinces and autonomous communities would be recruited as trial sites, and would offer SIH under trial conditions, it was only possible to carry out the study at one clinic in Granada, Andalusia. At present, the use of heroin remains limited to research (clinical or other), and in restricted quantities upon authorisation from the Spanish Agency of Drugs and Health Products. Within this frame, supervised heroin prescription is allowed only as an investigational product and is not available as part of routine treatment. Currently, patients at the supervised injectable maintenance clinic in Granada are receiving SIH under compassionate use ⁽⁵⁾ ⁽⁶⁾.

Description of implementation

National policy/legislation concerning SIH treatment

Since 2009, the supervised injectable maintenance clinic in Granada prescribes heroin under a compassionate-use law. The involvement of the national government entails the provision of the necessary authorisations for the importation, storage and delivery of pharmaceutical heroin to the individual user in the clinic through the Spanish Agency of Drugs and Health Products. The Andalusian government is responsible for the ongoing management and the funding of the clinic through the Foundation for Social Integration and Assistance, which carries out the courses of action commissioned by the Equality and Social Welfare Ministry.

Procurement, supply and distribution of diacetylmorphine

The clinic uses pharmaceutical heroin imported from Macfarlane Smith (Edinburgh) as raw powder, with the vials prepared by a hospital pharmacy unit.

⁽⁵⁾ Clinical trials are regulated by Article 23.1 Real Decreto 561/1993, revised by Capítulo V del Real Decreto 223/2004.

⁽⁶⁾ Compassionate use is intended to facilitate the availability to patients of new treatment options under development, which are not available or authorised in the country. See EMEA (2007), *Evaluation of medicines for human use*, European Medicines Agency, London. Online at: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004075.pdf

Description of operational delivery

Types of clinic models, setting and capacity

The SIH clinic in Granada City is situated in one of the biggest hospitals in the city and it is part of the addiction treatment services. The clinic targets long-term socially excluded opioid-dependent individuals with severe drug-related co-morbidities who are not benefiting from available addiction treatments.

Geographical coverage/accessibility

A total of 56 patients can be treated in this clinic (PEPSA, 2010); however, only 17 are currently (July 2011) receiving SIH treatment. Following the end of the trial, the future of the clinic was uncertain and this posed a significant burden on both the staff and the patients, possibly accounting for the small number of individuals currently engaging in SIH. More importantly, however, the primary reason for the small number of patients receiving treatment is the declining number of injectors in the geographical coverage area. In 2008, a total of 1 646 patients were receiving MMT in the province of Granada, and at treatment entry, less than 5 % reported injecting heroin (alone or in combination with other drugs) as the most frequent route of administration in the prior month (data for all Andalusia) (Consejería para la Igualdad y Bienestar Social, 2008, 2009).

Clinic opening hours and number of clinics per day

Patients attend the clinic to receive their medication or other concomitant treatment prescribed, to follow-up on treatment with antiretrovirals, for nursing and medical doctor appointments, for support and consultation with other specialists, and for use of the treatment centres' computers and recreational facilities, among others. Patients can visit the clinic for SIH consumption on weekdays (Monday–Friday) up to twice per day (morning session: 08.15–10.45; afternoon session: 15.15–17.15). At each visit, a minimum of 20 minutes is allocated for pre- and post-assessment for safety reasons.

Storage, preparation and administration of diacetylmorphine

The heroin is directly shipped to the hospital pharmacy, which shares premises with the SIH clinic. A pharmacist prepares the vials. The nurses from the SIH clinic then prepare patients' individual syringes. All doses are self-administered under supervision. Pre-dose assessment determines whether the patient is fit to receive

the medication. Following injection, patients' responses are assessed and they are discharged if no adverse reactions are present (Plaza et al., 2007).

Laboratory methods to differentiate between pharmaceutical and 'street' heroin use

During the study period, acetylcodeine was chosen as a marker for 'street' heroin use. However, this method returned too many false negatives and this practice was discontinued. Currently, no laboratory methods are used to detect 'street' heroin use.

Description of clinical practice and related issues

Use of clinical guidelines

Treatment is provided in accordance with a revised version of the clinical protocol developed for the purposes of the clinical trial. Monitoring of the clinical practice continues internally, including data collection on adverse events and other clinical outcomes and indicators. Guidance for good clinical practice is followed and practices are reviewed through conventional mechanisms, such as annual evaluations, regular visits to the clinics and routine reports.

Staff and staffing structure

The daily staffing in the supervised injectable maintenance clinic is as follows: three nurses, one physician, an administrative assistant and a security guard. Nurses are in charge of pre-dose assessment (e.g. whether the patient is fit to receive their injectable medication), support the compliance with and preparation of concomitant medications (e.g. antiretrovirals), injecting supervision and post-dose assessment (e.g. sedation). They provide primary care and health education on a variety of topics in consultation with the patient. Physicians, besides following the patients' treatment regarding the prescription of the medication, provide integral healthcare in consultation with another specialist, if required. Physicians and nurses coordinate with other agencies to reach individuals who might be eligible for SIH treatment, organise activities to engage patients' families and act as liaison with other addiction services. Nurses and physicians are trained in the prevention and treatment of drug dependency and drug-related problems. They participate in continued education and relevant workshops for specialist addictions professionals.

Following the end of the clinical trial, most of the healthcare workers were let go. However, since the compassionate-use programme began operating, the team has

been very stable. The programme has a total of six experienced nurses and two physicians, who have been working at the injectable clinic for a range of between 4–7 and 2–5 years, respectively.

Admission and discharge criteria

The majority of the patients in treatment at the injectable maintenance clinic are former participants of the 2003 trial. The trial inclusion criteria were as follows: opioid dependence for two years or more, age of 18 years or older, resident in Granada in the previous year, currently injecting, two previous MMT attempts and presenting at least two of the following conditions — infectious diseases related to injecting drug use (e.g. HIV), mental health problems (e.g. depression) and psychosocial problems (e.g. illegal activities). In 2009, three new patients who were not part of the 2003 trial were admitted to the SIH clinic. The admission criteria are similar to the trial eligibility criteria; however, the previous MMT treatment criterion has been replaced by two previous addiction treatments.

The reasons for patients' discontinuation of SIH treatment varied over time. Until the end of 2007, patient discontinuation guidelines followed the 2003 trial research protocol where those who failed to attend the clinic for five consecutive days (or 40 non-consecutive days) were discharged from treatment and could not be re-admitted. Other discontinuations involved disciplinary discharge, following which most of the patients were re-admitted into MMT. The most recent regulations state that patients can be transferred back onto MMT at any time and return to the clinic in the event of a relapse.

What are the debates and challenges for the implementation of SIH treatment in Spain?

In 2005, 59.9 % of the Spanish population indicated that the supervised medical administration of heroin to solve the drug problem was 'a very important measure' (Reitox, 2006). Since 1997, three Spanish autonomous communities have made proposals to provide SIH treatment — Andalusia (March et al., 2006), Catalonia (Colom, 2005) and the Basque Country (Iraurgi et al., 2005) — but these have not been approved, and it appears that approval is being considered only in the frame of an RCT.

Conclusion

Of the three autonomous communities, Andalusia was the only one that could actually carry out an RCT and that is still providing SIH treatment to a small number

of patients. In this case, the drastic decline in the use of injection as a primary route of administration of illicit heroin played a significant role in the non-expansion of SIH treatment in that community, even before the RCT started, when three sites were reduced to one. After a long-lasting political debate between the central and autonomic government to gain approval for the RCT, the study could not recruit the initial planned sample as the number of 'street' heroin injectors was already declining. With a group of heroin-dependent individuals not benefiting from oral methadone, Andalusia is still in need of pharmacological alternatives for the treatment of opioid dependency. In response to this situation, the Andalusian research team developed a proposal to test two oral formulations: diacetylmorphine and morphine in comparison with oral methadone (March et al., 2007). The study is still obtaining all the regulatory approvals needed to provide a non-licensed medication. A key aspect of this proposal is to test the feasibility of providing oral heroin formulations following procedures similar to those established in oral methadone service provision (i.e. mostly through the primary healthcare system). In time, if oral SIH is proven effective and the delivery through the primary healthcare system is likely to be feasible, its incorporation into the addiction treatment system may be a possible alternative for opioid-dependent individuals currently not injecting and not benefiting sufficiently from other treatment approaches.

Germany

Historical background

National policy/drug strategy/legal framework for substitution treatment/existing service provision

The discussion on the introduction of SIH treatment as an alternative to maintenance treatment for opioid-dependent patients with other substances was initiated in 1992, when the federal state of Hamburg introduced a respective bill to change the Narcotics Act (Betäubungsmittelgesetz) in order to allow the prescription of medical diacetylmorphine. In 1993, the city of Frankfurt applied for permission at the Ministry of Health to carry out a controlled medical trial on the prescription of diacetylmorphine. Both initiatives did not have sufficient political backing, but intensified the discussion on the topic. In 1999, the results of diacetylmorphine prescription in Switzerland then led to a joint initiative between cities and federal states together with the Ministry of Health to start a clinical controlled trial on

diacetylmorphine prescription. The trial was initiated in 2001 and carried out in seven cities, and the results, which showed that diacetylmorphine prescription was more effective than methadone maintenance in the treatment of severely dependent opioid addicts, were presented in 2006.

In November 2007, the Bundesrat (upper house of the German federal parliament) tabled a bill on SIH treatment in the Bundestag (lower house of the German federal parliament) (BT Drucksache 16/7249) and another one on the same subject in March 2009 (BT Drucksache 16/11515). The aim of both bills was to transfer SIH treatment into regular care. On 28 May 2009, the German Bundestag passed the 'Act on Diacetylmorphine-assisted Substitution Therapy', creating the legal preconditions for a transfer of the diacetylmorphine-assisted treatment into regular care by changing the Narcotics Act, the Medical Products Act and the Regulation on the Prescription of Narcotic Drugs. The act stipulates among others that diacetylmorphine (pharmaceutically produced heroin) becomes eligible to prescription — on very narrow criteria — as a narcotic drug used for severely dependent opioid addicts. The act was then presented to the Bundesrat and finally endorsed in a plenary session on 10 June 2009. The Act on Diacetylmorphine-assisted Treatment entered into force on 21 June 2009.

Drug and related health/social problems and rationale for SIH treatment

The decision to set up a clinical trial for the prescription of diacetylmorphine was based on a revised drug policy strategy by the German government in 1998, which introduced new harm-reduction measures. The rationale of the introduction of SIH treatment was based on epidemiological data showing that of the estimated 180 000 opioid-dependent persons in Germany, 50 % at most can be found in some type of maintenance treatment, yet of these, approximately 10–20 % do not achieve remission from illicit drug use, and therefore can be considered non-responders. Furthermore, mortality statistics had shown a renewed increase in drug-related deaths in the late 1990s, reaching almost the same level as the peak in 1991 despite an increase in treatment slots for maintenance treatment, which had been introduced in Germany in 1991 to try to reduce drug-related mortality. The specific rationale for SIH treatment was the growing number of patients in maintenance treatment that continued to inject illegal drugs and the large number of injectors in open drug scenes that were not presently in treatment.

Description of implementation

National policy/legislation concerning SIH treatment

In order to allow the prescription of diacetylmorphine within the framework of a clinical trial, an exceptional permission under the Narcotics Act was made. This permission allowed prescription within the clinical trial and continued treatment for patients who had completed the trial. A revision of the Narcotics Act became necessary in order for the treatment to be continued after the end of the trial. A bill for this revision passed the upper and lower houses of parliament in 2009, so that diacetylmorphine treatment is now regulated by the Narcotics Act.

Procurement, supply and distribution of diacetylmorphine

Diacetylmorphine is supplied in ampoules by the Swiss manufacturer DiaMo Narcotics GmbH, through a German subsidiary of the company.

Government/local direction/involvement

The authorities are not involved in the direct treatment, as all treating clinics are run by institutions involved in healthcare. However, local and some state authorities are involved in funding the treatment until other funding solutions are found. Furthermore, federal authorities have set up regulations for the implementation of treatment.

Description of operational delivery

Types of clinic models, setting and capacity

Presently, there are seven outpatient clinics in Germany where patients can receive diacetylmorphine treatment. They are the same seven clinics that were also involved in the trial. All clinics are outpatient, with either separate entrances only for patients receiving diacetylmorphine treatment or at least separate hours to avoid mingling of patients receiving diacetylmorphine maintenance with those receiving methadone maintenance. All clinics have both patients in diacetylmorphine and MMT (or buprenorphine treatment).

Clinic capacity varies from 12 to approximately 70 and depends mainly on financial resources controlled by the authorities. Presently (July 2011), there are around 300 patients in diacetylmorphine treatment.

Geographical coverage/accessibility

All seven clinics are located in a central part of their respective town and are easily accessible. Opening hours differ from one clinic to the next, but run from morning to evening, allowing for at least two injections daily, but in most clinics three. All clinics are open seven days a week.

Service provision and logistics

All clinics provide an injection room that is supervised by nursing staff, as stated by the respective regulations. Logistic controls include book-keeping of incoming amounts, storage amounts and daily dispensed doses per patient.

Storage, preparation and administration of diacetylmorphine

After delivery by the pharmaceutical company DiaMo Narcotics GmbH, diacetylmorphine is stored in a safe in the respective clinic. Diacetylmorphine ampoules contain diacetylmorphine in a powdered form. The ampoule is prepared with distilled water and the respective dose for a patient is then withdrawn from the ampoule. Ampoules are used not just for one patient, but for all consecutively treated patients in a clinic until the ampoule is empty. The syringe is then handed to the patient after identification and alcohol breathalyser test. The intravenous administration of diacetylmorphine is undertaken by the patient him- or herself.

Laboratory methods to differentiate between pharmaceutical and 'street' heroin use

As in the German heroin trial, urines are analysed for papaverine and acetylcodeine, which are considered to be probable indicators of 'street' heroin use. However, owing to limited financial resources, these urinalyses are not carried out on a regular basis.

Description of clinical practice and operational issues

Use of clinical guidelines

Presently, a treatment handbook, similar to the respective Swiss handbook, is being developed. Until completion of this handbook, physicians abide by the detailed regulations set out by the Narcotics Act, the guidelines set up by the Federal Physicians Board and, in some clinics, additional guidelines set up by the clinic.

Inter-agency partnerships between SIH treatment clinics and other health and social services

Most clinics have diversified links and partnerships to other services. The guiding principle is to cover as much as possible of all the health and social needs of patients. The degree of assistance provision varies considerably. Partnerships with external services are conditional for all needs which cannot be covered internally. Some of these external services are covered by health insurance, others are free of charge.

Social reintegration intervention

All clinics have social workers caring for an improvement of living conditions and, to the extent possible, vocational reintegration. Networking with other services for housing, jobs and other services are part of their responsibility.

Operational costs

Presently, the costs of diacetylmorphine treatment have to be carried by local authorities, as discussions on including diacetylmorphine treatment as a provision by insurance companies are still under way. Quality insurance is financed by the federal government through an evaluation carried out by the Zentrum für Interdisziplinäre Suchtforschung (ZIS) in Hamburg.

Admission and discharge criteria (particularly for disciplinary discharge)

Admission criteria are stated in the Narcotics Act and are based on criteria used in the clinical trial. Patients have to be at least 23 years old, have been dependent on opioids for at least five years and be using illicit drugs mainly intravenously, have considerable somatic and mental problems, and have had at least two unsuccessful treatment attempts.

Discharge criteria are set up by each clinic and mainly cover the aspects of criminal activity within the premises of the clinic, and especially (attempted) diversion of diacetylmorphine from the clinic. The leading physician takes the decision of discharge. Patients can also terminate their diacetylmorphine treatment and move on to other treatment options.

What works and what are the challenges for the implementation of SIH treatment in Germany?

The positive results of the clinical trial were so unambiguous that the political support developed sufficient momentum to convince a federal government that was originally sceptical of this type of treatment. The main challenge for the future of diacetylmorphine treatment in Germany lies in the negotiations concerning the financial aspects covered by the insurance companies. Should the negotiations lead to a positive result and insurance companies are asked to cover most of the costs, then SIH treatment will have a future in Germany and will most probably be extended to other cities. Should the negotiations lead to a result where insurance companies cover only a proportion of its cost, then SIH treatment will remain a marginal treatment option or even possibly wither away as public spending will not be available. Therefore, negotiations on SIH treatment are presently in a key situation.

Canada

Historical background

The idea of heroin treatment for opioid dependence is not new to Canada. Almost four decades ago, in 1972, the Canadian Government Commission of Inquiry into the Non-medical Use of Drugs chaired by Gerald Le Dain recommended in its report the 'implementation of a heroin prescription trial for addicts who could not be attracted into conventional forms of opioid addiction treatment' (Canadian Government, 1972).

Regrettably, no action was taken on this recommendation for several decades despite the fact that opioid dependence has remained a critical public health problem with an estimated 80 000 opioid users across Canada in 2006. Oral MMT remains to this day the most common and accepted treatment for opioid dependence, with approximately 26 % of the estimated opioid-user population in Canada enrolled in MMT in 2003 (Popova et al., 2006). While there has been a tenfold expansion of MMT in the last 15 years (College of Physicians and Surgeons in British Columbia, 2005; Popova et al., 2006), a recent study of all MMT treatment episodes in British Columbia over roughly the same period showed only a 42 % retention rate at 12 months (Popova et al., 2006). Among the significant predictors of time to discontinuation of treatment were age, medical co-morbidities, physician-patient load, neighbourhood-level socio-economic status indicators, compliance and daily

dose. There continue to exist many barriers to both attracting and retaining patients in MMT programmes.

Given that oral substitution treatment was not benefitting a significant subpopulation of opioid users in the United States, and given the positive reports from Switzerland about heroin prescription in supervised clinics, a group of scientists and treatment experts from across the United States and Canada came together in 1998 to examine the potential for SIH treatment in the North American context. This group formed the North American Opiate Medication Initiative (NAOMI) and met regularly over the next 24 months to produce and refine a clinical trial protocol while exploring the legal, regulatory, financial and logistical implications of such a trial in the two host countries. During this period, it became increasingly apparent that no United States site would be able to participate, but the Canadian members continued to work on implementing a trial in Canada.

The context for the SIH treatment trial in Canada

One of the most significant challenges to conducting the NAOMI trial in Canada was that, unlike Europe, governments were not proponents of the trial in Canada; rather, the proposal was put forward by a group of independent scientists and treatment experts who, on their own, had to obtain all the necessary approvals from government agencies that may not necessarily have been supportive of such a controversial study.

The NAOMI trial was successful at obtaining a EUR 5.9 million (CAD 8.1 million) research grant from the Canadian Institutes of Health Research (CIHR), a non-political peer-review research agency. Another EUR 1.8 million (CAD 2.5 million) was raised from other sources for expenses such as drug costs and renovations. The trial obtained ethics approvals from three host institutions. It also received approval from the Therapeutic Products Directorate of Health Canada, which regulates investigational treatments.

In Canada, heroin is controlled under Schedule I of the Controlled Drugs and Substances Act (1996), and is not a licensed medication. In order to provide SIH treatment, an exemption for importing, storing, prescribing, handling and receiving heroin is needed from the Office of Controlled Substances of Health Canada. This so-called 'Section 56 exemption' is granted '[...] if, in the opinion of the Minister, the exemption is necessary for a medical or scientific purpose or is otherwise in the public interest' (Controlled Drugs and Substances Act, 1996). To obtain such an

exemption, the NAOMI team was required to make significant renovations to the study clinics, mostly pertaining to security equipment and procedures, in order to ensure that study heroin would not be diverted into the black market.

Prior to initiation, it became apparent that the clinic in Toronto would not be able to begin the trial for more than six months after the other two sites, and also there were concerns about recruitment at the Toronto site. For these reasons, it was decided to concentrate the trial in Vancouver and Montreal.

The NAOMI trial

The NAOMI trial was a parallel, open-label, phase III RCT carried out in Vancouver and Montreal involving 251 participants, and was conducted between March 2005 and July 2008. A total of 251 participants were randomised to receive oral methadone ($n = 111$) or injectable heroin (diacetylmorphine hydrochloride; DiaMo Narcotics GmbH, Switzerland) ($n = 115$). In addition, a small group of participants ($n = 25$) was randomised to receive injectable hydromorphone instead of heroin for the purpose of validation of self-reported illicit heroin use by urine testing. Administration of MMT versus injectable drugs was not blinded, but heroin and hydromorphone were administered in a double-blind fashion.

The injectable medications were self-administered under supervision in the treatment clinics (one in each city) up to three times daily with a maximum daily dose of 1 000 mg for heroin and 333 mg for hydromorphone. Patients receiving injectable medications could at any time switch partially or totally to oral methadone if deemed appropriate. Methadone dosages and delivery were based on best practices and current clinical practice guidelines. All patients were offered a comprehensive range of psychosocial and primary care services, in keeping with Health Canada best practices. Study treatments were provided for 12 months followed by a three-month period during which participants still being treated with injectable drugs were transitioned to conventional therapies such as methadone. Heroin was not available to participants after this 15-month period.

The results of the NAOMI trial were very positive with respect to SIH treatment (Oviedo-Joekes et al., 2010a). The results regarding the small group of 25 people who received hydromorphone were surprising. At the end of the study, none of the participants in the hydromorphone group thought they were definitely receiving this drug. Retention rates with heroin and hydromorphone were virtually identical. So, too, were declines in the use of 'street' heroin. There were no differences in the safety

profile of the medications. The investigators concluded that hydromorphone may be as safe and effective as heroin and opioid-agonist substitution treatments, but larger studies are required to confirm this. This could have a significant impact in many settings where political considerations and stigma might deter the use of medically prescribed heroin.

Lack of SIH after the trial

In the latter half of the NAOMI trial, the investigators applied to Health Canada for 'compassionate access' to heroin beyond trial completion, but such access was denied. So was access to funding for the provision of hydromorphone at the clinics. Thus, from July 2008 to the present (July 2011), the two specially constructed clinics in Vancouver and Montreal have provided neither heroin nor hydromorphone-assisted therapy to any clients.

What are the challenges for the implementation of SIH treatment in Canada?

Challenges to implementing SIH in Canada exist at both the federal and provincial levels. The federal government is responsible for both regulating drugs and for the criminal law. Any physician who wishes to prescribe heroin will require a Section 56 exemption to the Controlled Drugs and Substances Act from the Federal Minister of Health. Without this, a prescribing physician would be subject to criminal prosecution. While the federal ministry may be willing to exempt a scientific study that is limited both in numbers of participants and in duration, it is unlikely to approve SIH treatment as ongoing regular healthcare practice at present. The stigma associated with heroin probably plays a key role in making injectable hydromorphone an attractive alternative.

Within the Canadian health system, the political problem is both stigma and cost, with immense pressure to curb health spending. However, the recent evidence from trials, as summarised in this Insights publication, points clearly to heroin treatment being incrementally more cost-effective than the treatments that are currently being funded, at least for the severe populations studied. This paradox can be partly explained by the fact that government departments tend to operate in silos and the savings that occur with heroin treatment in criminal justice, policing, jail and court costs are not actually savings seen within the healthcare system, which is shouldering the additional costs. It is thus difficult for health ministers to take the wider societal perspective that is critical in cost-effectiveness evaluation and policy.

United Kingdom

Historical background

National policy/drug strategy/legal framework for substitution treatment/existing service provision

It is estimated that there are around 300 000 problematic drug users (using heroin and cocaine) in England (Hay et al., 2010). Just over half (167 256) are opiate users in contact with drug treatment services in any one year (National Treatment Agency for Substance Misuse, 2010). The majority of those in treatment report opiate drugs (primarily heroin) as their main problem drug.

There are a wide range of services in the United Kingdom aimed at treating heroin use and related problems. Services in the United Kingdom are shaped by the government's national drug strategy. However, service provision is uneven within the United Kingdom and the type of service or intervention offered reflects local funding and local philosophies. Drug services are provided by a wide range of providers including National Health Service (NHS) providers — general practitioners, specialist NHS drug services, hospital inpatient detoxification units and, increasingly, the voluntary and private sector such as street-based agencies, residential rehabilitation units, crisis intervention units and self-help groups, and private doctors.

Interventions include those providing substitute maintenance prescribing and those providing abstinence-based treatment such as residential treatment units and day centres providing structured psychosocial services. Efforts to reduce the problems associated with heroin use have largely centred on drug substitution treatment, most commonly the prescription of oral methadone and, more recently, buprenorphine. There has been a major expansion of opiate substitution treatment and there has been a fourfold increase in the number of patients in substitution treatment over the last 15 years. Methadone accounts for around 80 % of NHS opiate prescriptions for heroin dependence in England and Wales and buprenorphine accounting for around 16 % (Strang et al., 2007). Any doctor in the United Kingdom may prescribe methadone or buprenorphine for the purposes of treating addiction and there is no limitation on this treatment.

Uniquely in the United Kingdom, methadone ampoules can also be prescribed. Historically, they have at times been a substantial part of opiate substitution treatment in the United Kingdom (e.g. around 30 % in the 1970s and approximately 10 % in

the early 1990s), but they now account for approximately 2 % of all methadone prescriptions in England and Wales (Strang et al., 2007). Injectable heroin can also be prescribed in the United Kingdom to heroin addicts as an opiate treatment and has been a treatment option for over 80 years, and this has historically been important. However, over the last 30 years, this practice has become progressively rarer and now comprises less than 1 % of all opiate substitution treatment in the United Kingdom. The established method of heroin prescription in the United Kingdom has been as a 'take-away' supply, which is then injected in an unsupervised context. In practice, few doctors have prescribed it and few patients have received it (Metrebian et al., 2002).

The practice of prescribing injectable opiate substitution treatment for heroin dependence has been steadily diminishing in the United Kingdom, while the proportion of opiate prescriptions for methadone and buprenorphine have remained fairly stable. Prescriptions for methadone ampoules have significantly reduced from 9.3 % of all methadone prescriptions in England and Wales in 1995 (Strang et al., 1996) to 1.85 % of all methadone prescriptions in 2005 (Strang et al., 2007). Moreover, prescriptions for heroin have gone down from 1.6 % of opiate prescriptions in 1995 (Strang et al., 1996) to 0.3 % in 2005 (Strang et al., 2007). The prescription of injectable opiates and particularly heroin has steadily decreased, firstly owing to an increase in the international confidence in the benefits of oral MMT (and more recently oral buprenorphine maintenance treatment), with an accompanying substantial scientific evidence base for these oral treatments (NICE Technology Appraisal TA 114, 2006; Mattick et al., 2008, 2009); secondly, there has been more awareness of the marked potential for abuse of prescribed injectable drugs and the potential for their diversion on to the illicit market (with increased risk of spread of abuse and addiction and the danger of overdose); thirdly, the lack of evidence for its effectiveness; and fourthly, more recently there has been more awareness of the greater cost of these injectable medications compared with oral formulations (Metrebian et al., 2002, 2007). Heroin is prescribed in England and Wales, with huge regional variations, with some regions prescribing to over 100 patients whereas others prescribe to only one or two patients (Stimson and Metrebian, 2003).

In 2002, the United Kingdom government recognised the potential of heroin prescribing (the recent trials undertaken in Switzerland and the Netherlands had reported promising results) and in its Updated Drugs Strategy (Home Office, 2002)

called for heroin prescribing to be expanded and delivered under medical supervision to all those with a clinical need for it. In response, the NTA published a guidance report (National Treatment Agency for Substance Misuse, 2003) on the potential role of injectable heroin and methadone within treatment services. This guidance signified a considerable shift from the existing approaches to delivering injectable heroin and methadone maintenance in the United Kingdom by recommending that it should be a second-line treatment and that it should be considered only for those patients not responding to oral substitution treatment delivered under optimal conditions. Moreover, the guidance recommended that patients entering injectable maintenance programmes should have fully supervised dosing of their injectable opioids through the establishment of new clinics with the capacity for supervised injecting. Such supervision would allow the use of higher maintenance doses with safety and security.

In 2002, the House of Commons Home Affairs Select Committee recommended that there should be a thorough evaluation of heroin-prescribing treatment (House of Commons Home Affairs Committee, 2002). As a result, funds were made available for the establishment of new pilot supervised injecting clinics providing both injectable heroin and injectable methadone treatment under strict daily supervision.

Drug and related health/social problems and rationale for SIH treatment

Oral MMT is the most common drug treatment for opiate dependence and there is strong evidence for its effectiveness for most heroin users entering treatment (Mattick et al., 2009). Buprenorphine is the second most commonly prescribed opiate substitution treatment, comprising approximately 15 % of all opiate substitution treatment prescriptions in England, although less in Scotland and more in Northern Ireland (Strang et al., 2007). However, there is a significant minority of heroin addicts who appear unable to make much progress with oral methadone treatment and continue to inject 'street' heroin despite receiving conventional treatment. For these most severe and entrenched heroin addicts, it has been argued that treatment with pharmaceutical heroin (diacetylmorphine) may be a better solution. Heroin treatment has been a feature of the British response to illicit opiate use over the past 80 years. However, unlike recent European developments, where treatment centres have been established to deliver supervised injectable opioid treatment (IOT), the British approach has provided heroin for unsupervised injections at home and had a limited capacity for the supervised dosing of injectables. There have been concerns regarding this practice, including concerns regarding the cost of heroin treatment,

the potential for the diversion of medications and the prolongation of drug use and injecting 'careers' of patients (Zador, 2001). In the light of the small number of British studies of heroin prescribing and the promising results from studies in other European countries examining heroin treatment delivered within supervised injecting clinics, the English randomised trial was established to specifically answer the research question of whether efforts should be made to optimise conventional treatment for such patients (e.g. encouraging high oral doses, supervised dosing, psychosocial interventions and regular attendance) in order to reduce regular illicit heroin use, or whether such patients should be treated with injected methadone or injected heroin in newly developed supervised injecting clinics.

Description of implementation

National policy/legislation concerning SIH treatment

The medical use of pharmaceutical heroin (diacetylmorphine) for palliative care and for the treatment of addiction has always been legal in the United Kingdom. In 1926, the Rolleston Report (Ministry of Health, 1926) established the right of doctors to treat heroin dependence by long-term or maintenance prescribing of opiates (including heroin). Later, in the late 1960s, the Dangerous Drug Act of 1967 restricted the prescribing of heroin in the treatment of addiction to those doctors licensed by the Home Office to do so. The doctors who obtained licences were mostly psychiatrists in charge of addiction treatment centres or clinics set up by the NHS. Doctors still require a special licence to prescribe heroin for addiction, but prescribing heroin for the treatment of other medical conditions has been unaffected.

Heroin prescribing for the treatment of addiction continues to be a legal option for the treatment of heroin problems. Some doctors continue to prescribe heroin for unsupervised consumption at home, but this is becoming progressively rarer.

The three supervised injecting RIOTT clinics continue to provide supervised injectable heroin (and injectable methadone) treatment as a second-line treatment to chronic opiate-dependent treatment-refractory patients outside of the trial.

Supply of diacetylmorphine

Up until mid-2008, specially imported supplies of pharmaceutical heroin from the Swiss pharmaceutical manufacturer DiaMo Narcotics GmbH were used in the clinics. The pharmaceutical heroin was presented as 10-g multi-dose vials (in comparison

with British diacetylmorphine in single-use ampoules), which were considered to be more appropriate for use in the supervised clinics and less expensive than the diacetylmorphine available from British pharmaceutical companies. In addition, the supply from DiaMo Narcotics GmbH was considered to be more reliable than the uncertain supply of British diacetylmorphine in 2005, following problems with pharmaceutical production.

However, following British concern about the potential for bacterial contamination of reconstituted diacetylmorphine when reconstituting diacetylmorphine under non-aseptic conditions (although following manufacturers' guidelines), and the desire to remove expensive import duty costs, the supply of diacetylmorphine was reviewed. The clinics now use the recently approved British Auralis diacetylmorphine single-dose ampoules (available as 100 mg and 500 mg, freeze-dried).

Government/local direction/involvement

The clinics are funded centrally by the Department of Health. In the 2008 United Kingdom government's drug strategy 'Drugs: Protecting Families and Communities' (HM Government, 2008), the government committed itself to supporting the treatments that were found to be most effective, including injectable heroin.

Description of operational delivery

Types of clinic models, setting and capacity

At present, there are three supervised injecting clinics in operation in the United Kingdom, with a total capacity of up to 100 (capacity for individual clinics: 24, 30 and 40). The clinics were established within existing large NHS community drug services providing oral substitute maintenance treatment. Two of the clinics are physically located within existing drug service buildings and the smaller clinic (capacity 24) is situated a short distance from it, in its own building (shared with a community counselling service).

Accessibility

The three supervised injectable maintenance clinics were established in south London, Darlington and Brighton. The clinics are situated within larger specialist drug clinics providing treatment to between 320 and 800 patients. The clinic in south London is located in an inner-city area, with very high levels of deprivation, substance misuse

and mental health needs. It has a catchment area with a population of 747 400. The clinic in Darlington is located in a residential area in a historic market town with a population of 97 838. The clinic situated in the seaside city of Brighton and Hove has a population of 250 000 and is in an area with very high numbers of drug problems and fatal overdoses. The clinic is housed in a central residential area with a mix of privately owned homes, council housing and rented accommodation.

Each clinic is a dedicated service, open seven days per week; patients are able to attend the clinic for injections in the morning and/or afternoon. The clinics are open for two hours each morning and afternoon session – usually between 9–11 a.m. and 3–5 p.m. (Monday to Friday) and 9–11 a.m. and 2–4 p.m. (Saturday, Sunday and public holidays).

Description of clinical practice and related issues

Detailed guidelines drawn from those for the Dutch and Swiss clinics and originally developed for the RIOTT trial are used in the clinics in England. These guidelines also draw upon work previously published by the National Treatment Agency for Substance Misuse (2003). The NTA convened an expert advisory group to develop guidelines on the role of prescribing injectable heroin and injectable methadone, which were published in 2003 (National Treatment Agency for Substance Misuse, 2003). The guidance identified this treatment as a second-line treatment to be considered for those patients not responding to oral substitution treatment delivered under optimal conditions.

The guidelines include eligibility criteria, screening assessment, dose titration and conversion from oral methadone to diacetylmorphine, procedures for supervising injecting, observation and monitoring pre- and post-injection, emergency procedures in case of overdose or anaphylactic shock, and pharmacy procedures including the storage, reconstitution and dispensing of heroin ampoules.

The clinics offer both injectable heroin and injectable methadone for self-injection under medical supervision. There are no take-home injections. Patients are able to receive oral methadone 'take-home' supplements and receive psychosocial interventions.

The clinics (with a capacity of 30–40 patients) are typically staffed by one consultant physician, one lead nurse (team leader) and four nursing staff with additional nurses (2.0 full-time equivalent (FTE)) for weekend cover and a pharmacist (0.5 FTE).

Each clinic shares reception staff with the larger general clinic. The smaller stand-alone clinic in Brighton has no pharmacist and no reception staff. All nursing and medical staff receive training in cardiopulmonary resuscitation (including use of oxygen); preventing, recognising and treating intoxication and overdoses (including Naloxone); pre- and post-injection assessment; vein management and safer injecting; and first aid and treatment of anaphylaxis. The injecting room is supervised by at least two registered nurses (or medical staff) at all operating times, of whom at least one has received training in all identified procedures.

Doses are individualised with the aim of reducing illicit opiate use. Initial doses are converted from oral methadone to injectable heroin. Heroin doses are in the range of 300–500 mg per day. Patients have the option of also having supplementary prescribed oral methadone. Treatment with heroin typically involves two injections a day. Patients who are unable to attend for injectable opioid treatment (IOT) will have access to take-away doses of oral methadone according to contingency-based criteria.

To minimise the risk of adverse events due to the concomitant use of central nervous depressants (e.g. alcohol, benzodiazepines), patients are routinely assessed before and after dose administration. This may involve an instant drug-screen urine test (by means of a single-use, rapid, one-step test strip) or breath alcohol test using an alcometer. More extensive monitoring takes place when tolerance to the prescribed doses cannot be established.

The use of correct, safe and hygienic injecting practices is strictly monitored by the nursing team. Patients have the option to inject intravenously, intramuscularly and subcutaneously; however, the choice of route is subject to assessment by the nursing team and is guided by the condition of the client's veins — deep vein injecting (e.g. groin) is prohibited. Although injecting in the femoral vein was originally permitted, this was reviewed following clinical concerns (Zador et al., 2008) and is no longer permitted in the RIOTT clinics.

Up to three clients are allowed in the injecting room at any one time. On average, the process of assessment, preparation and injection takes 10 minutes for each patient.

Patients are assigned a key worker, with weekly sessions during the initial three-month period. Thereafter, the frequency of reviews may reduce to two weekly. All patients have reviews every three months with a physician and have access to other ancillary services (e.g. psychology, counselling) available at each site.

Although clinical practice has been governed by the trial's clinical protocols, not all clinical issues encountered by the staff were anticipated by these protocols, nor could they be given the unprecedented nature of this clinical service in the United Kingdom. Changes to clinical practice have been implemented as part of an ongoing process of service improvement guided by clinical/service review, clinical audit and review of untoward incidents. Such changes have been operationally led, not directed by policy and included, among others, the change from allowing groin injecting to excluding it after reflecting that it was impossible to have a safer groin-injecting practice (Zador et al., 2008), and moving from supervising four patients at one time to only three, owing to the change in diacetylmorphine preparation from multi-dose vials and pre-prepared syringes to single-dose ampoules and the nurses having to prepare injections in the clinical room, and thus finding that they could safely supervise only a maximum of three patients at a time.

Supply, storage, preparation and administration of diacetylmorphine

There are locally agreed standard operating procedures for the supply, storage, preparation and administration of diacetylmorphine. Injectable diacetylmorphine stock is stored at the clinic pharmacy in a locked, controlled drugs cabinet, according to British controlled drug legal requirements and health trust regulations. All diacetylmorphine received and administered is recorded in a controlled drugs book.

Laboratory methods are used to differentiate pharmaceutical from 'street' heroin use

A special laboratory test, which can differentiate prescribed from illicit heroin in urine drug screens, has been developed and validated in the context of the trial, and thus provides the ability to establish whether the patient has been taking any supplementary 'street' heroin while in the injecting clinic. This laboratory test is able to identify 'street' heroin through its contaminants by looking for markers of metabolites such as papaverine and its derivatives, which are not present in pharmaceutical heroin. Both the method and the results from this new laboratory assay have been published (Paterson et al., 2005) and the laboratory test is applied in everyday clinical practice in the supervised injectable maintenance clinics.

Admission and discharge criteria

The supervised injecting clinics are reserved for treatment of the most difficult cases where ordinary first-line treatment has failed to deliver the expected benefits. Hence, it is typically the most severe and entrenched heroin addicts who are the patient

population of these clinics. The entry criteria include an age between 18 and 65 years with a minimum 3-year history of injecting heroin use, regular injecting heroin use and no active significant medical or psychiatric condition, no severe alcohol dependence and not abusing benzodiazepines in an erratic manner — patients taking stable prescribed doses of benzodiazepines are not excluded.

The NTA expert working group estimated that SIH was probably applicable to the most severe 5 % of the heroin addict population.

Patients are regularly reviewed and, depending on their progress, will receive fewer restrictions or more intensive treatment with greater scrutiny.

Operational costs

The annual operating costs of the three clinics are EUR 1 683 088 (GBP 1 500 000) and individual costs fall into three main categories: buildings and corporate overheads at EUR 168 304 (GBP 150 000); staff costs at EUR 1 290 379 (GBP 1 150 000); and drug costs at EUR 224 405 (GBP 200 000). The cost per patient per annum is around EUR 16 830 (GBP 15 000).

Description of patient characteristics

The majority of patients attending the clinics are those who were eligible and successfully enrolled in the trial. Patients were heroin addicts with long histories of addiction and of previous treatments. The majority were male (73 %), white (96 %) and with a mean age of 37 years. They were most likely to be unemployed (95 %) — their main source of income was state benefit (96 %), with one-quarter (24 %) reporting family or partner as providing a main source of income. Nearly one-half of the patient sample lived alone (46 %) and one-quarter lived with a partner or spouse. Patients reported first using opiates at the age of 20 years and first injected at the age of 23 years. They had used opiates for a mean of 17 years and had injected for a mean of 14 years. Patients had first received drug treatment at the age of 27 years and had received treatment for a mean of 10 years. All had previously received oral methadone treatment and had a mean number of four previous opiate treatment episodes. At enrolment, all (100 %) were using 'street' heroin virtually daily (mean 28 days/month), nearly three-quarters (74 %) were using crack/cocaine (mean 10 days/month), over one-third (35 %) were using non-prescribed benzodiazepines (mean 7 days/month) and one-half were drinking alcohol 15 days per month. Nearly three-quarters (73 %) had previously been to prison, with a mean of six periods of past imprisonment.

What works and what are the challenges for the implementation of SIH treatment in England?

The new supervised injectable maintenance clinics deliver a highly intensive, moderately expensive treatment. The supervised injecting clinics (all of which have contributed to the trial) have all been based on the design and approach of the German, Dutch, Swiss and Canadian clinics. While there is nothing new about prescribing heroin for the treatment of opiate addiction in the United Kingdom, the way heroin treatment is delivered — within these European-style supervised injecting clinics — is new and it is a radical departure from previous clinical practice in the United Kingdom. First, they are open 365 days per year. Second, all injectable doses are supervised, so there is no potential for diversion or abuse. However, this makes the procedure more labour intensive for the clinic providing the treatment and more demanding on the patient. Patients must comply with the regular attendance schedule (typically, twice-daily injections of heroin).

In May 2011, the NTA and the Department of Health in England announced that, following the model demonstrated in the trial and the benefit observed for the identified extreme patient population, they would commence the process of establishing new supervised injectable opiate maintenance clinics.

At present, all three supervised injectable maintenance clinics in England are open for two sessions per day, every day. This appears to be acceptable to patients (with additional oral methadone), even with the long overnight interval between injecting sessions. However, it is possible that with more experience with this new type of treatment, it might be found that a more extended schedule of three opening sessions per day might be more effective (at the present time it is not possible to give an opinion on this, but this should be kept in mind as a possible means of achieving further improvement of benefit, especially as heroin is such a short-acting drug).

Clinics in mainland Europe (Germany, the Netherlands and Switzerland) and Canada all use large-dose multi-use vials which are considered to be well suited to the supervised clinic situation, and which also reduce medication costs to less than half the British price. In the United Kingdom, the Swiss diacetylmorphine multi-dose vial has been used for much of the period of the RIOTT trial, and this has significantly reduced operating costs. While the clinics are now using British single-dose ampoules, it is hoped that it will be possible to establish a regular supply of multi-dose pharmaceutical heroin in the future.

The UK Government has given approval (January 2012) for cautious roll-out of Phase 2 of such RIOTT-style clinics, specifically for the small number of individuals severely

affected by their chronic heroin addiction where all orthodox treatments have failed to have a significant impact: in the Department of Health's own words, supervised injectable opiate treatment 'is now evidenced as a clinically-effective second-line treatment for the small number of people who have repeatedly failed to respond to standard methadone treatment or residential rehabilitation' (please see the Department of Health's website: <http://www.dh.gov.uk/health/2012/01/iot-service-provider-briefing> (accessed in January 2012)).

Conclusion

SIH treatment clinics have been found to be feasible and effective in the United Kingdom. The next stage is to identify how best to expand this treatment to more opiate addicts with a clinical need for it and what models of service delivery might work best.

Denmark

Historical background

National policy/drug strategy/legal framework for substitution treatment/existing service provision/rationale for SIH treatment

In Denmark, substitution treatment of substance abusers is taken care of by the municipalities, and treatment with medically prescribed heroin is an integrated part of the overall treatment and care services for substance abusers in the individual municipality. Thus, there is continuity between the medical treatment and the interventions addressing the social problems of the individual substance user. Patients in SIH treatment are therefore encouraged to engage with local agencies offering help and support with life problems (e.g. housing), as well as with services dedicated to the psychological well-being and individual livelihood. At patient level, all medical and other treatment services are free of charge.

In 2007, there were approximately 6 500 patients in substitution treatment with methadone and about 1 000 with buprenorphine. Of the overall number of patients in long-term maintenance treatment, about 10 % were estimated to meet the criteria for SIH, with an actual target group set at 300 opioid-dependent individuals (National Board of Health, 2007).

As from May 2009, SIH has become available for a specially delimited target group of opioid-dependent individuals in Denmark (National Board of Health, 2010).

Following the launch by the Danish government of a scheme for SIH provision as a second-line treatment for the most vulnerable heroin users who have failed to benefit sufficiently from long-term oral substitution treatments, a proposal was put forward by the Ministry of Health and Prevention for amendment of the Controlled Substances Act for SIH to become available for this select group of patients. Adoption of the proposal on 29 May 2008 and its coming into force on 1 July 2008 enabled SIH to be offered as a second-line treatment to opioid-dependent individuals in the country. Subsequently, the National Board of Health established rules around the prescription of and treatment with heroin (National Board of Health, 2009a).

According to current regulations, initiation of SIH may be undertaken only as part of treatment in services for opioid dependence that have a special permission from the Danish Medicines Agency, which has laid down rules with regard to safety measures, admission and accounts (National Board of Health, 2009b). Furthermore, the Medicines Agency has established a special guidance on ordering and storage of diacetylmorphine by the treatment institutions and on importation and delivery of this substance by companies (Medicines Agency, 2009).

Description of clinical practice and related issues

At present in Denmark, SIH treatment cannot be delivered in hospital settings or in institutions that are part of the prison service. SIH treatment is a specialised medical task that involves special requirements with regard to treatment and patient safety. These requirements are imposed by the complexity and the significantly greater risks in comparison with risk related to conventional oral substitution treatment, for which reason there are specific requirements as to professional competence and staffing.

The medical doctors who are allowed to prescribe heroin must be approved by the National Board of Health, and the doctor in charge of treatment must have experience of substance-misuse treatment. The doctor must be a specialist within a relevant medical field (e.g. general medicine, psychiatry, social medicine, internal medicine) and have documented clinical experience of substance-misuse (and co-morbidity) treatment.

The doctor in charge of treatment may use assistance from other healthcare professionals (e.g. nurses) who have knowledge and experience of substance-misuse treatment, including undertaking acute treatment of life-threatening conditions such as anaphylactic shock or overdose.

Medically prescribed heroin may be taken only by self-administration and under supervision by the healthcare staff at the injecting clinics. Typically, patients attend the clinic twice per day, mornings and afternoons, and they are issued with oral methadone for the night. Doses of heroin are never given out for home use, and so the clinic is open to patients for 8–10 hours per day, each day of the year.

As a minimum requirement, the supervised injecting clinic is staffed at all times with one medical doctor and at least two authorised healthcare professionals.

Indications for SIH include:

- enduring intravenous misuse of prescribed or illegal opioids despite participation in long-term oral substitution treatment within the preceding 12 months;
- age of 18 years or over;
- no active or untreated severe psychiatric condition which would mean that the patient cannot participate in the injection treatment;
- no severe somatic disorder that contraindicates treatment;
- no significant alcohol abuse, that is the patient must be able to appear in person twice daily without symptoms of severe intoxication or withdrawal;
- no significant abuse of benzodiazepines. Patients in stable treatment with benzodiazepines are not excluded from injection treatment;
- no pregnancy, breastfeeding or current plans to become pregnant; and
- acceptance of the requirement to appear in person and undertake supervised self-administration of injectable opioid treatment.

The medical doctor in charge of treatment submits electronic reports on a six-monthly basis to the National Board of Health. The reports cover patient treatment progress in three domains:

- (i) continued substance misuse;
- (ii) health (physical and psychological); and
- (iii) social functioning (including criminal activity).

In 2008, the government and the political parties behind the parliamentary agreement on the 'rate adjustment pool' (Satspuljen) allocated to municipalities EUR 1 342 329.83 (DKK 10 million) of the total 2008 budget towards preparation and implementation

of the SIH scheme (establishing the supervised injecting clinics, staff training) and the development of a coordinated monitoring system by the National Board of Health (National Board of Health, 2008). In 2009, the 'rate adjustment pool' included an agreement according to which EUR 8 322 035 (DKK 62 million) per year would be allocated yearly to a sustained funding stream for SIH provision in Denmark.

To date (July 2011), five clinics have been launched and SIH has been initiated in the municipalities of Copenhagen, Odense, Glostrup, Århus and Esbjerg.

The operating supervised injectable clinics are not seeing an overwhelming demand for their services. Since they became operational in April 2010, 120 patients have started SIH. It is estimated that by the end of 2012, the number of patients in SIH will reach 300 patients. The anticipation is that the clinic in Copenhagen Municipality will be looking after about 120 patients, and each of the remaining four clinics will see about 40 patients.

Belgium

(Translated and compiled from media publication and coverage)

Historical background

In Belgium, methadone substitution treatment was introduced in the late 1980s and buprenorphine was introduced in 2003. However, a royal decree on substitution treatment was adopted only in 2004. In the Dutch-speaking part of Belgium, most methadone maintenance programmes are provided by low-threshold drug services. In the French-speaking part of the country, general practitioners (GPs), outpatient specialist drug units and mental health facilities offer access to methadone, but GPs are the main providers. In 2007, 16 275 drug users were receiving substitute treatment, of whom 15 383 were receiving methadone.

Despite the presence of an extensive drug treatment and care network in Liège, a fraction of severely dependent heroin users is failing to benefit from treatment, experiencing negative health and social consequences. An application to introduce SIH and to develop an injectable maintenance clinic in Liège was relayed to the federal government. In 2007, initial governmental approval was given for SIH to be provided as a scientific experiment and granted the required funding.

The University of Liège is responsible for the scientific evaluation of the SIH treatment initiative. Since June 2007, a research protocol and a clinical project protocol have

been developed, based on the research experience from the SIH RCTs conducted internationally. The SIH trial in Belgium has received ethical approval from the Liège University Ethics Committee and was begun in January 2011.

Description of clinical practice under the trial

SIH treatment in Liège takes place in a purpose-built secure 'issuing clinic'. The treatment of each patient is supervised by a medical team, including an experienced psychiatrist, a GP and a team of nurses.

Medication doses are individually tailored by physicians at the supervised injectable maintenance clinic in consultation with the patient. Additional doses of oral methadone are available to patients on a daily basis.

At treatment entry, the medical team meet with the patient to explain the clinic rules and develop a weekly schedule for clinic attendance. Pharmaceutical heroin (obtained from the Netherlands) is available to patients for supervised self-administration in an injectable or inhalable form.

A pharmacist prepares individual patient medication doses. Nurses give doses to the patients and provide pre- and post-dose assessment, supervision and monitoring, and assistance in case of medical emergency. They also liaise with external treatment and social care service providers and coordinate and follow-up the care of SIH patients.

Patients are free to withdraw from SIH at any time, and the medical team ensure best transition and care continuity within the Liège network of addiction services.

Aims of the SIH treatment pilot project in Liège

The pilot project seeks to add to the existing evidence base for SIH treatment by testing the efficacy of SIH treatment in comparison with optimised oral methadone (OOM), using an RCT design. This study also aims to evaluate the ideal conditions for implementation of this treatment in Belgium.

Number of patients and timescale for the pilot project

It is intended that the study will recruit 200 patients over a 12-month period. Following allocation, patients commence their randomised treatment as soon as possible to avoid early drop-out. Each patient is treated and followed up by an independent research team for 12 months after the start of treatment. Upon completion of the trial period, patients are to be directed by the medical team to another type of existing treatment.

Selection criteria

Participating patients are entrenched heroin users (daily use for at least the last 5 years; injecting or inhaling), ≥ 20 years old and residents of Belgium (or with legal right to stay in the country) who have experienced failed treatment attempts in oral methadone maintenance (OMM) programmes.

Supervision of the project

Management and scientific monitoring and evaluation are entrusted to a research team at the University of Liège.

The clinical protocol has been developed with input from foreign experts in the field, and approved by the medical authorities in the country (Committee on Ethics, Commission Medicale Provinciale, College of Physicians).

In summary of the current clinical practice and service provision of SIH in Europe and Canada, Table 6 gives the prominent characteristics that describe this treatment:

| Country | Number of clinics | Total capacity (range) | Numbers in treatment (as of July 2011) | Catchment area | Number of block opening hours | SIH is part of routine clinical practice |
|-------------|-------------------|------------------------|--|---|-------------------------------|--|
| Switzerland | 23 | 1 454 (15–210) | 1 356 | German-speaking part (22 clinics) and Geneva (1 clinic) | 2–3 | Yes |
| Netherlands | 17 | 745 (20–75) | 650 (1) | Country-wide | 3 | Yes |
| Spain | 1 | 56 | 17 | Granada city | 2 (weekdays only) | No (?) |
| Germany | 7 | 300 (12–70) | 300 | Seven towns across Germany | 2–3 | Yes |
| Canada | 2 | 140–180 | 0 | Vancouver and Montreal | N/A | No (?) |
| England | 3 | 100 (24–40) | 100 | South-east London, Brighton and Darlington | 2 | Yes |
| Denmark | 5 | 300 (40–120) | 120 | Municipalities of Copenhagen, Odense, Glostrup, Århus and Esbjerg | 2 | Yes |

(1) 590 inhaling and 60 injecting.

(?) SIH treatment is available under compassionate use.

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Chapter 7: Conclusions

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Chapter 7: Conclusions

The aim of provision of supervised injectable heroin treatment (SIH) is often misunderstood and the method of provision of the treatment is also frequently described in a confusing manner. One of the important objectives of this Insights publication is to provide a clear account of the aims, the delivery of the treatment and the research findings.

Let us first consider the context for and history of the development of this new and controversial treatment, and then remind ourselves of the aims of treatment, after which we should identify the key consistent research findings, consider the implications for the evolution of policy and practice, and reflect on what the next steps could or should be.

Context and history

Supervised heroin treatment was developed and initially introduced in Switzerland during the 1990s, and subsequently in other European countries and beyond, as summarised in this publication. The approach was an adaptation of the previous heroin treatment which had been prescribed in the treatment of addiction, most notably in the United Kingdom (and hence was often referred to as the 'British system'). However, the significance of the adaptation that was made for the Swiss clinics should not be underestimated — indeed, it could reasonably be argued that this was not merely the next incremental adaptation but was in fact a step change. In this Insights publication, we have concentrated on examining the research evidence and the clinical and policy experience with this new adaptation — supervised injectable heroin treatment.

At first glance, the notion of prescribing diacetylmorphine (pharmaceutical heroin) as a treatment of heroin addiction seems counterintuitive, or at least confusing. How can the drug of addiction itself be the treatment? However, across many areas of the addiction field, we encounter instances where there may be ways in which some degree of provision of the drug of addiction (or a closely related other agonist) may enable people to break with some particularly damaging aspect of their addictive behaviour, and thereby make significant progress in recovery. Examples include the provision of oral opiate substitution treatments (such as oral methadone and sublingual buprenorphine in many countries of the world, and also slow-release oral morphine in Austria, for example), where the provision of the substitution treatment enables significant other changes in behaviour and health to occur. Similarly, with tobacco smoking, the development and provision of a range of nicotine replacement

therapies (gum, tablet and nasal spray) has brought a pharmacological adjunct which leads to better rates of successful quitting of the harmful smoking behaviour. It is because our concern is not only about the physiological or psychological dependence, but is also importantly about the associated health and societal consequences of the heroin use. Thus, it is the reduction of risk of heart disease or stroke or of lung cancer, etc. in the former cigarette smoker which constitutes an important health gain, even while the replacement nicotine supply is maintained. And similarly with the injecting heroin user, it is the quitting of involvement with use of 'street' heroin, disengagement from criminal activities and improvements in health and social well-being which are some of the important gains sought.

Since the original introduction of SIH treatment in the mid-1990s in Switzerland, this clinical approach has been tested as new clinical practice, sometimes in the context of a randomised clinical trial, in more than half a dozen countries across Europe, plus Canada. The research findings from the structured randomised trials are described above, and we also present summaries of the important related clinical and policy experiences in these countries. The purpose is to inform the public debate and to make available a better understanding of the research, clinical and policy experiences to date so that future policymakers and practitioners can be best guided in their decisions.

Many of the data reported here are already available in other forms (such as the original research reports from the individual trials). However, the particular advantage of this Insights publication is that these findings are brought together in a single analysis, and are also accompanied by the clinical and policy perspectives from the relevant countries in which the treatment has recently been provided.

Besides the results of a meta-analysis of the main studies done on SIH treatment, the outcome of a Cochrane Review on this topic also has been included in this publication. A special section helpfully describes the Cochrane review process. Cochrane Reviews are held in high regard in the scientific community, and are primarily concerned with analyses of findings from robustly designed randomised trials which meet the stringent criteria of the Cochrane review process. On the negative side, these reviews have to be, by definition, very selective with respect to studies included owing to methodological shortcomings frequently found in them. Reading results from both our wider review and the Cochrane Review in parallel allows us to combine the strengths of both approaches.

Since the publication of the results from the first randomised trial of SIH in Switzerland (Perneger et al., 1998), there have now been five further randomised

trials of SIH treatment, each of which has been in a different country (Germany, Spain, Netherlands, United Kingdom, Canada) and each of which generally builds on the growing scientific evidence base achieved by the previous work. To quote Isaac Newton (who was himself referring to Greek mythology and the blind giant Orion and his servant Cedalion), it is by standing on the shoulders of giants that each research group has been able to move forward. They have conducted an evolving series of studies, each building on the previous, and each adding a new aspect to our overall understanding. In contrast, the clinical practice has remained remarkably consistent and has, by and large, been replicated from one country to the next so that the series of trials (and the collective clinical experience) can reasonably be considered together.

Other approaches have also been investigated, such as the smokable heroin studied as parallel investigation in the trial in the Netherlands (van den Brink et al., 2003), the injectable hydromorphone studied in the Canadian North American Opiate Medication Initiative (NAOMI) trial (Oviedo-Joekes et al., 2009) and the injectable methadone studied in the UK Randomised Injecting Opioid Treatment Trial (Strang et al., 2010). However, even though these variations may legitimately warrant attention and possible further study, it is with the application of SIH treatment that we find the largest amounts of evidence from well-designed trials and with which we can look for generalisable robust conclusions. Furthermore, it is reassuring that, in this exercise, many of these publications have been judged to be of sufficiently high quality in the peer-review process and that they have appeared in high-impact high-quality scientific journals, such as the *BMJ*, *New England Journal of Medicine* and the *Lancet*.

Aims and objectives

If heroin itself is being prescribed, then what is the objective of the treatment? In fact, the answer to this question is remarkably similar to the answer for other medication-based treatments — it is the quitting of use of ‘street’ heroin, alongside other improvements in physical and psychological well-being, as well as the disengagement from any criminal activity and broader social integration. These might be considered the aims of most addiction treatments, and they are generally the aim of SIH treatment also.

So why do we need to utilise such a potentially controversial treatment approach, if other treatments already exist and are approved, and have the same therapeutic objectives? The answer is that there remains a substantial minority of patients who

fail to benefit from these treatments and for whom we may need to consider more intensive and alternative forms of treatment. For those patients who repeatedly fail with existing orthodox treatments, are they just ‘untreatable’ or might we be able to devise alternative and/or more intensive treatments which enable them to achieve the gains that have, thus far, been unattainable? Hence, this treatment is typically reserved as a second-line treatment (or third-line, etc., depending on the schematic), reserved as an expensive intensive treatment which might be considered for a patient population which otherwise appears unresponsive to conventional treatment. Thus, the typical patient population considered for SIH will be those with a long-standing history of injectable heroin use and an entrenched addiction, with major physical and social complications and who are treatment refractory. In many instances, these patients may have been considered as ‘heartsink patients’ and will often have had previous extensive involvement with the criminal justice system and prison, as well as diverse treatment and rehabilitation agencies.

The findings from these trials of SIH contribute much to the improvement of our understanding of effective treatments for opiate dependence — in particular, what can be achieved with a severely affected treatment population for whom previous treatments had appeared consistently unable to deliver benefit.

Research findings

A consistent finding from this series of randomised trials is of the substantial improvement in health and well-being of the patients receiving SIH compared with those provided with oral methadone treatment. This improvement includes, in particular, a major reduction in the extent of continued injecting of ‘street’ heroin, improvements in general health, psychological well-being and social functioning, as well as major disengagement from criminal activities (such as acquisitive crime to fund continued use of ‘street’ heroin and other street drugs).

Good retention rates are generally seen with SIH. However, evidence of good retention in treatment can only be a benefit if there is a strong relationship between retention and the health and social benefit sought. Better retention rates in the supervised heroin treatment compared with oral methadone were not observed across all trials, although the SIH itself achieves good retention for the different randomised trial periods that were studied (ranging from 6 to 12 months).

While mortality is lower for persons in SIH treatment than for those in oral methadone treatment, the risk of adverse events — including death directly related

to medication — are higher. Even if the absolute numbers are small, this means that precautions have to be taken through adequate staff and equipment in the treatment centre. The substance also requires more efforts on the side of security. This explains to a large extent why treatment costs for heroin treatment are well above methadone even in routine application: EUR 12 700–20 400 per patient per year compared with EUR 1 600–3 500. However, if an analysis of cost utility takes into account all relevant parameters, especially related to criminal behaviour, SIH saves money. Figures from the United Kingdom debate, of EUR 18 300 per year for SIH treatment still compare positively with EUR 50 400 per year for imprisonment (approximate data obtained from different analyses, presented merely to illustrate).

Implications for policy and practice

While SIH has developed to become a useful addition to our treatment ‘toolbox’ for opiate addicts, it seems unlikely to become the solution for the heroin problem. The objective to provide a second-line intervention for hard-to-reach and highly problematic heroin users is reflected by the small number of persons in such treatment. In 2011 all across Europe, only 2 500 clients were enrolled in SIH treatment — approximately 0.5 % of all those enrolled in substitution treatments in Europe. In those countries where application is already well established, these figures were stable at between 5 % and 8 %.

Let us also examine the clinical practice as it is actually delivered. There is strong consistency between countries regarding the delivery and clinical practice of SIH treatment. The treatment is strongly structured, with the patient having to attend for all injected doses, which are taken under direct medical supervision within the clinic. The treatment is also embedded within the provision of wider psychosocial support and rehabilitation, with attention to family reunion, criminal charges and debt, etc., as well as to outstanding health and psychological disorders. In conversation with patients in this treatment, the provision of the prescribed heroin is seen as one component part — perhaps an important part, but just one part nevertheless — and the wider therapeutic engagement and rehabilitative effort is considered to be of equal importance.

Clinical precautions remain vital, however, since occasional life-threatening adverse events are seen, often unexpectedly. While these events are rare, they are enormously important given their severity. These include, in particular, instances of overdose, often for reasons which are not immediately apparent and in a number of cases are very hard to predict even with a carefully applied standard practice of testing. If we consider

these events to be unpredictable (or at least difficult to predict), and if they occur in the region of one in every 6 000 injections, then it is important for clinical teams to be appropriately trained and resourced to deal with such occasional emergencies and for clinical protocols, training and facilities to be established in advance.

The high costs of the provision of this intensive treatment, especially alongside the potentially controversial status of the medication being prescribed (pharmaceutical diacetylmorphine), may be a potentially major limiting factor. The extent to which these factors are obstacles will vary according to the audience considering them and the national and international context. However, it must be remembered that diacetylmorphine is a medicinal product prepared by the pharmaceutical industry in accordance with all of the usual quality and safety controls. Also, the costs have to be compared with the gains and, notwithstanding the greater cost of SIH treatment, the cheaper oral opiate substitution treatments can never be cost-effective for this selected group of heroin addicts if they do not derive the expected benefits from these treatments, as clearly articulated by many observers, including Archie Cochrane himself (1972).

Different pharmaceutical companies are now involved with the production of pharmaceutical diacetylmorphine in Europe, and an overview of the situation is presented in this book. For more than a century, there has been a pharmaceutical industry producing diacetylmorphine, from the late nineteenth century onwards (synthesised in 1874 and brought to market by Bayer in 1898). However, until the 1970s there was not a great deal of interest in the production (with pharmaceutical supply continuing in the United Kingdom). During the 1990s, new Swiss clinics required their own supply of diacetylmorphine, and a new pharmaceutical industry was established; since this time, particularly in recent years, several further companies have established their own supply. As far as we are aware, the active pharmaceutical ingredients of all of these different formulations are exactly the same. However, their preparation in different formulations varies, and this will have a direct bearing on their use within clinical practice of the future according to the fit with the operational practice of the clinics.

Next steps

Where next?

An important clinical and policy step forward has been achieved. A patient population that was previously considered to be resistant to treatment and with whom it appeared impossible to achieve therapeutic benefit has now been found to

be responsive to this intensive SIH. Not all of the refractory heroin addict patients respond to this treatment, and not all will find it acceptable. But for those among whom the benefit is observed, there are major benefits for themselves, their families and society. The challenge will be to establish a viable operational system of provision of this form of treatment in such a way that makes it available to severely affected heroin addicts, while not inadvertently undermining the commitment of other patients to orthodox forms of opiate addiction treatment. Retention in treatment is high for heroin treatment, but field studies showed in some of the countries that after 2 years of treatment about one-third of clients had left, and at least half of them went back to methadone substitution treatment in a better and more stable shape than before.

Other injectable opiate maintenance medications should also be explored further, especially in light of the encouraging preliminary results with supervised injectable hydromorphone seen with the small subset of the Canadian NAOMI trial, but more serious robust study in this area will be required.

Future clinical and research studies are likely to involve further investigation of administration of diacetylmorphine by different possible routes, including the study of heroin by smoking/chasing the dragon (as in the Dutch trial; van den Brink et al., 2003), and also the recent descriptions of the provision of oral heroin (Frick et al., 2006, 2010) as well as the small preliminary report of the potential of intranasal diacetylmorphine (Mitchell et al., 2006). These approaches are also highly relevant because, in some countries, particularly in Spain and the Netherlands, today the majority of heroin users do not use heroin intravenously.

Much has been achieved, and there is still much to be explored — as always. However, it is important to be clear that sufficient knowledge has now been gained from a series of well-designed randomised trials from different groups in different countries to conclude that real clinical benefits can be achieved through the provision of SIH to this patient population that was previously considered untreatable. Future work will build on the success of SIH and include the study of the longer-term outcome of patients receiving this treatment, and potential methods of securing further continuing gains. These will inform future reviews and later editions of this Insights series.

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Statement of interests with potential for conflict

John Strang has contributed to National Treatment Agency/Department of Health English Guidelines on the role of injectable prescribing in the management of opiate addiction (2003; chaired by John Strang), and he also chaired the broader-scope pan-United Kingdom working group when preparing the 2007 'Orange Guidelines' for the United Kingdom Department of Health, providing guidance on management and treatment of drug dependence and misuse. John Strang has separately provided consultancy advice and received honoraria, travel and conference support, and consultancy fees from various pharmaceutical companies including current and potential future suppliers of diacetylmorphine and methadone. John Strang and Nicola Metrebian have previously undertaken research study of British heroin policy and have given varied commentaries and contributed to professional and public debate.

Ambros Uchtenhagen has been mandated to document and evaluate the Swiss cohort study on heroin-assisted treatment by the Federal Office of Public Health. Out of this came a number of (unpaid) scientific publications and (unpaid) presentations at conferences (expenses reimbursed); expert consultation and project participation for the World Health Organization and United Nations Office on Drugs and Crime on substitution treatment for opiate addiction.

Wim van den Brink is chair of the working group that is currently preparing the Netherlands Interdisciplinary Guideline on Opioid Addiction Treatment. He also was the scientific director of the Central Committee on the Treatment of Heroin Addiction (CCBH), which was responsible for the planning, execution and reporting on the Dutch trial on heroin-assisted treatment. Wim van den Brink has separately provided consultancy advice and received honoraria, travel and conference support, and consultancy fees from various pharmaceutical companies including current and potential future suppliers of buprenorphine (Reckitt Benckiser), extended-release naltrexone (Alkermes) and nalmefene (Lundbeck).

Helle Petersen has, on behalf of the National Board of Health (NBH) been responsible for the Danish Guidance on prescribing injectable diamorphine in the management of opiate addiction (NBH 2010) and she is also on behalf of NBH, responsible for the Danish Guidance on management and treatment of opioid dependence and misuse (NBH 2008). Helle Petersen has, as medical advisor for NBH, given varied commentaries and contributed to professional and public debate, but has never received honoraria from any pharmaceutical companies.

Christian Haasen has contributed to the German guidelines on opioid substitution treatment of the German Medical Association and has provided consultancy advice to the German Ministry of Health on the development of the revisions of the Narcotics Law. Christian Haasen has undertaken research evaluation of the German and European drug policy and has given varied commentaries and contributed to professional and public debate. He has also provided consultancy advice and received honoraria, travel and conference support, and consultancy fees from various pharmaceutical companies including current and potential future suppliers of diacetylmorphine and other opioids.

The rest of the authors declare no interests with potential for conflict.

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Glossary

Benzodiazepine: a class of drugs that have a hypnotic and sedative action, and are prescribed mainly as tranquillisers to control symptoms of anxiety, but are also used for recreational purposes.

Cost–benefit analysis: a type of economic evaluation that compares treatment interventions by exploring the relationship between the value of the resources used for each intervention and the value of a single or multiple benefits (e.g. victimisation, criminal justice expenses, lost work due to illness, etc.) produced by the same interventions.

Cost–utility analysis: a type of economic evaluation that compares competing treatment interventions in terms of both quantity and quality of life, expressed by utilities (e.g. cost per quality-adjusted life year).

Diacetylmorphine (the principal psychoactive constituent of heroin): a short-acting opiate agonist. Illicit ('street') heroin may be smoked or solubilised with a weak acid and injected.

Hydromorphone: a centrally acting opioid, derivative of morphine, three to four times stronger than morphine but with a lower risk of dependency.

Intention-to-treat (ITT) analysis: a method of analysing results of a randomised controlled trial that includes in the analysis all those cases that should have received a treatment regimen but for whatever reason did not. All cases allocated to each arm of the trial are analysed together as representing that treatment arm, regardless of whether they received or completed the prescribed regimen.

Liquid chromatography-mass spectrometry: an analytical chemistry technique used for the specific detection and potential identification of chemicals in the presence of other chemicals (in a complex mixture) whereby compounds are separated chromatographically, usually in a mixture of water and organic solvents, before they are introduced to an ion source and mass spectrometer.

Morphine: a naturally occurring alkaloid extracted from opium; a powerful narcotic substance with strong analgesic (painkilling) action and other significant effects on the central nervous system.

Noscopine: a naturally occurring substance, a non-addictive derivative of opium.

Opiate: one of a group of alkaloids derived from the opium poppy (*Papaver somniferum*) with the ability to induce analgesia, euphoria and, in higher doses, respiratory depression and coma. The term excludes synthetic opioids.

Opioid: a generic term applied to alkaloids from the opium poppy (*Papaver somniferum*), their synthetic analogues and compounds synthesised in the body which interact with specific receptors in the brain and have the ability to induce analgesia, euphoria (a sense of well-being) and, in higher doses, respiratory depression and coma.

Opioid agonist: any morphine-like substance that produces effects that mimic the action of the naturally occurring substance, including pain relief, respiratory depression, etc.

Opioid antagonist: a substance (e.g. naloxone, naltrexone) that blocks mu, kappa or delta opioid receptors, used primarily in the treatment of opioid-induced respiratory depression.

Overdose: an accidental or intentional use of any drug in an amount that produces acute adverse physical or mental reactions — transient or lasting — or death; the lethal dose of a particular drug varies with the individual and with circumstances.

Papaverine: a non-addictive opium derivative.

Quality-adjusted life year (QALY): a numerical description of the values, in terms of quantity and quality of life, that treatment clients consider to be gaining during a treatment episode.

Randomised controlled trial (RCT): a study in which people are allocated at random (by chance alone) to receive one of several clinical interventions. One of these interventions is the standard of comparison or control. Someone who takes part in an RCT is called a participant or subject. RCTs seek to measure and compare the outcomes after the participants receive the interventions. The RCT is one of the most powerful tools in clinical research.

Relapse: in addiction, relapse is the resumption of drug use after trying to stop taking drugs. It is a common occurrence in many chronic disorders, including addiction, that requires behavioural adjustments to treat effectively.

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