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DOI:
10.1016/j.drugalcdep.2023.109869

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
McNair, R, Monaghan, M & Montgomery, P 2023, 'Heroin assisted treatment for key health outcomes in people with chronic heroin addictions: A context-focused systematic review', *Drug and Alcohol Dependence*, vol. 247, 109869. https://doi.org/10.1016/j.drugalcdep.2023.109869

Drug and Alcohol Dependence 247 (2023) 109869

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Review

Heroin assisted treatment for key health outcomes in people with chronic heroin addictions: A context-focused systematic review

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ARTICLE INFO

Keywords:
Heroin assisted treatment
Systematic review
Opioid substitution treatment
Chronic heroin use
Health outcomes

ABSTRACT

Background and aims: Randomised controlled trials in Europe and Canada have shown that supervised heroin assisted treatment (HAT) is an effective treatment option for people with long-term heroin addictions for whom the standard opioid substitution treatments (OST) have not been effective. This review aims to evaluate the effectiveness of supervised HAT and analyse the significance of context and implementation in the design of successful HAT programmes.

Methods: PubMed, CENTRAL, Embase, and Web of Science were searched to identify randomised controlled trials (RCT) and systematic reviews evaluating supervised HAT compared to any other OST. Studies were eligible for inclusion if they were published in English, evaluated a supervised form of HAT, and included illegal drug use and/or health as a primary outcome measure. There were no restrictions on publication date. The following outcomes of the included studies were analysed using narrative synthesis and meta-analysis where possible: retention, street drug use, health, and social functioning.

Results: Nine randomised controlled trials spanning eight studies (n = 2331) and three systematic reviews met the inclusion criteria. Seven of the eight studies compared HAT to methadone maintenance treatment (MMT). One study compared HAT to injectable hydromorphone in a double-blind non-inferiority trial. Meta-analysis was performed on pooled results of retention across all included studies and found that HAT has a statistically significant effect on retention [Z = 7.65 (P > 0.0001)]. Five of the eight included studies found that supervised HAT reduces participants' use of illegal drugs more significantly than MMT. Evidence of improved health in participants receiving supervised HAT compared to other OSTs was inconsistent; positive effects were observed in three of the included studies (n = 1626).

Conclusion: When compared to methadone maintenance treatment (MMT), heroin assisted treatment (HAT) more consistently retains people with heroin addictions in treatment and reduces their consumption of illicit drugs.

Trial registration: PROSPERO registration: CRD42022341306.

1. Background

Approximately 31 million people use opiates worldwide (United Nations Office on Drugs and Crime, 2022). In 2017, global opium production was at its highest recorded level (United Nations Office on Drugs and Crime, 2022). Of all drug groups, opiates cause the highest levels of health harms related to deaths and disability adjusted life years (DALYs) (UNAIDS, 2018). Deaths related to opioid addiction in OECD[3] countries have risen by 20% in recent years, emphasising the need for effective treatment programmes that reduce harms related to chronic opioid use (OECD, 2019).

The prescription of diamorphine (medical-grade heroin) as a treatment for heroin dependency - heroin-assisted treatment (HAT) - has been trialled in a number of countries across Europe and North America over the past 40 years (Bell et al., 2018). Randomised controlled trials in Switzerland (Perneger et al., 1998), The Netherlands (van den Brink et al., 2003), Germany (Haasen et al., 2007), Spain (March et al., 2006), Canada (Oviedo-Joekes et al., 2009; Oviedo-Joekes et al., 2016),

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https://doi.org/10.1016/j.drugalcdep.2023.109869
Received 16 January 2023; Received in revised form 31 March 2023; Accepted 31 March 2023
Available online 6 April 2023

England (Strang et al., 2010), and Belgium (Demaret et al., 2015) indicate that HAT administered in supervised, clinical settings can be an effective treatment for long-term, refractory heroin addiction for people who have been unresponsive to standard forms of opioid substitution treatment (OST) (Strang et al., 2015). The potential benefits of supervised HAT and its intended impacts are described in the proposed Theory of Change (Table 1).

Prescribing diamorphine as a treatment for heroin addiction is not a new practice in the UK (Fischer et al., 2007). Starting in the 1920s, doctors could prescribe diamorphine to patients struggling with opioid dependency (Metrebian et al., 2006). Due to the implementation of strict licensing regulations in the 1960s, only a small number of doctors across the country can legally prescribe diamorphine for heroin addiction today (Fischer et al., 2007). Methadone maintenance treatment (MMT) is the primary OST used to treat opioid addiction in the UK and internationally because its effectiveness and safety are well evidenced (Bart, 2012). It remains the recommended first line treatment for people with heroin addictions (NICE, 2007; Bao et al., 2009).

Table 1
Proposed Theory of change of supervised HAT.

PROPOSED THEORY OF CHANGE FOR SUPERVISED HAT PROGRAMMES **Primary treatment population:** middle-aged men who are addicted to heroin and have previously failed to benefit from opioid substitution treatments			
ACTIVITIES	**OUTPUTS**	**OUTCOMES**	**IMPACTS**
The prescription of diamorphine by whatever method (approximately 274.5 mg – 573 mg) plus optional methadone one to three times per day, every day, under the supervision of qualified nursing staff and clinicians The provision of additional psychosocial support services	Number of participants completing treatment	Participants are retained in treatment Participants experience improved health and social functioning Participants reduce their consumption of street drugs	*Individual (primary outcomes)* **Improved health and wellbeing of treatment-resistant heroin addicted individuals** Participants are less likely to experience harm (health issues and disease) when consuming street heroin and are more likely to engage with social services and additional psychosocial interventions that offer further health benefits *Community (secondary outcomes)* **Reduced public costs related to chronic heroin addiction** Participants are less likely to cause harm (engage in criminal activity) when acquiring illicit heroin and other illegal drugs **Improved community cohesion and reduced fear of crime** Participants' public drug use can negatively impact their communities. This can be mitigated through treatment programmes that disincentivize public drug use

In 2019/2020, approximately 261,000 people living in England were using heroin regularly (Adult Substance Misuse Treatment Statistics 2019 to 2020: Report, 2020). Drug addiction is a chronic mental disorder characterised by habitual drug use despite its associated negative consequences (National Institute on Drug Abuse, 2020). Long-term heroin addiction compromises the health of people who use heroin considerably. Premature mortality (Hulse et al., 1999) and increased risk of morbidity, cardiovascular disease, respiratory issues, and blood-borne viruses and infections are common amongst people with heroin dependence (Degenhardt et al., 2011; Black, 2020). Currently, heroin-related deaths in England are at their highest ever, having increased by 70% from 579 deaths in 2012–1213 deaths in 2021 (White and Public Health England, 2016; Breen and Butt, 2022). The social and economic impacts of drug addiction extend far beyond the affected individual; homelessness, over-prescribed social care, and crime are all linked to long-term drug addiction (Black, 2021). Harms related to drug addiction in England are thought to cost over £19 billion (Black, 2020).

People with heroin addictions seeking treatment in the UK are typically treated with methadone or buprenorphine (Clinical Guidelines on Drug Misuse, 2017). Around 5–10% of this population remains addicted following such interventions and an alternative is required (Byford et al., 2013; Gossop et al., 2003). HAT is a treatment option for this treatment resistant population specifically. Intended as a harm reduction programme, HAT delivers approximately 274.5 mg – 573 mg of diamorphine to patients one to three times per day under the supervision of qualified nursing staff and clinicians. Patients receive diamorphine every day during the treatment programme and are often offered optional methadone as well. Due to the cost and high risk of adverse events associated with HAT, Public Health England advises that only patients currently unresponsive to optimised oral OST and who have a history of unsuccessful attempts at treatment should be eligible (GOV.UK, injectable opioid treatment). The successful treatment of this small but significant population is important because the average annual societal cost of an individual with a heroin addiction in the UK is estimated to be approximately £58,000 (Black, 2021).

In the last 20 years, three systematic reviews analysing a total of 10 randomised controlled trials on HAT have been published, including a Cochrane review, which was updated in 2011 (Ferri et al., 2011; Smart and Reuter, 2022; Strang et al., 2015). These reviews have described and summarised strong evidence for the effectiveness of HAT, particularly in regard to retaining participants in treatment and reducing their consumption of illicit drugs. As a result, countries including Denmark, Germany, the Netherlands, Switzerland, and the UK have approved it as a medicinal product and are integrating HAT into local addiction programmes and services (Strang et al., 2012; Uchtenhagen, 2017). Additionally, Norway (University of Oslo, 2021) and Scotland (Heroin-Assisted Treatment to be Provided in Glasgow, 2022) have announced plans to pilot HAT programmes.

Growing support for HAT and a greater understanding of its benefits means that treatment programmes are now launching in countries where trials have not taken place. In the UK, small-scale HAT programmes are being piloted to develop an evidence base supporting the need for its adoption into clinical practice (Poulter et al., 2021). Despite clear evidence of the treatment's effectiveness at reducing participants' illicit drug use, many members of the public are apprehensive of the treatment and unsupportive of HAT programmes opening in their local communities due to fears of the 'honey-pot effect': increased numbers of people who inject drugs moving into the area (Miller et al., 2010). A paper analysing the community impacts of England's first supervised HAT trial in 2010 found no evidence of the 'honey-pot effect' or elevated levels of crime in the community (Miller et al., 2010). It is therefore important to explore questions related to the design and implementation of HAT in addition to its effects, in order to achieve the best possible outcomes for participants, treatment providers, and the public.

2. Research question

Is heroin assisted treatment effective, and if so, to what extent does context and implementation influence its effectiveness?

3. Method

The reporting of this review follows the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). The review was registered with PROSPERO (registration number: CRD42022341306) in July 2022.

3.1. Search strategy

Randomised controlled trials and systematic reviews evaluating supervised HAT were targeted through database searches of PubMed, CENTRAL, Embase, and Web of Science. Databases including ClinicalTrials.gov, ISRCTN, and PROSPERO were also searched for ongoing trials and reviews evaluating HAT. Only titles and abstracts were searched. There were no restrictions on publication year. Searches were optimised for each database and included a combination of the following key words and phrases: "diamorphine assisted treatment", "heroin assisted treatment", "supervised injectable heroin", "heroin addiction", "heroin treatment", "opioid dependency", "opioid", "heroin", "diacetylmorphine", "diamorphine", "treatment", "prescription", "maintenance", "therapy", "randomised controlled trial", "randomised controlled trial", "RCT", "systematic review", "review", and "trial".

3.2. Inclusion and exclusion criteria

Studies were eligible for inclusion if they were randomised controlled trials (RCTs) or systematic reviews evaluating supervised HAT and published in English. The search was limited to RCTs and systematic reviews because of their scientific quality and low probability of bias. Only studies administering HAT in supervised clinical settings were included because supervised HAT is standard clinical practice due to the increased compliance, monitoring, and safety of the design (Injectable Opioid Treatment: Clinical and Operational Elements, 2021; Strang et al., 2012). In addition, only studies reporting on illegal drug use or health as one of their primary outcomes were eligible for inclusion in accordance with the proposed theory of change (Table 1).

Exclusion criteria for the review were: papers presenting interim or duplicate reports on RCTs, studies evaluating participant and community perspectives of the treatment, and earlier editions of updated papers.

3.3. Study selection and data extraction

Study selection was performed by one review author (R.M.) under the supervision of the other two authors' cross-check. The reference manager software, EndNote, was used to store and code the retrieved records. Prior to the screening, all duplicate texts were removed. Titles

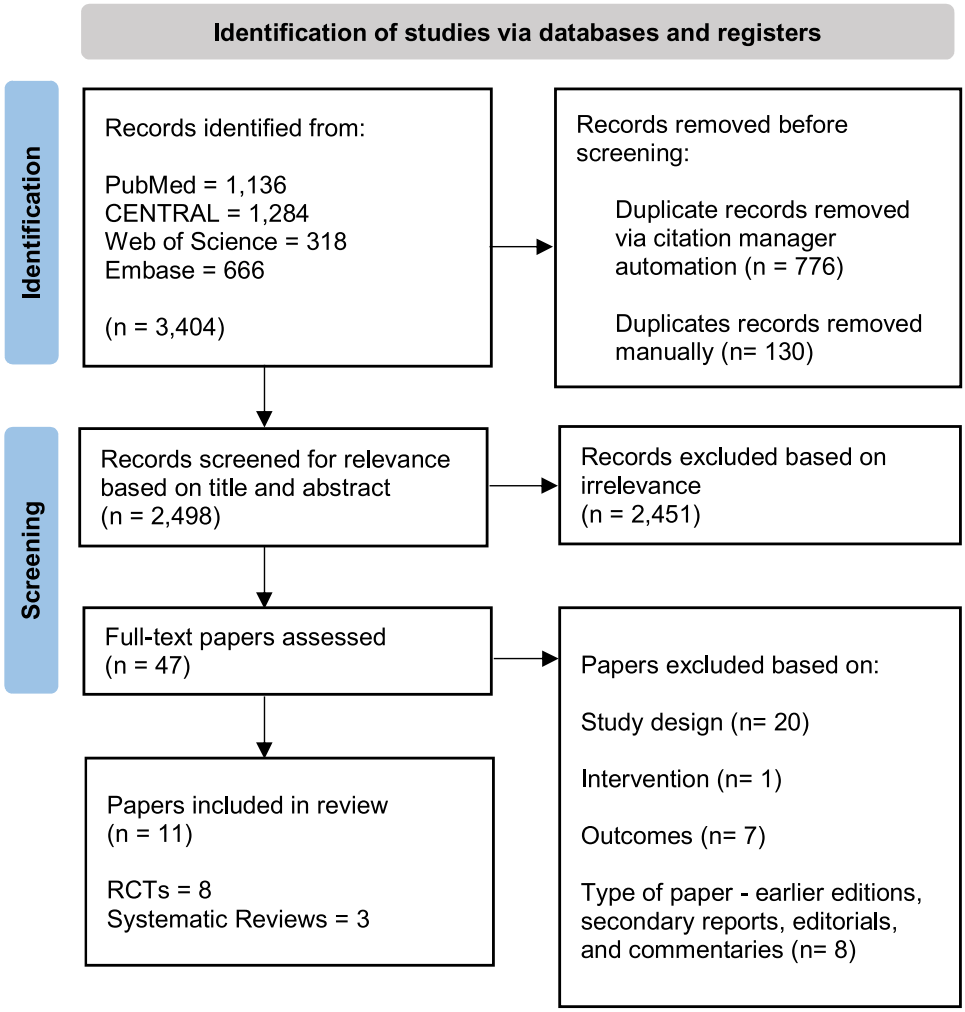

Fig. 1. Selection of studies using the PRISMA flow chart.

and abstracts of the remaining unique texts were then screened for relevance. Full texts of the relevant papers were assessed for eligibility, and data were extracted from all papers that met the inclusion criteria. Reference lists from published reviews were also checked for relevant studies. Data on the following key outcomes were extracted from the included studies: retention, reduction of street drug use, health, social functioning, and criminal activity (Fig. 1).

3.4. Risk of bias assessment

Risk of bias in the included studies was evaluated using the Cochrane risk-of-bias tool for randomised trials (RoB 2) (Revised Cochrane Risk-of-Bias Tool for Randomized Trials (RoB 2), 2019). The RoB 2 tool assesses five domains of bias, which include the randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Observations related to bias are reported in Table 3.

3.5. Data analysis

The PROGRESS-Plus framework was used to identify characteristics that may affect participants access to and experience of HAT (PROGRESS-plus, 2022). The acronym describes the following: place of residence, race/ethnicity, occupation, gender, religion, education, social capital, socioeconomic status, age, disability, and sexual orientation. There are a number of factors related to the context, implementation, and setting of HAT that influence its success, and ultimately, its effectiveness. The Context and Implementation of Complex Interventions (CICI) framework formalises these factors into a structure that allows for a comprehensive analysis of HAT (Pfadenhauer et al., 2017). The CICI framework aims to simplify analyses of the role of context in complex interventions by organising the concept of context into seven different domains, including geographical, epidemiological, socio-cultural, socio-economic, ethical, legal, and political (Pfadenhauer et al., 2017). Elements of the CICI framework were used to interpret the significance of context and implementation in the included studies. Random-effects

Table 2
Characteristics of included studies.

Study	Sample	Intervention	Study Design	Comparator (control)	Setting & Provider	Primary Outcomes	Evaluation Period
Perneger et al. (Switzerland, 1998)	**N=51** T=27 C=24	SIH + oral MMT	Open label RCT	Any available drug treatment *Primarily oral MMT	Outpatient clinic at Geneva University Hospitals in Geneva, Switzerland	Use of illicit heroin and other drugs Health status Social functioning	6 months
van den Brink et al. (The Netherlands, 2003)	**N=549** T1=76 C1=98 T2=117 C2=139 COMP=119	T1) SIH + oral MMT T2) Supervised inhalable heroin + oral MMT	Two open label, multi-site RCTs	Control = Oral MMT Comparison group = Oral MMT alone then oral MMT plus diamorphine	Newly established outpatient clinics with new clinical staff in six cities across the Netherlands MMT was dispensed to the control group in existing treatment locations with existing staff	Physical health Mental status Social functioning Criminal activity	12 months
PEPSA study - March et al. (Spain, 2006)	**N=62** T=31 C=31	SIH + oral MMT	Open label RCT	Oral MMT	Designated outpatient programme at the Virgen de las Nieves Hospital in Granada, Spain	Physical health Quality of life Drug-addiction-related problems Nonmedical use of heroin Risk behaviour for HIV and HCV Psychological, family, and social status	9 months
Haasen et al. (Germany, 2007)	**N=1015** T=515 C=500	SIH + optional oral MMT	Open label, multi-site, RCT	Oral MMT	Outpatient treatment centres in seven German cities: Hamburg, Frankfurt, Hanover, Bonn, Cologne, Munich, and Karlsruhe	Health illegal drug use	12 months
NAOMI study - Oviedo-Joekes et al. (Canada, 2009)	**N=251** T=115 T2=25 C=111	T1) SIH + oral MMT T2) Supervised injectable hydromorphone + oral MMT	Open label, multi-site, RCT	Oral MMT	Outpatient treatment clinics in two Canadian cities: Montreal and Vancouver MMT was dispensed in various clinics and community pharmacies	Retention in treatment Illegal drugs use	12 months
RIOTT study - Strang et al. (England, 2010)	**N=127** T=43 T2=42 C=42	T1) SIH + oral MMT T2) Supervised injectable methadone + oral MMT	Open label, multi-site, RCT	Optimised oral MMT	Outpatient treatment clinics in three cities in England: London, Brighton, and Darlington	Street heroin use Retention in treatment Serious adverse events	6 months
TADAM study - Demaret et al. (Belgium, 2015)	**N=74** T=36 C=38	SIH + oral MMT OR supervised inhalable heroin + oral MMT	Open label RCT	Oral MMT	Newly developed outpatient clinic in Liège MMT dispensed in a partner centre	Street heroin use Health Criminal involvement	12 months
SALOME study - Oviedo-Joekes et al. (Canada, 2016)	**N=202** T=102 C=100	SIH + oral MMT	Double-blind noninferiority trial	Supervised injectable hydromorphone + oral MMT	Outpatient clinic in Vancouver, Canada	Street heroin use	6 months

SIH = supervised injectable heroin | MMT = methadone maintenance treatment.

Table 3
Observations from risk of bias assessment.

Study	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of outcome	Selection of reporting
Perneger et al. (1998)	Low risk	Low risk	Low risk	Some concerns	Some concerns
Van den Brink et al. (2003)	Some concerns	Low risk	Low risk	Some concerns	Low risk
March et al. (2006)	Low risk	Low risk	Low risk	Some concerns	Low risk
Haasen et al. (2007)	Low risk	Low risk	Low risk	Low risk	Low risk
Oviedo-Joekes et al. (2009)	Low risk	Low risk	Low risk	Low risk	Low risk
Strang et al. (2010)	Low risk	Low risk	Low risk	Some concerns	Low risk
Demaret et al. (2015)	Low risk	Low risk	Low risk	Some concerns	Low risk
Oviedo-Joekes et al. (2016)	Low risk	Low risk	Low risk	Low risk	Low risk

meta-analysis was used to analyse pooled results of studies with comparable outcome measures. The statistical analysis was performed using RevMan 5 (RevMan, 2022).

4. Results

Eight studies encompassing nine trials with a total of 2331 participants are included in this review (Perneger et al., 1998; van den Brink et al., 2003; Haasen et al., 2007; March et al., 2006; Oviedo-Joekes et al., 2009, 2016; Strang et al., 2010; Demaret et al., 2015). The studies' characteristics are detailed in Table 2. Three systematic reviews met the inclusion criteria; however, none of these reviews contained trials eligible for inclusion that were not already retrieved by the search. All of the included trials except for one were designed as open label randomised controlled trials comparing HAT to MMT. The most recent trial to be published, the SALOME study, was a double-blind non-inferiority trial comparing HAT to injectable hydromorphone (Oviedo-Joekes et al., 2016). Six of the studies were based in Europe (Perneger et al., 1998; van den Brink et al., 2003; Haasen et al., 2007; March et al., 2006; Strang et al., 2010; Demaret et al., 2015), and two were based in Canada (Oviedo-Joekes et al., 2009, 2016). 77.2% of participants in the eight studies were male, and the mean age of all participants was 38.6 years.

4.1. Participants and design

Each factor in the PROGRESS-Plus acronym can help to identify risk factors in disease burden and the potential for interventions to reduce these differential effects (PROGRESS-plus, 2022). Factors reported by the included studies are described in Table 4.

Overall, the characteristics of participants across the included studies were similar. Participants were predominantly young and middle-aged men with insecure employment and criminal histories. All of the studies except for two (Oviedo-Joekes et al., 2009, 2016) recorded employment at baseline. Across the six studies that recorded employment status, an average of 7.9% of participants were employed when enroled in the treatment programme. Convictions and criminal histories were highly prevalent amongst participants in the four studies that recorded criminal activity at baseline (Haasen et al., 2007; Oviedo-Joekes et al., 2009; Strang et al., 2010; Demaret et al., 2015). In these studies, the average proportion of participants who had convictions, had charges, or were previously incarcerated, ranged from 73.6% to 97%.

Housing status was captured at baseline in six of the studies enclosing a total of 2153 participants (van den Brink et al., 2003; Haasen et al., 2007; March et al., 2006; Oviedo-Joekes et al., 2009, 2016; Demaret et al., 2015). Housing security of participants varied between the studies; however, the two Canadian studies showed similar figures. 61.8% and 72.9% of participants in the Canadian studies were living in unstable housing, whereas participants in the Dutch, Spanish, German, and Belgian studies were predominantly living in secure housing. All of the studies were located in cities or large urban areas. Cities and regions were targeted for HAT based on the prominence of illicit opiate use in the area. Religious beliefs, education, and sexual orientation of participants were not consistently reported across the studies and therefore, not included in the analysis.

The studies' designs varied more noticeably. All of the studies implemented a supervised approach to HAT and delivered a mean daily dose of between 274.5 mg and 573 mg of injectable or inhalable diamorphine to participants one to three times per day, every day. Three studies required participants to engage with additional psychosocial interventions, including psychological counselling, HIV prevention counselling, social work, legal services, psychoeducation, case management, motivational interviewing, and medical reviews (Perneger et al., 1998; Haasen et al., 2007; Strang et al., 2010). There were no

Table 4
Characteristics of participants in the included studies at baseline.

PROGRESS PLUS Factors		*Gender/Sex*	*Age*	*Occupation*	*Socioeconomic status*	*Social capital*
Study	**Sample**	**Gender** *% male*	**Age** *mean* (standard deviation)	**Employment** *% mean in employment*	**Housing** *% mean in non-stable housing*	**Criminal History** *% mean with charges or convictions*
Perneger et al. (1998)	N=51	75% male	31.9	25.5%	-	-
van den Brink et al. (2003)	N=549	80.7% male	39.1	8%	14.2%	-
March et al. (2006)	N=62	90.3% male	37.2 (5.5)	4.8%	21%	-
Haasen et al. (2007)	N=1015	79.8% male	36.4	4.5%	30.5%	96.3%
Oviedo-Joekes et al. (2009)	N=251	61.4% male	39.7 (8.6)	-	72.9%	94.4%
Strang et al. (2010)	N=127	73.3% male	37.2 (6.5)	2%	-	73.3%
Demaret et al. (2015)	N=74	88% male	43 (7)	3%	28%	97%
Oviedo-Joekes et al. (2016)	N=202	69.3% male	44.3 (9.63)	-	61.8%	-

significant differences in outcomes between studies offering additional psychosocial interventions and studies requiring participation in psychosocial interventions.

Sample size and treatment duration constituted the most significant differences between studies. The Swiss study was the smallest with (n=52) participants, while the German study was the largest with (n=1015) participants. Four of the eight studies (van den Brink et al., 2003; Haasen et al., 2007; March et al., 2006; Demaret et al., 2015) were 12 months long and showed more significant differences in retention between treatment and control groups. Retention rates in three (Haasen et al., 2007; March et al., 2006; Demaret et al., 2015) of these four studies were at least 27% higher in HAT compared to the control. The other four studies (Perneger et al., 1998; Oviedo-Joekes et al., 2009, 2016; Strang et al., 2010) were six months or nine months long and showed less significant differences in retention between the treatment and control groups (1–19%).

4.2. Context and implementation

The epidemiological, socioeconomic, socio-cultural, legal, and political aspects of context are important to consider when designing a HAT programme because of the way they interact with the implementation of the intervention. These contextual elements are analysed using the CICI framework in Table 5 (Pfadenhauer et al., 2017).

Participant characteristics form part of the epidemiological and socioeconomic context of an intervention. Participants in the included studies were predominantly unemployed, middle-aged men with criminal histories. A significant portion of participants also had poor mental health. The economic and health status of participants influences both the setting and design of the intervention. To accommodate participants with limited or no income, all of the studies were located in accessible places – urban areas or town centres where participants lived. Four of the studies (van den Brink et al., 2003; Haasen et al., 2007; Oviedo-Joekes et al., 2009; Strang et al., 2010) were multi-site RCTs, implementing treatment programmes in between two and seven different locations. One of these studies (Haasen et al., 2007) found a significant effect of study centre on participants' illicit drug use, indicating that response rates can be affected by setting. All of the trials offered psychosocial interventions, such as legal services, case work, and counselling in conjunction with HAT. Participation in these additional services was a mandatory part of three (Perneger et al., 1998; Haasen et al., 2007; Strang et al., 2010) of the eight studies; however, no significant differences in outcomes were observed.

Four of the studies (Perneger et al., 1998; van den Brink et al., 2003; Haasen et al., 2007; March et al., 2006) involving a total of 1677 participants captured data on involvement in street drug culture, which is an element of the socio-cultural context of HAT. Participation in the 'drug scene' could affect participants' social functioning and retention in treatment. The design of the included trials accounted for this. All of the studies used injection or inhalation as the delivery route for diamorphine, depending on the drug consumption culture in the area and/or participants' individual preferences. Also, diamorphine was delivered to participants between one and three times per day, every day, and participants were able to access small dosages of methadone in addition to the diamorphine as a means of reducing cravings throughout the day, and in turn, the need to source heroin from the illicit drug market.

The legal and political aspects of context influence the implementation of HAT as well. The illegal status of heroin forces people with addictions to engage in illicit activities, which contributes to the harms of long-term heroin addiction. All of the studies delivered diamorphine to participants under the supervision of nurses and clinical staff. The supervised approach to HAT is standard amongst OST programmes because it ensures community safety by eliminating the potential for diamorphine to be diverted to the illicit drug market (Lintzeris 2009). However, this approach has significant costs associated with it, which can affect the implementation and likely success of the treatment (Table 6).

Table 5
Application of the CICI Framework to HAT.

Contextual Aspect	Definition	Influence on Intervention
Epidemiological	The distribution of conditions, the attributable burden of disease, and the determinants of needs in human populations.	• Prevalence of HIV and other long-term health conditions related to prolonged heroin use and unsafe injecting practices exist within the population (Oviedo-Joekes et al., 2009; Strang et al., 2010).
Socioeconomic	A community's economic resources and its population's access to these resources.	• High incidence of mental health disorders, unemployment, and criminal activity exist within the population (Perneger et al., 1998; van den Brink et al., 2003; Haasen et al., 2007; Oviedo-Joekes et al., 2009; Strang et al., 2010; Demaret et al., 2015).
Socio-cultural	Explicit and implicit behaviour patterns, including knowledge, beliefs, conceptions, customs, institutions and any other capabilities and habits acquired by a group.	• Street drug culture is a potential motivator for individuals with heroin addictions to continue using illicit opiates and disengage with treatment programme (Perneger et al.,1998; van den Brink et al., 2003; March et al., 2006; Haasen et al., 2007)
Political	The distribution of power, assets, and interests within a population, as well as the range of organisations involved, their interests, and the formal and informal rules that govern interactions between them.	• Red tape and fears of HAT having a 'honeypot effect' and negatively impacting community safety influences local and national governments' interest in and ability to fund and deliver HAT (Miller et al., 2010; Strang et al., 2010) • Pushback from the local community and high start-up costs related to recruitment, staffing, and health and safety can be prohibitive (Farrell and Hall, 2015; Martins F et al., 2021)
Legal	The rules and regulations that have been established to protect a population's rights and societal interests.	• Many harmful consequences of heroin use stem from the illegal status of street drugs (Perneger et al., 1998) • Heroin is an illegal substance in all European and North American nations • The use of diamorphine in research and clinical settings must be legalised prior to the implementation of HAT programmes (Demaret et al., 2015)

4.3. Outcomes

4.3.1. Effects on retention

Retention rates for HAT across the included studies ranged from 67% (Haasen et al., 2007) to 93% (Perneger et al., 1998). All of the included trials reported on retention. Four of the eight studies (Haasen et al., 2007; Oviedo-Joekes et al., 2009; Strang et al., 2010; Demaret et al., 2015) showed higher retention in the treatment groups compared to the control groups. Three studies (Perneger et al., 1998; March et al., 2006; Oviedo-Joekes et al., 2016) showed no meaningful difference, and one

Table 6
Overview of outcomes and statistically significant effects of supervised HAT compared to other OSTs in the included studies.

Study	Sample	Intervention (s) of interest	Retention	Reduction of illegal drug use	Health	Social functioning
Perneger et al. (1998)	N=51	**SIH + oral MMT** *Mean daily dose of 509 mg + unspecified dose of oral methadone*	0	+	0	+
van den Brink et al. (2003)	N=549	**T1 = SIH + oral MMT** *Mean daily dose of 548 mg + 57 mg of oral methadone a day* **T2 = Supervised inhalable heroin + oral MMT** *Mean daily dose of 509 mg + unspecified dose of oral methadone*	-	NR	+ *	+ *
March et al. (2006)	N=62	**SIH + oral MMT** *Mean daily dose of 274.5 mg + 42.6 mg of oral methadone a day*	0	+	+	0
Haasen et al. (2007)	N=1015	**SIH + optional oral MMT** *Mean daily dose of 442 mg + 8 mg of oral methadone a day*	+	+	+	NR
Oviedo-Joekes et al. (2009)	N=251	**T1 = SIH + oral MMT***Mean daily dose of 392 mg + 34 mg of (optional) oral methadone a day*	+	+	NR	NR
Strang et al. (2010)	N=127	**T1 = SIH + oral MMT***Mean daily dose of 398.9 mg + 41.8 mg of oral methadone a day*	+	+	0	0
Demaret et al. (2015)	N=74	**SIH + oral MMT *OR* supervised inhalable heroin + oral MMT** *Mean daily dose of 573 mg*	+	0 *	0	NR
Oviedo-Joekes et al. (2016)	N=202	**SIH + oral MMT** *Mean daily dose of 506.4 mg + 23.64 mg of oral methadone a day*	0	0	0	NR

+ = positive effect | - = negative effect| 0 = no effect | NR = not reported | * = part of a treatment response index – disaggregated data unavailable | SIH = supervised injectable heroin | MMT = methadone maintenance treatment.

study (van den Brink et al., 2003) showed higher retention in the control group (Fig. 2).

The considerable heterogeneity between studies in the meta-analysis (Fig. 2) may be explained by the designs of the Dutch (van den Brink et al., 2003) and SALOME (Oviedo-Joekes et al., 2016) studies. Participants randomised to MMT in the Dutch study were entitled to admission in HAT after completing the trial, which could have affected retention rates in the control group. This was also a condition of the Spanish study (March et al., 2006), which allowed participants randomised to MMT to access diamorphine under compassionate use after they completed the trial. In the Dutch study, 6% of participants in the experimental group were expelled from treatment for repeatedly violating the programme's rules. This impacted the group's lower retention rate as well.

Overall, retention rates in the Dutch study (van den Brink et al., 2003) were high in both experimental and control groups at 69.9% and 86% respectively. The SALOME study (Oviedo-Joekes et al., 2016) was the only trial to compare injectable HAT to injectable hydromorphone, which might explain its equally high retention rates in both groups of participants. After conducting a sensitivity analysis which involved removing the Dutch and Spanish studies from the meta-analysis due to their designs, the heterogeneity dropped to 69% and the significance of the effect increased.

4.3.2. *Effects on illegal drug use*

The most consistent finding across the included studies was that supervised HAT reduces participants' consumption of illicit drugs by between 13% (Haasen et al., 2007) and 47% (Strang et al., 2010) more than MMT. All of the studies except for the Dutch study reported participants' street drug use as a primary or secondary outcome. Five studies (Perneger et al., 1998; Haasen et al., 2007; March et al., 2006; Oviedo-Joekes et al., 2009; Strang et al., 2010) showed that HAT is more effective than MMT at reducing street drug consumption (total n across these five trials = 1506). Two trials (Demaret et al., 2015; Oviedo-Joekes et al., 2016) with a combined total of 276 participants found similar levels of reduction amongst both treatment and control groups. However, street heroin use was one of three domains reported in a multidomain index as the primary outcome in one of the trials (Demaret et al., 2015), meaning participants' reduction in illegal drug use could not be analysed alone.

4.3.3. *Effects on health and social functioning*

Seven of the eight studies reported on health, either on its own or as part of a treatment response index (Perneger et al., 1998; van den Brink et al., 2003; Haasen et al., 2007; March et al., 2006; Oviedo-Joekes et al., 2016; Strang et al., 2010; Demaret et al., 2015). In these studies, health was defined as physical health, general health, or physical and psychological health. Three of the studies (van den Brink et al., 2003; Haasen et al., 2007; March et al., 2006) (total n = 1626) showed that HAT had a statistically significant effect on health. The other four studies (Perneger et al., 1998; Oviedo-Joekes et al., 2016; Strang et al., 2010; Demaret et al., 2015) (combined n = 454) showed no meaningful difference in health between participants in the treatment and control groups. Social functioning was reported on in four of the included studies; however, only three of these studies (Perneger et al., 1998;

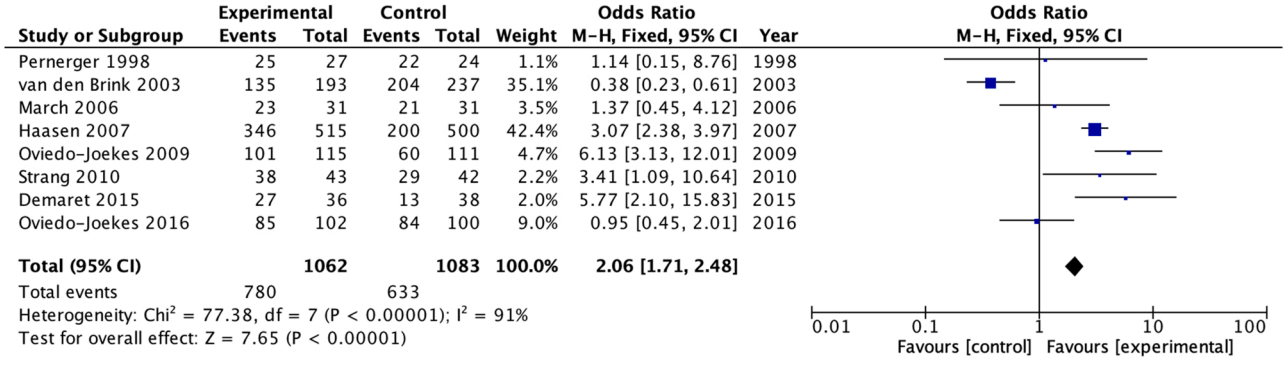

Fig. 2. Meta-analysis of retention in supervised HAT compared to any other OST.

March et al., 2006; Strang et al., 2010) reported social functioning as its own outcome. Of those three studies, the Swiss study (Perneger et al., 1998) was the only one to find a statistically significant positive effect.

5. Discussion

Evidence from eight studies with a total of 2331 participants suggests that supervised HAT is an effective treatment for people with heroin addictions who have previously failed to respond to traditional OSTs, namely MMT. Across the included trials, the most consistent findings were that supervised HAT has a positive effect on treatment retention and reduction of street drug use compared to MMT. These findings were not observed in the study comparing supervised HAT to injectable hydromorphone; however, the study was included in the meta-analyses and narrative synthesis because of its alignment with the intervention's proposed Theory of Change (Table 1). This decision is supported by the results, which suggest that both supervised HAT and injectable hydromorphone effectively retain patients in treatment and reduce their use of street drugs.

Both the consumption and acquisition of heroin from the illicit drug market is associated with significant harms to the individual and the community. Prolonged heroin use poses several health risks to people with heroin addictions, including increased risk of morbidity and premature mortality, cardiovascular disease and respiratory issues, bloodborne viruses, and HIV and Hepatitis C infection (Black, 2020). Heroin addiction is linked to criminal activity too. In the studies that recorded data on participants' criminal histories, over 90% of participants had criminal charges or convictions.

The retention of people with heroin addictions in treatment is important because it provides them with more opportunities to engage with additional psychosocial interventions and support services that can improve their health and wellbeing long-term. In 2020/2021, 51% of people enroled in treatment for drug addiction in England were being treated for opioid dependency (Adult Substance Misuse Treatment Statistics 2020 to 2021: Report, 2021). Only 25% of them completed treatment that year (Adult Substance Misuse Treatment Statistics 2020 to 2021: Report, 2021). People with heroin addictions often struggle with health issues and have less access to economic and social resources that can aid their recovery (Alcohol and Drug Treatment for Adults: Statistics Summary 2017 to 2018, 2018). Providing access to support services such as employment and housing assistance can potentially strengthen the benefits of treatment. Though the health and social functioning benefits of supervised HAT are less consistent, the treatment's ability to retain patients and reduce their use of illicit drugs is well documented. As such, supervised HAT is a promising alternative for the growing number of people with heroin addiction who struggle to engage with treatment.

Analysis of the participants, design, context, and implementation of the included trials has provided some valuable insights on potential strategies for increasing participants' compliance with the intervention. Setting is important to the success of supervised HAT. Retention in treatment groups was high across the included studies (between 67% and 93%), which were all located in accessible, urban areas. The duration of the treatment is equally important; retention in trials lasting 12 months was higher on average than in trials lasting six or nine months. Positive effects were observed in both the injectable and inhalable diamorphine trials suggesting that the method of administration may not be an important dimension of treatment success. Indeed, offering participants a choice of administration route (injectable or inhalable diamorphine) might also help to further increase retention in HAT programmes.

To fully understand the benefits of supervised HAT, consensus amongst researchers in the field needs to be achieved. A lack of consistency in outcomes and measures across the nine trials makes analysis of pooled results challenging. The field would benefit from the development of a core outcome set. This is especially true for reduction of illicit drug use, which could not be meta-analysed due to considerable variation in its measurement across the studies; five studies relied on self-report data from participants at different points in the intervention, and two studies used urinalysis to capture patients' street drug use. Criminal activity was not analysed in this review for the same reasons. A review published by Smart and Reuter in 2021 found that participants in HAT reduce their criminal activity, particularly drug and property-related offences; however, the statistical significance of these reductions varied noticeably across the trials (Smart and Reuter, 2022). Importantly, the German study (Haasen et al., 2007), which is the largest RCT published to date (n = 1015), found more significant reductions in criminal activity amongst participants randomised to HAT compared to those randomised to MMT; the number of participants engaging in criminal activity in the last 12 months dropped from 78.7% to 45.4% in the HAT group and from 79.1% to 62.7% in the MMT group (Löbmann and Verthein, 2009).

Reduction of illicit drug use was the most consistent finding across the studies in this review, and yet a statistical analysis of the combined results could not be performed. This is a significant limitation of this review and reveals a gap in the existing literature on the effectiveness of supervised HAT. Though supervised HAT has been successfully trialled with positive effects in seven different countries, more data are needed for robust analyses of the scope of these effects. In particular, more recent data on the effects of the treatment are needed, as all of the included studies are between five and 25 years' old. Further investigation into the role of context in relation to the physiological impacts of the intervention would be useful for advancing knowledge on best practices for treatment implementation. This is because the implementation of HAT trials and programmes are not without complications. A successful heroin assisted treatment programme in Middlesbrough, UK, is now ending after three years due to a lack of funding (Pioneering Heroin Support Programme in Middlesbrough to End after 3 Years Due to Lack of Funding, 2022).

Future work in this field should prioritise the development and implementation of standardised core outcome measures in trials evaluating the effectiveness of HAT. More data on participants' compliance with the intervention, uptake of additional psychosocial interventions, and experiences of undergoing treatment would also be valuable for determining best practices for the design and implementation of HAT programmes. Furthermore, meta-analyses of participants' illicit drug use, health, and criminal activity in supervised HAT studies would bring much needed clarity on the short- and long-term impacts of the treatment.

CRediT authorship contribution statement

Riley McNair: Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Mark Monaghan:** Funding acquisition, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Paul Montgomery:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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