Evidence on the Effectiveness of Heroin-Assisted Treatment

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Methadone, a full opioid agonist, is the most studied pharmacotherapy for opioid use disorder (Sharma et al., 2017). Oral liquid methadone, administered in regulated clinics, has been a leading medication treatment for opioid dependence in the United States since the early 1970s. As a full opioid agonist, methadone has a high affinity for opioid receptors, i.e., methadone competes with other opioids to activate the (primarily mu) opioid receptors. A large advantage of methadone to heroin and other illicit opioids is its long duration of action or half-life. A single "adequate" dose will activate opioid receptors for a full day or more – versus a few hours of activation by heroin. This allows users to stabilize over time – and fits well into a daily medication treatment regimen. Methadone is an effective substitute for other opioids in that it requires only once daily dosing and builds opioid receptor tolerance; however, because it is a full opioid agonist, withdrawal from methadone can be very difficult, and the possibility of overdose is always a consideration.

Nonetheless, not all patients are successfully recruited or retained in these medication therapies, and research has indicated that individuals with heroin use disorder – most of whom inject heroin – may face particular challenges in terms of treatment retention and treatment outcomes, in part due to higher rates of co-occurring mental and physical health problems, unemployment, and history of interaction with the criminal justice system (Bart, 2012; Cousins et al., 2016; Krebs et al., 2017; Moore et al., 2007; Wu et al., 2011).

As a treatment option for individuals with chronic heroin dependence who have not responded to traditional medication therapies, several countries have experimented with offering pharmaceutical-grade heroin as treatment for opioid use disorder. Today, heroin-assisted treatment (HAT) is available in 58 clinics across eight countries, with four countries offering

HAT as part of the standard treatment system (Uchtenhagen, 2017). With the dramatic rise in overdose mortality related to heroin and synthetic opioids, there has been increased attention to the role of innovative harm reduction programs for combatting the rising social costs of the opioid crisis (Ciccarone, 2017). This has included calls for action by both researchers and policymakers to expand access to conventional medication treatments for opioid use disorder as well as alternative therapies such as injectable heroin or hydromorphone (Fairbairn et al., 2017; 2017; Lavitt, 2015). While evidence from European countries and Canada have supported the potential benefits of HAT, the treatment remains controversial, with a range of concerns regarding therapeutic, social, and economic aspects (Uchtenhagen, 2017).

The purpose of this study is to provide a comprehensive overview of existing scientific evidence for HAT through a systematic review of the literature. We adopt a structured approach to review a range of outcomes, broadly classified as patient-level, community-level, and economic. We begin with an overview of systematic reviews regarding HAT efficacy for patient-level outcomes. This overview is complemented by discussion of evidence from source randomized controlled trials (RCT) studies contributing to the included reviews and supplementary evidence from additional studies captured through our literature search. While we prioritize RCT evidence for our review of HAT's comparative effectiveness for patient-level outcomes, we adopt broader inclusion criteria to provide narrative reviews synthesizing existing evidence on community-level and economics outcomes associated with HAT.

Figure 1. Flow diagram of studies included in review of heroin-assisted treatment literature

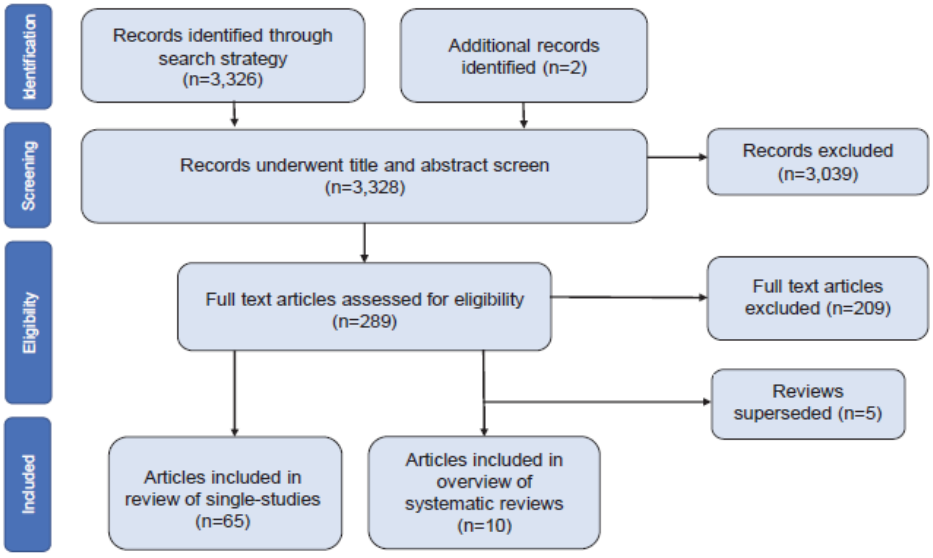

Table 2. Included Articles, by Outcome Domain

	Patient-level	Community-level	Economic
Number of included systematic reviews	10	0	3
Number of included individual articles [a]	55	5	7
Number of included source articles	25	N/A	4
Number of included supplementary articles	30	5	3

Notes: [a]One article spans all three outcome domains.

Table 3. Summary Table of Scope of Included Systematic Reviews for Patient-Level Outcomes

Review (Year)	Years Search Covered	# (HAT) Studies Included	HAT study method eligibility
Egli et al. (2009)	1960 – 2009	46 (6)	RCTs, quasi-experimental studies, & pre-post studies
Dalsbo et al. (2010)	2005 – Mar 2010	8 (8)	High-quality systematic reviews & more recent RCTs
Ferri et al. (2011)	Until Nov 2009	8 (8)	RCTs
Koehler et al. (2014)	Not stated	14 (8)†	Controlled evaluations in Europe (any European language)
Fingleton et al. (2015)	1996 – 2011	22 (4)	RCTs & national cohort studies with follow-up of at least 12 months (English language)
Perry et al. (2015)	Until May 2014	14 (1)	RCTs
Strang et al. (2015)	Not stated	6 (6)	RCTs of supervised injectable heroin treatment (English language)
Timko et al. (2016)	2010 – 2014	55 (6)	Comparative studies (English language)
Ali et al. (2017)	2010 – Jun 2016	5 (2)	Intervention-based RCTs with methadone as comparator

Notes: HAT = Heroin assisted treatment. †Numbers listed here disagree with Table 1 of Koehler et al. (2014), which suggests 15 studies (10 HAT). We consider the Dutch trials as two instead of three separate studies, consistent with prior literature. Additionally, Koehler et al. (2014) appears to incorrectly list one study of dihydrocodeine (Robertson et al., 2006) as a study of HAT.

Table 4. Overview of Heroin-Assisted Treatment Randomized Controlled Trials

Trial (period)	Intervention condition (T)	Control condition (C)	Sample size	Duration (months)
Early UK trial (1972–1975)	Unsupervised injectable HAT + oral methadone	Oral methadone	T: 44 C: 52	12
Swiss trial (1995–1996)	Supervised injectable HAT + oral methadone	Other conventional drug treatment	T: 27 C: 24	6
Injectable Dutch trial* (1998-2001)	Supervised injectable HAT + oral methadone	Oral methadone	T: 76 C: 98	12
Inhalable Dutch trial* (1998–2001)	**T1**: Supervised inhalable HAT + oral methadone **T2**: Oral methadone for 6mo then inhalable heroin + optional oral methadone for 6mo	Oral methadone	T1: 117 T2: 119 C: 139	12
Spain PEPSA (2001–2004)	Supervised injectable HAT + oral methadone	Oral methadone	T: 31 C: 31	9
German study* (2002–2004)	Supervised injectable HAT + oral methadone and: **T1**: psychoeducation & counseling **T2**: case management & motivational interviewing	Oral methadone plus: **C1**: education & counseling **C2**: case management/MI	T1: 258 T2: 257 C1: 255 C2: 245	12
Canada NAOMI* (2005–2008)	**T1**: Supervised injectable HAT + oral methadone **T2**: Supervised injectable hydromorphone + oral methadone	Oral methadone	T1: 115 T2: 25 C: 111	12
UK RIOTT* (2005–2008)	**T1**: Supervised injectable HAT + oral methadone **T2**: Supervised injectable methadone + oral methadone	Optimized oral methadone	T1: 43 T2: 42 C: 42	6
Belgium TADAM (2011–2013)	Supervised injectable or inhalable HAT + oral methadone	Oral methadone	T: 36 C: 38	12
Canada SALOME (2011–2013)	Supervised injectable HAT + oral methadone	Supervised injectable hydromorphone + oral methadone	T: 102 C: 100	6

Notes: *Multi-site study. HAT=heroin-assisted treatment.

The purpose of these RCTs has not been to evaluate the potential for HAT to serve as a first- line treatment option or as a replacement for oral methadone. Instead, trials have largely focused on testing the effectiveness of HAT for a particular group of treatment-refractory individuals with a history of chronic heroin dependence and multiple prior attempts at conventional treatment modalities, primarily oral methadone. Most RCTs have thus had relatively stringent participant eligibility requirements that differ from those required to participate in conventional behavioral or medication treatments for opioid use disorder.

While there is some variation across the trials, participants have tended to be over age 35 and male; with a heroin use history that spans more than one decade; and at least three prior attempts at treatment for opiate dependence, primarily methadone.

Table 5. Baseline Characteristics of Participants in HAT Randomized Controlled Trials

Trial (# Participants)	Average Age	% Male	Average Duration Drug Use (Years)	Prior Treatment (Average or %)
Early UK RCT (n=96)	23.9	75%	Opiates: 5.9 Misuse of non-opiates: 8.2	Not stated
Swiss RCT (n=51)	31.9	75%	Injected heroin: 12	# drug treatment episodes: 8 # methadone treatment episodes: 3.2

Injectable Dutch trial (n=174)	38.5	82.2%	Heroin: 15.9 Cocaine: 16.6	Years regular methadone use: 12.1
Inhalable Dutch trial (n=375)	39.6	79.7%	Heroin: 16.7 Cocaine: 14.6	Years regular methadone use: 12.4
Spanish PEPSA (n=62)	37.2	90.3%	Heroin: 19	# methadone treatment episodes: 3.1
German RCT (n=1015)	36.4	79.9%	Heroin: 13.6 Cocaine: 5.5 Benzodiazepines: 5.2	Any medication treatment: 89.3%
Canadian NAOMI (n=251)	39.7	61.4%	Injected drugs: 16.5	# drug treatment episodes: 11.1 # methadone treatment episodes: 3.2
UK RIOTT (n=127)	37.2	73.4%	Opiates: 16.5 Injected drugs: 13.7	# treatment episodes: 4.4
Belgian TADAM (n=74)	43.0	87.8%	Heroin: 20	# treatment episodes: 9
Canadian SALOME (n=202)	44.3	69.3%	Injected heroin: 15.4	# methadone treatment episodes 5.1

Notes and sources: Descriptive statistics were reproduced or calculated based on a combination of articles included in our literature review

Table 6. Details of Treatment Conditions in Heroin-Assisted Treatment Randomized Controlled Trials

Trial	HAT intervention dosage		Control dosage
	Heroin dose/day	Oral methadone dose/day	Oral methadone dose/day
Early UK	Average: 60 mg Range: 30-120 mg	Unspecified	Average: 60 mg Range: 10-120 mg
Swiss trial	Average: 509 mg Quartiles: (400, 480, 630 mg)	Unspecified	Unspecified
Dutch injectable & inhalable trials	Average: 444.1 mg 95% CI: 357.4-530.7 mg Visits/day: average 1.7 in last month of treatment	Average: 58.3 mg 95% CI: 46.5-70.1 mg Max imposed: 150 mg	Average: 59.9 mg 95% CI: 55.2-64.5 mg Max imposed: 150 mg

	Max imposed: 1000 mg		
Spain PEPSA	Average: 274.5 mg Range: 15-600mg	Average: 42.6 mg Range: 18-124 mg	Average: 105 mg Range: 40-180mg
German study	Average: 442 mg	Average (days received): 39 mg Average (all days): 8 mg	Average: 99 mg Min imposed: 60 mg
Canada NAOMI	Average (no methadone): 392.3 mg Average (w/ methadone): 365.5 mg Max imposed: 1000 mg	Average: 34.0 mg	Average: 96.0 mg
UK RIOTT	Average: 398.9 mg SD: 163.6 mg Max imposed: 900 mg	Average: 41.8 mg SD: 12.7 mg	Average: 107.3 mg SD: 39.9 mg Doses >100 mg generally encouraged
TADAM	Average: 573 mg Visits per day: 2.3	Average: 20 mg	Average: 77 mg
SALOME	Average total-dose: 506.4 mg Range: 51-933.2 mg Max imposed: 1000 mg Visits per day: 2.5	Average (days received): 23.6 mg	**Injectable hydromorphone:** Average total-dose: 261.18 mg Range: 82.65-497.85 mg Visits per day: 2.3

Notes: Statistics compiled from a variety of articles included in the systematic review.

Given the shorter half-life of heroin, participants receiving supervised heroin could generally visit clinics up to three times daily to receive an injection. In all trials, the HAT participants were also given the opportunity to take home oral methadone in order to stave off withdrawal symptoms. In control groups receiving oral methadone, participants generally had to visit the clinics once in the morning to receive methadone. Participants in the RCTs have been offered a range of medical and psychosocial services in addition to study medications. Thus, while the objectives of HAT provision have been similar across all RCTs, the results of this review should be considered in light of heterogeneity in the context, design, and implementation of the trials (Fischer et al., 2007).

As shown in Table 7, the nine systematic reviews draw on a relatively small number of original studies. While the nine reviews considered evidence from 25 different articles, those 25 articles were based on just nine RCTs of HAT and four non-RCT studies.

Table 7. Overlap of Heroin-Assisted Treatment Studies Included in Systematic Reviews of Patient-Level Outcomes, by Outcome

	Illicit Drug Use					Treatment Retention				Criminal Activity					Social or Health Function				Adverse Events			Death		
	Dalsbo et al. (2010)	Ferri et al. (2011)	[illegible] (2014)	Strang et al. (2015)	Ali et al. (2017)	Dalsbo et al. (2010)	Ferri et al. (2011)	Strang et al. (2015)	Timko et al. (2016)	Egli et al. (2009)	Ferri et al. (2011)	[illegible] (2014)	Perry et al. (2015)	Ali et al. (2017)	Dalsbo et al. (2010)	Ferri et al. (2011)	[illegible] (2015)	Ali et al. (2017)	Dalsbo et al. (2010)	Ferri et al. (2011)	Strang et al. (2015)	Dalsbo et al. (2010)	Ferri et al. (2011)	Strang et al. (2015)
RCT Studies																								
UK (1970s): Unsupervised injectable HAT	X	X	X			X	X			X	X	X			X	X						X	X	
Swiss (95-96): Supervised injectable HAT	X	X	X	X		X	X	X		X	X	X			X	X	X					X	X	X
Netherlands (98-01):* Supervised injectable HAT		X	X	X		X				X	X	X									X	X	X	X
Netherlands (98-01):* Supervised inhalable HAT		X	X			X				X	X	X										X	X	
Spain (2003-04): Supervised injectable HAT	X	X	X	X		X	X			X	X	X			X	X	X		X	X	X	X	X	X
Germany (2002-04) * Supervised injectable HAT	X	X	X	X		X	X	X	X	X	X	X	X			X	X		X		X	X	X	X
Canada (2005-08):* Supervised injectable HAT	X	X		X		X	X	X	X		X				X	X	X		X	X	X	X	X	X
UK RIOTT (2005-08):* Supervised injectable HAT	X	X		X	X	X	X	X	X										X	X	X	X	X	X
Belgium (2011-13): Supervised injectable HAT					X									X				X						
Non-RCT Studies																								
UK: McCusker and Davies (1996)			X									X												
UK: Metrebian (2001)			X									X												
Swiss: Killias et al. (1999)										X														
Netherlands: Blanken et al. (2010a)									X															
# Studies	6	8	8	6	2	8	6	4	4	6	7	8	1	1	2	5	4	1	4	3	5	8	8	6
# RCTs	6	8	6	6	2	8	6	4	3	5	7	6	1	1	2	5	4	1	4	3	5	8	8	6

Notes: *Multicenter or multi-site randomized controlled trials (RCTs).

The most commonly studied patient-level outcomes were criminal activity or criminal offenses (Ali et al., 2017; Egli et al., 2009; Ferri et al., 2011; Koehler et al., 2014; Perry et al., 2015) and illicit drug use (Ali et al., 2017; Dalsbo et al., 2010; Ferri et al., 2011; Koehler et al., 2014; Strang et al., 2015), followed by treatment retention (Dalsbo et al., 2010; Ferri et al., 2011; Strang et al., 2015; Timko et al., 2016) and social or health functioning (Ali et al., 2017; Dalsbo et al., 2010; Ferri et al., 2011; Fingleton et al., 2015). Three reviews evaluated evidence for effects on serious medical adverse events and mortality (Dalsbo et al., 2010; Ferri et al., 2011; Strang et al., 2015).

Treatment Retention

Four of the nine systematic reviews evaluated the effectiveness of heroin-assisted treatment on retention in treatment (Dalsbo et al., 2010; Ferri et al., 2011; Strang et al., 2015; Timko et al., 2016), where retention was defined as having remained in treatment by the end of the trial period. These four reviews spanned eight RCTs and one prospective cohort study. Study arm length among the included RCTs ranged from 6 to 12 months, while the prospective cohort study assessed four-year treatment retention among HAT patients with no comparator.

Table 8. Comparison of Heroin-Assisted Treatment versus Control Treatments from Source Studies, Retention in Treatment

Experimental v Control Condition	Included in Review:				Experimental	Control	
Study: Treatment Duration	**Dalsbo**	**Ferri**	**Strang**	**Timko***	**Events/Total**	**Events/Total**	**RR [95% CI]**
Unsupervised injectable heroin v oral methadone							
Early UK trial: 12 months		X			32 / 44	15 / 52	2.52 [1.59, 4.01]
Early UK trial: 12 months	X				31 / 44	13 / 52	2.82 [1.70, 4.68]
Supervised injectable heroin (+ oral methadone) v other drug treatment							
Swiss trial: 6 months		X			27 / 27	22 /24	1.09 [0.95, 1.26]
Swiss trial: 6 months	X		X		25 / 27	22 / 24	1.01 [0.86, 1.19]
Supervised injectable heroin (+ oral methadone) v oral methadone							
German trial: 12 months	X	X	X		346 / 515	200 / 500	1.68 [1.48, 1.90]
NAOMI: 12 months		X			77 / 115	45 / 111	1.65 [1.27, 2.14]
NAOMI: 12 months	X		X		101 / 115	60 / 111	1.62 [1.35, 1.95]
UK RIOTT: 6 months	X	X	X	X	38 / 43	29 / 42	1.28 [1.02, 1.61]
Spain PEPSA: 9 months	X	X			23 / 31	21 / 31	1.10 [0.80, 1.51]
Dutch injectable trial: 12 months	*X*				*55 / 76*	*83 / 98*	*0.85 [0.73, 1.01]*
Supervised inhalable heroin (+ oral methadone) v oral methadone							
Dutch inhalable trial: 12 months	*X*				*80 / 117*	*121 / 139*	*0.79 [0.68, 0.90]*
Supervised injectable heroin (+ oral methadone) v supervised injectable hydromorphone (+ oral methadone)							
NAOMI: 12 months				X	101 / 115	22 / 25	1.00 [0.85, 1.17]
Supervised injectable heroin (+ oral methadone) v supervised injectable methadone (+ oral methadone)							
UK RIOTT: 6 months				X	38 / 43	29 / 42	1.09 [0.91, 1.31]

Notes: *As Timko et al. (2016) presented rates but not risk ratios, information on counts was drawn from our review of the source studies, from which we calculated risk ratios and 95% confidence intervals.

Three of the source studies comparing supervised injectable heroin to oral methadone found that HAT was significantly more effective for retaining patients in treatment. In the large German trial (Haasen et al., 2007), 67% of the HAT group completed 12 months of treatment whereas only 40% of the methadone group did. The average number of treatment days was also higher, at 290 days compared to 195 days. In the Canadian NAOMI trial (Oviedo-Joekes et al., 2009a), treatment retention rates at 12-month follow-up in the heroin group were 88%, significantly higher than the 54% rate in the methadone group. Finally, the UK RIOTT trial

(Strang et al., 2010), which had a shorter treatment duration of 6 months, similarly showed higher treatment retention for injectable heroin relative to oral methadone, although differences between the groups (81% vs. 69%) were smaller than in the trials with longer treatment duration. The two trials finding insignificant treatment retention differences between supervised injectable heroin and other treatments (primarily oral methadone) were smaller studies and had treatment durations less than 12 months.

Illicit drug use

Five of the nine systematic reviews evaluated the comparative effectiveness of HAT for reducing illicit drug use (Ali et al., 2017; Dalsbo et al., 2010; Ferri et al., 2011; Koehler et al., 2014; Strang et al., 2015). However, because Koehler et al. (2014) grouped HAT with a variety of other treatment modalities for the outcome of illicit drug use, we exclude that review. The four remaining reviews spanned nine RCTs. Two (Ali et al., 2017; Strang et al., 2015) examined illicit or "street" heroin use as a specific outcome, and two evaluated illicit drug use more broadly with discussion of changes in illicit heroin use where applicable (Dalsbo et al., 2010; Ferri et al., 2011).

All four found HAT was more effective than oral methadone for reducing illicit heroin use, although the reviews interpreted these findings with varying degrees of certainty.

As outlined in **Table 9,** only one study comparing HAT to oral methadone found no significant difference between the two groups for changes in illicit opiate use. Namely, the early UK trial allowing unsupervised injectable heroin showed no significant difference for the outcome of daily average of illicit opioid use during the past 12 months, measured by interviews and regular urine samples taken over the trial.

Table 9. Comparison of Heroin-Assisted Treatment to Control Treatment Condition among Source Studies Included in Systematic Reviews, Findings for Illicit Drug Use

Experimental v Control		Experimental		Control		Findings
Study: Follow-up	**Illicit drug use measure**	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**	
Unsupervised injectable heroin v oral methadone						
Early UK trial: 12 months	(Near) daily use illicit opiates in past month:	NR	27 / 42	NR	27 / 46	p > 0.05
	Non-opiate substance use (primarily barbiturates and amphetamines)	NR	NR	NR	NR	p > 0.05
Supervised injectable heroin (+ oral methadone) v other drug treatment						
Swiss trial: 6 months	Daily use in past month: Street heroin	27 / 27	1 / 27	19 / 21	10 / 21	p = 0.002
	Other opiates	2 / 27	0 / 27	1 / 21	0 / 21	p = 1.00
	Alcohol	6 / 27	5 / 27	3 / 21	4 / 21	p = 1.00
	Tobacco	25 / 27	26 / 27	21 / 21	20 / 21	p = 1.00
	Cannabis	6 / 27	4 / 27	1 / 21	3 / 21	p = 0.49
	Cocaine	1 / 27	1 / 27	2 / 21	2 / 21	p = 1.00
	Barbiturates	4 / 27	2 / 27	3 / 21	3 / 21	p = 1.00
	Benzodiazepines	12 / 27	0 / 27	9 / 21	7 / 21	p = 0.049
Supervised injectable heroin (+ oral methadone) v oral methadone						
Dutch trial: 12 months	Average days illicit heroin use during past month[≠]	Mean difference (HAT–methadone): –13.0 days; 95% CI: [–16.3, –9.6]				p < 0.05
Spain PEPSA: 9 months	Days street heroin use in past month: Mean (standard deviation)	24.5 (8.6)	8.3 (10.5)	23.3 (10.5)	16.9 (12.0)	p = 0.020
German trial: 12 months	>50% negative specimens for street heroin and no increase in cocaine use in the past month	NR	356 / 515	NR	276 / 500	p < 0.001

NAOMI: 12 months	Use street heroin at least one day of past month	NR	54 / 115	NR	79 / 111	p < 0.05
	Average days illicit heroin use in past month	26.6	5.3	27.4	12.0	p < 0.001
	Average days cocaine use in past month[†]	17.5	17.5	15	14	p > 0.05
UK RIOTT: 6 months	>50% negative specimens for street heroin over past 12 weeks	NR	28 / 43	NR	8 / 42	p < 0.001
	Zero positive specimens for street heroin over past 12 weeks	NR	5 / 43	NR	1 / 42	p = 0.100
	Self-reported abstinence from street heroin in past month	NR	22 / 43	NR	7 / 42	p = 0.001
Supervised injectable heroin or methadone (+ oral methadone) v oral methadone						
UK RIOTT: 6 months	>=50% negative specimens for street heroin over past 12 weeks	NR	28 / 43	NR	14 / 42	p = 0.003
Supervised injectable or inhalable heroin (+ oral methadone) v oral methadone						
Belgium TADAM: 12 months	Average days illicit heroin use in past month	27 days	8 days	28 days	16 days	p < 0.001
	With use of cocaine in past month	14 / 36	NR	20 / 38	NR	p > 0.05
	With use of benzodiazepine in past month	18 / 36	NR	13 / 38	NR	p = 0.022
Supervised inhalable heroin (+ oral methadone) v oral methadone						
Dutch trial: 12 months	Average days illicit heroin use during past month[‡]	Mean difference (HAT–methadone): –13.9 days; 95% CI: [–16.6, –11.2]				p < 0.05

Notes: NR=Not reported. [‡]Estimates were not directly reported in the source study but were provided in Ferri et al. (2011). [†]Estimates were not directly reported in the source study but were shown in figures; hence, the estimates in this row are approximate based on visual inspection of the figures.

Criminal offenses

Five of the systematic reviews considered criminal activity or criminal offenses as an outcome (Ali et al., 2017; Egli et al., 2009; Ferri et al., 2011; Koehler et al., 2014; Perry et al., 2015). In all, the five reviews spanned eight heroin-assisted treatment RCTs, plus findings from three non-RCT studies – one case-control study, one observational study, and one pre-post study. Four of the reviews concluded that HAT plus optional oral methadone showed significant benefits relative to oral methadone in terms of reducing criminal activities and criminal justice involvement, while one found uncertain effects.

Table 10. Comparison of Heroin-Assisted Treatment to Control Treatment Condition among Source Studies Included in Systematic Reviews, Findings Criminal Offenses

Experimental v Control		Experimental		Control		Findings
Study: Follow-up point	Criminal activity measure	Baseline	Follow-up	Baseline	Follow-up	
Unsupervised injectable heroin v oral methadone						
Early UK trial: 12 months	Crime as source of income, past year	NR	15 / 42	NR	16 / 46	Not stat sig
	Crime a major income source, past year	NR	18 / 42	NR	28 / 46	Not stat sig[a]
	Any arrest over past year	NR	22 / 42	NR	33 / 46	$p < 0.05$
	Incarceration/imprisonment in past year	NR	8 / 42	NR	15 / 46	$p < 0.05$
Supervised injectable heroin (+ oral methadone) v other drug treatment						
Swiss trial: 6 months	Charged in past 6 months: Any	20 / 27	5 / 27	7 / 21	12 / 21	$p < 0.001$
	Drug use/possession	11 / 27	3 / 27	2 / 21	8 / 21	$p = 0.008$
	Drug dealing	7 / 27	0 / 27	1 / 21	2 / 21	$p = 0.067$
	Property/theft	7 / 27	1 / 27	2 / 21	5 / 21	$p = 0.015$

	Aggression	3 / 27	1 / 27	1 / 21	1 / 21	p = 1.00
	Traffic offense	2 / 27	0 / 27	1 / 21	0 / 21	p = 1.00
	Other	3 / 27	0 / 27	0 / 21	3 / 21	p = 0.10
	Commercial sex past 6 months	4 / 27	3 / 27	2 / 21	2 / 21	p = 1.00
Supervised injectable heroin (+ oral methadone) v oral methadone						
Dutch trial: 12 months	Average days illicit activities, past month	Mean difference (HAT – methadone): −5.81 95% CI: [−8.68, −2.94]				p < 0.05
Spain PEPSA: 9 months	Days per month involved in illegal activities: Mean (SD)	11.5 (13.2)	0.6 (1.6)	8.0 (11.0)	4.1 (8.6)	Absolute diff, p=0.096
German trial: 12 months	Self -reported criminal activity, past year:					
	Any	406 / 515	234 / 515	396 / 500	314 / 500	p < 0.05
	Drug offenses	342 / 515	171 / 515	328 / 500	238 / 500	p < 0.05
	Violent crime	92 / 515	53 / 515	100 / 500	70 / 500	Not stat sig
	Property crime/damage	208 / 515	119 / 515	223 / 500	181 / 500	p < 0.05
	Fraud	106 / 515	38 / 515	120 / 500	53/ 500	Not stat sig
	Police-recorded criminal activity, past yr:					
	Any	224 / 419	173 / 419	206 / 406	209 / 406	p < 0.05
	Drug offenses	162 / 419	122 / 419	143 / 406	147 / 406	p < 0.05
	Violent crime	36 / 419	28 / 419	31 / 406	35 / 406	Not stat sig
	Property crime/damage	134 / 419	96 / 419	116 / 406	125 / 406	p < 0.05
	Fraud	22 / 419	18 / 419	24 / 406	25 / 406	Not stat sig
	Any conviction in past year	NR	49.7%	NR	65.9%	p < 0.05
	Any imprisonment in past year	NR	13.8%	NR	23.6%	p < 0.05
NAOMI: 12 months	20%+ reduction in illegal activity (non-drug) & <10% deterioration other scores	NA	1 / 115	NA	6 / 111	Not stat sig
	Illegal activities ASI subscale score	0.37	0.20	0.35	0.18	p = 0.12
Supervised injectable or inhalable heroin (+ oral methadone) v oral methadone						
Belgium TADAM: 12 months	# of acts committed or experienced as a victim during past month	NR	NR	NR	NR	Not stat sig
Supervised inhalable heroin (+ oral methadone) v oral methadone						
Dutch trial: 12 months	Average days illicit activities, past month	Mean difference (HAT – methadone): −4.27 95% CI: [−6.62, −1.92]				p < 0.05

[a]No longer statistically significant once differential pre-trend between oral methadone and HAT group taken into account.

Two reviews evaluated social functioning, defined as integration at work and family or other social relationships, based on the same set of RCTs (Dalsbo et al., 2010; Ferri et al., 2011). Since several trials did not report on individual-level outcomes for social functioning, conclusions were based on the findings of the early UK trial comparing unsupervised injectable heroin to oral methadone (Hartnoll et al., 1980), the Swiss trial comparing supervised injectable heroin to other treatments (Perneger et al., 1998), and three studies comparing supervised injectable heroin to

oral methadone (Haasen et al., 2007; March et al., 2006; Oviedo-Joekes et al., 2009a). For integration at work, the three studies comparing supervised injectable heroin to oral methadone found improvements for both the experimental and control conditions by treatment end, although only one study (Oviedo-Joekes et al., 2009a) found significantly greater improvement among the HAT group in employment satisfaction (p=0.02) and social relations (p=0.05) as assessed by the European Addiction Severity Scale Index (ASI) subscale scores. The early UK trial and Swiss trial showed no evidence of significant changes in employment for either treatment condition. For family relationships, there was little evidence showing a significant difference across treatment conditions in any study.

One review (Fingleton et al., 2015) evaluated effects of various opioid substitution treatments on mental health outcomes. The review included results from four RCTs comparing supervised injectable heroin to other treatments. For the Swiss trial (Perneger et al., 1998), with follow-up assessment at 6 months, those receiving supervised injectable heroin showed significant improvements relative to those receiving other conventional drug treatments for mental-health related quality of life (as measured by the SF-36 health survey; difference in SD units = 0.58, 95% CI 0.07-1.10). However, no significant differences were found across a range of other mental health measures, including suicide attempts, severe depression, cognitive problems, or problems controlling violent behavior. At 12-month follow-up, both the German trial and Canadian NAOMI trial found significant improvements in mental health for those receiving supervised injectable heroin relative to those receiving oral methadone (Oviedo-Joekes et al., 2009a; Reimer et al., 2011). At 9-month follow-up, the Spanish PEPSA trial also found significant improvements in mental health measures across both study conditions, but no significant benefit of supervised injectable heroin relative to oral methadone (March et al., 2006).

Finally, the review by Ali et al. (2017) included mental health results from the Belgian TADAM trial comparing supervised injectable or inhalable heroin to oral methadone (Demaret et al., 2015). The trial found significantly greater improvement in the experimental condition on domains of depression and psychoticism as measured by the Symptom Check-List (SCL-90-R; p=0.002), although the review did not draw conclusions based on the finding of the one study.

Serious Adverse Events

Three reviews evaluated evidence for the effects of HAT on serious medical adverse events (Dalsbo et al., 2010; Ferri et al., 2011; Strang et al., 2015). Two of these reviews defined serious medical adverse events as those probably or definitely related to the study medication (i.e.,

related to the prescribed pharmaceutical heroin or methadone) and conducted meta-analyses (Ferri et al., 2011; Strang et al., 2015), while the other provided a narrative discussion of all serious adverse events described in the trials (Dalsbo et al., 2010). Findings spanned results of seven RCTs. While these RCTs may have varied slightly in which incidents were reported as serious adverse events (SAEs), they generally included incidents that were life-threatening (including overdoses necessitating treatment with an antagonist), required inpatient hospitalization or prolonged duration of existing hospitalization, or resulted in persistent or significant disability or injury.

SAEs probably or definitely related to the study medication. Evidence from all reviews supports a significantly higher risk of study medication-related adverse events among the heroin treatment arms. Meta-analyses comparing supervised injectable heroin versus oral methadone resulted in risk ratios of 4.99 [95% CI 1.66, 14.99] (Strang et al., 2015) or 13.50 [95% CI 2.55, 71.53] (Ferri et al., 2011), with the higher estimate based on pooled effects that excluded the German and Dutch injectable trials.

The highest relative risk of serious medical adverse events was found in the Canadian NAOMI trials (RR = 47.31 [94% CI, 2.91, 768.63]), where serious adverse events were defined as overdoses related to study diacetylmorphine medication that required treatment with naloxone or any other medical issues judged to be related to the study medication. A total of 29 serious adverse events were judged to be related to the study medications (24 in the heroin treatment group; 5 in the hydromorphone treatment group). The most frequently observed serious adverse events related to HAT were overdoses and seizures, with infections also reported commonly in the hydromorphone treatment arm (Oviedo-Joekes et al., 2009a). All other source studies found higher risk of serious adverse events for supervised injectable heroin relative to oral methadone, although confidence intervals around estimates from individual studies were generally wide. Across studies, serious adverse events commonly resulted from other illicit drug use, such as respiratory depression associated with concurrent use of benzodiazepines (Reimer et al., 2011), potentially reflective of high rates of co-occurring drug use problems among the patient population recruited into the trials.

All SAEs. One review (Ferri et al., 2011) estimated pooled relative risk for SAEs, regardless of their association with the treatment medication. Based on their meta-analysis, the heroin treatment arm remains at elevated risk relate to oral methadone, but the magnitude of the effect size is greatly reduced (RR = 1.61 [95% CI 1.11, 2.33]).

The large German trial (n=1015) reported a total of 315 SAEs among 212 participants over the 12-month trial period. Comparing treatment arms, 24% (18%) of participants receiving HAT (methadone only) experienced an SAE. SAEs were significantly more likely to be possibly, probably, or definitely related to the study medication for those receiving HAT. Adjusting for the longer average treatment length among those receiving supervised injectable heroin, medication-related SAEs occurred about 2.5 times more often among those receiving HAT, with commonly cited SAEs related to respiratory depression and seizure (Haasen et al., 2007). Similarly, the

Canadian NAOMI trial reported a total of 79 SAEs among 54 participants, with nearly two-thirds (65%) occurring in the HAT group, nearly one-quarter (23%) in the oral methadone group, and the remaining 10 events in the smaller pilot hydromorphone group of 25 patients (Oviedo-Joekes et al., 2009a).

The Dutch injectable trial (n=174) reported a total of 18 SAEs among 16 patients. The proportion of patients experiencing at least one SAE did not significantly differ between those receiving HAT or methadone, and none of the SAEs were considered probably or definitely related to the study medication. The study also separately reported on drug overdoses registered during the trial period. Of the five drug overdoses reported (one classified as mild, three as moderate, and one as an SAE), all occurred within the HAT group. Two of the overdoses were classified as being definitely related to co-prescribed heroin but were not of a severity level to be considered an SAE based on the study's protocol (van den Brink and Blanken, 2002).

The Dutch inhalable trial (n=375) reported a total of 40 SAEs among 37 patients, with slightly higher rates of SAE among those receiving HAT. Six drug overdoses were registered, half of which occurred among those receiving oral methadone. All three overdoses occurring in the oral methadone group and one occurring in the HAT group were considered SAEs (van den Brink and Blanken, 2002). In the Spanish PEPSA trial, 14 SAEs occurring among 14 patients were also split evenly across the oral methadone and heroin-assisted treatment arms (March et al., 2006).

UK RIOTT was the only trial to report a higher rate of SAEs among the oral methadone group (Strang et al., 2010). Twenty total SAEs were reported, with nine occurring in the oral methadone group, seven in the supervised injectable heroin group, and four in the injectable methadone group. Of note, there were two overdoses reported in the oral methadone group (one related to antidepressants and the other to acetaminophen); two overdoses in the HAT group (both after diamorphine injection); and one overdose after methadone injection in the injectable methadone group.

While the early UK trial (Hartnoll et al., 1980) did not report on medical adverse events, the authors noted that during the 12-month trial period 21% (11%) of the heroin-assisted (methadone) treatment arm were admitted to a hospital for treatment of physical conditions related to drug use. By contrast, in the Swiss trial (Perneger et al., 1998), four participants in the HAT arm (14.8%) and six in the methadone treatment arm (25%) experienced at least one overdose over the trial period. The study found a significant reduction in overdose prevalence for the heroin treatment arm (i.e., 48% of the experimental group had overdosed at least once in the past 6 months at baseline); however, given the small sample size of the Swiss trial, this reduction did not significantly differ from that observed in the methadone treatment arm.

Mortality

The same three reviews evaluated evidence for effects on mortality (Dalsbo et al., 2010; Ferri et al., 2011; Strang et al., 2015). All three showed an effect that pointed in the direction of a

protective effect of HAT, but the differences between treatment and control groups were not statistically significantly. In a meta-analysis comparing any HAT provision to methadone alone (five RCTs with 1573 participants), Ferri et al. (2011) estimated a risk ratio of 0.78 [95% CI: 0.32, 1.89]. Estimated effect size was similar for meta-analyses comparing supervised injectable heroin plus optional oral methadone to oral methadone alone (RR = 0.65; 95% CI = [0.25 – 1.69]) based on pooling effects across four RCTs with 1,477 participants (Ferri et al., 2011; Strang et al., 2015).

Given the relatively short follow-up period for mortality measurement, there were very few deaths in either the control or treatment groups across all RCTs. Among the source studies assessing mortality at 6 months (Perneger et al., 1998; Strang et al., 2010), neither treatment arm experienced a death, which precludes estimation of relative risk ratios. Among the five other RCTs with mortality assessed at nine or twelve months, eleven deaths occurred across the methadone treatment groups and seven deaths occurred across the heroin treatment groups (Dalsbo et al., 2010). Given the rareness of mortality events over the time periods of assessment, there is a high degree of imprecision in effect size estimates from any given study (see **Table 11**).

Table 11. Mortality Estimates from Source Studies Included in Systematic Reviews

Experimental v control conditions	Included in Review:			Experimental	Control	
Study: Follow-up length	**Dalsbo**	**Ferri**	**Strang**	**Events/Total**	**Events/Total**	**RR [95% CI]**
Unsupervised injectable heroin v oral methadone						
Early UK trial: 12 months	X	X		2 / 44	1 / 52	2.36 [0.22, 25.20]
Supervised injectable heroin (+ oral methadone) v other drug treatment						
Swiss trial: 6 months	X	X	X	0 / 27	0 / 24	Not estimable
Supervised injectable heroin (+ oral methadone) v oral methadone						
Spanish PEPSA: 9 months	X	X	X	0 / 31	1 / 31	0.33 [0.01, 7.88]
German trial: 12 months	X	X	X	5 / 515	7 / 500	0.69 [0.22, 2.17]
Canadian NAOMI: 12 months	X	X	X	0 / 115	1 / 111	0.32 [0.01, 7.82]
UK RIOTT: 6 months	X	X	X	0 / 43	0 / 42	Not estimable
Dutch injectable trial: 12 months	X	X	X	1 / 76	1 / 98	1.29 [0.08, 20.28]
Supervised inhalable heroin (+ oral methadone) v oral methadone						
Dutch inhalable trial: 12 months	X	X		0 / 117	0 / 139	Not estimable

Notes: (+ oral methadone) indicates that oral methadone was offered as an optional supplement to heroin-assisted treatment.

Some source studies reported on cause of death (Haasen et al., 2007; Hartnoll et al., 1980; March et al., 2006; Oviedo-Joekes et al., 2009a). For five deaths in the methadone treatment arm where cause of death was reported, fatalities were related to barbiturate overdose (suicide likely),

overdose from co-administration of cocaine and heroin, opioid overdose, ruptured aneurysm, and reason unknown. For five deaths in the heroin treatment arm where cause of death was reported, fatalities were related to barbiturate overdose (suicide likely), drug overdose of uncertain nature, intoxication with illicit pneumonia, pneumonia and myocarditis complications, and spleen rupture from falling.

Perneger et al. (2000) conducted a follow-up assessment of opiate use patterns among participants from the Swiss trial up to 30 months after entry into HAT. Of the 37 patients eventually placed in HAT, ten (27%) had switched to oral methadone or detox treatment. Accounting for days of treatment received, the authors estimated this translated to one "successful" treatment transition per 6 patient-years. Over the entire 30-month period, about half of patient-days corresponded to combined use of prescribed injectable heroin and oral opiates (methadone or morphine), about 40% corresponded to use of prescribed injectable heroin alone, and about 7% corresponded to use of oral methadone alone.

Following the conclusion of the 12-month Dutch RCT treatment period, study protocol stipulated that those receiving HAT would cease treatment for at least two months; participants who exhibited substantial deterioration during this follow-up were allowed to re-enroll in HAT for an unspecified period of time. During the two-month discontinuation period, 82% of those classified as "treatment responders" from HAT had shown significant deterioration such that the multi-domain outcome index measuring treatment response had returned to baseline levels. However, it is unclear whether this finding reflects the importance of remaining on HAT to retain treatment benefits, participant behavioral or reporting responses driven by the knowledge that deterioration would result in HAT, or an adjustment period whereby participants transitioned to an inadequate dose of an alternative treatment medication. Blanken et al. (2010a) conducted

an observational cohort study to evaluate four-year outcomes for 149 participants eligible to continue HAT following the Dutch trial conclusion. Treatment retention at four years was 55.7% (95% CI = 47.6, 63.8), with the majority of discontinuations attributable to insufficient treatment response and administrative discharge for rule violations, primarily due to attempts to divert prescribed heroin outside the treatment center. Of those who discontinued HAT, nearly 85% were in some form of treatment, mainly methadone treatment. Those who remained in HAT at four-year follow-up exhibited significantly greater health improvement than those who discontinued, which likely reflects selection effects.

Following the conclusion of the nine-month PEPSA trial in Andalusia, Spain, all 23 participants who had been randomized to the supervised injectable heroin arm continued receiving it from the clinic under the protection of Spain's compassionate use law. Additionally, treatment completers who had been randomized to the oral methadone group were offered the option of switching to supervised injectable heroin after the trial end; 13 (61.9%) of the 21 eligible oral methadone participants elected this option. In a follow-up cohort study of the participants from this trial, Oviedo-Joekes et al. (2010d) compared outcomes across current HAT recipients, former HAT recipients, and those who had never received HAT. Changes were assessed between baseline (prior to randomization) and at two-years after the trial's conclusion.

For the 54 participants with follow-up data (of the 62 original trial participants, three had died, three were unreachable, and two were incarcerated outside of Andalusia), 44% were continuing to receive HAT, 46.3% were receiving oral methadone, 5.6% reported no longer using drugs, and 3.7% were not receiving any form of treatment. From baseline to two-year follow-up, all three groups (current HAT, former HAT, never HAT) experienced significant reductions in illicit heroin use, with those currently receiving HAT reporting significantly less frequent illicit heroin use than the other two groups at follow-up. Declines in cannabis use, binge drinking, and HIV risk behavior reported by current or former HAT recipients were not observed for those who had never received HAT. Finally, those continuing to receive HAT exhibited significantly greater improvements in mental health scores (SF12) and ASI psychiatric composite scores than those no longer receiving HAT.

As noted in the overview of systematic reviews for treatment retention, a relatively higher percentage of individuals assigned to supervised injectable heroin or hydromorphone in the Canadian NAOMI trial voluntarily transferred to oral methadone during the course of the 12-month trial. Oviedo-Joekes et al. (2014a) conducted a follow-up assessment 12 months after trial end comparing treatment retention and illicit heroin use on an intent-to-treat basis, with subgroup analysis comparing those who had voluntarily transitioned to oral methadone to those who were involuntarily transitioned off of injectables due to trial end. Despite higher treatment retention (defined as engagement in treatment or abstinence from illicit heroin use) in the HAT group at the 12-month trial end, by the 24-month follow-up there were no longer significant differences between the HAT and oral methadone groups. Among those assigned to supervised injectable treatment, comparisons of those who voluntarily versus involuntarily transitioned showed those

who voluntarily switched to oral methadone had significantly higher treatment retention (AOR = 5.55; 95% CI: 1.11, 27.81) and marginally significant lower illicit heroin use days in the past month (-5.58; 95% CI: -11.62, 0.47) at 24-month follow-up.

Finally, three articles conducted two-year follow-up studies of participants randomized to supervised injectable heroin or oral methadone within the German trial. In the German trial, after the initial phase of 12-months treatment with HAT or methadone, patients who completed HAT were allowed to continue treatment for another 12 months; patients who completed methadone treatment and exhibited "unsatisfactory" clinical progress as determined by doctors' assessment were allowed to switch to HAT for 12 months. Of the first phase treatment completers, 99.4% (344/346) of the HAT group elected to continue treatment, and 40% (90/200) of the methadone treatment group were transferred to HAT (Verthein et al., 2011).

Verthein et al. (2008)'s prospective cohort study followed participants assigned to the HAT group for a two-year period. Of the 515 participants initially randomized to HAT, 54.8% were still receiving HAT after 24 months. The majority of dropout was due to participants switching to other medication treatment (27.1%) or abstinence treatment (9.3%); incarceration (16.0%); or theft/diversion of prescribed heroin (7.6%). Analyses of the methadone-HAT switching group (Verthein et al., 2011) showed a similarly high proportion of dropouts during HAT receipt related to uptake of conventional maintenance treatment (38.9%) or abstinence-based treatment (11.1%), and lower rates of dropout due to imprisonment (5.6%). During the second study phase, the methadone-HAT switching group showed improvements in physical health and drug use such that they "caught up" with the two-year HAT group by the end of the second trial phase. However, by definition, the methadone-HAT switching group members were negatively selected from the original methadone group; patients who did well on methadone during the first trial phase were automatically excluded from the trial's second phase. Thus, while this evidence may support the efficacy of HAT for opioid-dependent patients who do not respond to oral methadone, the study does not provide causal evidence on how longer-term HAT compares to longer-term methadone for the initial RCT target population.

Soyka et al. (2011) recruited a subset of patients receiving long-term HAT (n=20) as part of the second phase of the German HAT RCT in order to compare their cognitive functioning to that of methadone (n=24) or buprenorphine (n=22) patients participating in a separate RCT. Cognitive performance was assessed using a standardized instrument (the Act and React Test System) that measures neuropsychological functions related to driving ability, including reactivity, visual perception, and stress tolerance. While the HAT group performed significantly worse on some tests (attention under monotony and reactivity under stress conditions), other tests showed limited differences. However, as patients were recruited from different RCTs with different participant eligibility requirements, these findings may reflect baseline differences (e.g., HAT patients have longer histories of dependence) as opposed to causal effects of the treatment.

Evidence from other cohort studies. We identified eight additional cohort studies that evaluated the long-term outcomes of individuals receiving HAT – one in the UK context and

seven in the Swiss context. The sample population from these studies are not drawn from RCTs, instead drawing on information from countries where HAT is a legally available treatment for heroin dependence. Given the absence of a comparison group, we focus discussion primarily on providing descriptive evidence of long-term outcomes for HAT participants recruited outside of an RCT setting.

In the UK, heroin prescription for treatment of opioid dependence has been available since the early 1920s, though since 1968 physicians must obtain a special license to prescribe this treatment. Metrebian et al. (2006) reviewed patient case notes from 27 of the 42 UK clinics providing HAT in 2000 in order to assess treatment patterns and characteristics among individuals receiving a heroin prescription. Of the 210 patients evaluated, the vast majority of patients were receiving HAT for take-home administration (88%) and in injectable formulation (88%), but daily doses ranged widely (median = 200 mg; range = 10-900 mg). The length of HAT receipt ranged from a few months to 36 years, with a median treatment length of six years. When followed up with two years later in 2002, most participants (70%) were still receiving HAT and just over 10% had transferred to an oral maintenance treatment or become abstinent.

In Switzerland, the Medical Prescription of Narcotics Programme (PROVE) was an experimental prospective cohort study conducted from 1994 to 1996 that accepted admission of 1,035 individuals into a treatment program offering prescribed heroin, methadone, and morphine plus an intensive suite of social services. Participants were at least 18 years old, had at least two years of heroin dependence, had at least two prior treatment episodes, and experienced health or social problems as a result of their heroin use. Beginning in 1998, a new decree allowed HAT centers to admit new patients beyond the initial experimental cohort. We identified one study of Swiss HAT participant outcomes up to 2.5 years after enrollment (Steffen et al., 2001); five articles studying outcomes from 4 to 7 years after enrollment (Guttinger et al., 2003; Rehm et al., 2005; Rehm et al., 2001; Ribeaud, 2004; Sendi et al., 2003); and one article with follow-up data more than ten years post-enrollment (Frick et al., 2010).

Steffen et al. (2001) evaluated trends in seroprevalence among 1,035 individuals enrolled in the 1994 to 1996 PROVE cohort from baseline to 30 months post-enrollment. Baseline rates of seroprevalence for human immunodeficiency virus (HIV; 15%), hepatitis B (HBV; 73%), and hepatitis C (HCV; 82%) were high among participants, similar to the high rates observed among HAT RCT participants. Most participants experienced viral co-infections (Sendi et al., 2003). Risk for HBC and HCV infection dropped by nearly 50% after the first six months of treatment and persisted at this lower level up to 30 months after treatment entry, paralleling a decline in self-reported needle sharing behavior from 16% to 5%.

Ribeaud (2004) evaluated long-term trends in criminal justice involvement for a sample of 882 HAT patients who entered the PROVE trials between January 1994 and July 1996 and were alive four years after HAT admission. For the 426 patients (48%) who remained in the program all four years, police records showed the prevalence (incidence) rates of offenses unrelated to heroin use/possession significantly declined from 54% to 31.5% (1.86 to 0.73) from the year

before to the year after treatment, with a slower rate of decline through the fourth year of treatment. These effects are seen across drug and property offense types, with the largest effects for shoplifting and cocaine use/possession. Incidence rates related to heroin use/possession also declined significantly, falling from 1.2 the year before treatment to about 0.05 one year post-treatment. Individuals who left the HAT program before four years experienced similar declines in offense rates over the four-year period, with one exception. The group who left HAT before one year experienced a much slower and smaller decline in incidence rates; however, this appeared to be driven by a few outliers.

Similar crime drops between those who remained in HAT and those who discontinued treatment may be related to the fact that many who left HAT transferred to alternative treatment regimes. Regardless of time to treatment discontinuation, approximately 60% of patients who left transferred to methadone or abstinence-based treatment. Among those who dropped out before one year of HAT, 43.2% enrolled in methadone and 21.1% in abstinence-based treatment. Dropout seemed to cluster within the first year of treatment, a finding also borne out in another Swiss study with follow-up assessed up to 14 years after initial HAT entry (Frick et al., 2010).

Guttinger et al. (2003) evaluated six-year outcomes from the first cohort of individuals who entered into PROVE between January 1994 and March 1995 (n=366). Of those clients who were still alive (88.2%), 148 were still in or had reentered HAT (mean cumulative length of stay in HAT of 6.1 years), while 175 had left HAT in the evaluation period without re-entering (mean length of stay 2.4 years). While it was unknown how many individuals had entered an alternative treatment program, the most common self-reported reasons for discharge were problems with adherence to treatment protocol (30.6%), transfer to abstinence-oriented treatment (24.3%), or transfer into methadone treatment (21.6%); these rates are comparable to those from a larger PROVE cohort study (Rehm et al., 2001). Interestingly, comparing outcomes from baseline to 6-year follow-up showed no significant improvement in employment for those currently or previously receiving HAT; those clients still receiving HAT actually experienced a significant increase in dependence on social benefits (19.1% to 39.7%). There were also no significant changes from baseline in social integration outcomes, despite significant declines in (near) daily use of heroin.

Rehm et al. (2005) examined deaths during HAT treatment among clients in Switzerland over the seven-year period from 1994 to 2000. The time in treatment was defined as admission through the month after discharge. Using this definition, their time period covered just over 4600 person-years in treatment and 49 deaths, yielding a crude rate of 0.011 deaths per person-year. This is a substantially higher mortality risk than sex- and age-adjusted rates in the general population; but it is substantially lower than mortality risk estimates based on other opioid-using populations. Examining cause of death, over one-third of deaths were due to AIDS or HIV-related outcomes; nearly two-fifths were from accidents; 16.3% and 10.2% were from suicide and intoxication/overdoses, respectively.

Summary of Findings for Community-Level Outcomes

Our review of the literature found no adverse effects of HAT on community-level outcomes of public disorder and crime and some positive effects. There are, however, three significant limitations concerning this conclusion. First, the relevant literature is very small and included no RCTs and no quasi-experimental studies with a comparison group. Second, the trials for which community-level outcomes were studied enrolled relatively few participants, making it hard to detect adverse (or beneficial) effects at the community level; it is unclear the extent to which this evidence base would generalize to larger scale implementation of HAT. Third, the outcome measures studied to date do not address many of the community-level concerns raised about HAT (e.g., normalization of heroin use, traffic accidents, and diversion of pharmaceutical heroin to illicit markets).

The processes by which HAT clinics operate may also determine their effects on the broader community. For instance, the RIOTT program site in South London operated out of an existing community-based alcohol and other drug use service provider's clinic, a facility which already provided oral methadone or other services to about 300 patients. By incorporating HAT into existing facilities, there may have been less realized and/or perceived impact on the community in which the clinic was located. Operating hours, capacity, accessibility, and the availability of other social services within HAT facilities are also likely to be important factors in determining community impact. Furthermore, it likely that HAT implementation could generate heterogenous community-level impacts depending on where clinics are located. To date, all HAT facilities have been located in urban areas. Proximity to other service providers, the existence and characteristics of local drug markets, and the pre-existing socioeconomic and built environment characteristics of the communities where HAT facilities are located may interact to generate differential impact for both patient-level outcomes as well as community-level outcomes.

Finally, by exploiting the timing of heroin-assisted RCTs' implementation to measure community-level impact, the evidence base has implicitly embedded the procedures taken by each RCT, some of which were designed specifically to limit community impact. For instance, all RCTs have imposed some type of residency requirement (see **Appendix Table A2**), limiting the extent to which opioid dependent individuals might migrate to the trial cities to receive HAT. Additionally, several trials have discharged HAT participants for violating program rules by attempting to divert medications outside the treatment facility, suggesting that efforts to prevent attempted diversion may be important for wider HAT implementation. Overall, the ability to generalize existing evidence to allowing HAT outside an RCT context will depend on the specific design, implementation, and enforcement of allowing broader HAT availability.

Summary of Findings for Economic Outcomes

Overall, evidence across studies finds that supervised injectable HAT is much more expensive than oral methadone but is more cost-effective in a societal sense, primarily because the models credit HAT with doing more to reduce participants' levels of criminal justice involvement and associated damages to victims of their crime activity. Most trials also showed

higher QALYs among the HAT arm. Among the two studies comparing the cost-effectiveness of supervised injectable heroin to other supervised injectable medications (injectable methadone or injectable hydromorphone), there were no significant differences between injectable heroin or the other injectables in terms of costs or QALYs. While further evidence is needed, combined with evidence of hydromorphone noninferiority from the SALOME trials, this suggests that supervised injectable hydromorphone may offer a preferable alternative to HAT in regimes that can support the higher programmatic costs of injectable treatments but that face particular political, legal, or regulatory barriers to allowing treatment with pharmaceutical heroin.

There are several limitations to these findings, including the fact that some outcomes of interest are difficult to monetize. First, the estimates for crime costs in several cases either do not adjust for baseline crime rates or are dependent on model assumptions drawn from evidence outside the trial data. Second, several costs are omitted from analyses. Only one study (Dijkgraaf et al., 2005) incorporated the costs to participants of program-related travel. None of the RCT studies incorporated potential gains in productivity, which may be important to consider over longer time horizons. Crime costs seem to have been restricted to property and violent crimes, excluding costs associated with illicit drug dealing, prostitution/solicitation, disorderly conduct, or major traffic violations. Third, while several studies incorporated some of the costs of and QALY losses associated with HCV and HIV among the patient population, the potential economic implications of reduced transmission of HIV and HCV to the broader population due

to reduced injection of illicit heroin were not explicitly modelled. Also, to our knowledge, no economic analysis considered potential benefits from reduced chronic skin and soft tissue infections, which significantly contribute to morbidity and premature mortality among people who inject drugs (Harris et al., 2018; Larney et al., 2017). Finally, when considering economic outcomes for wider scale implementation of HAT, one might also evaluate the potential effects of HAT on costs within the methadone treatment system; however, we did not identify any empirical evidence to this effect.

Additionally, all reviewed studies found significantly higher costs of providing heroin-assisted treatment relative to oral methadone, and these higher total costs may serve as an important barrier to implementation, regardless of findings on cost-effectiveness. The high costs of renovating existing facilities to meet the requirements for a heroin-assisted treatment center in Vancouver were noted as a primary factor for the nearly two-year delay in identifying a Vancouver site for the NAOMI trial (Gartry et al., 2009). When considering implementation of HAT outside of a clinical trial setting, one must also consider who will be responsible for the costs of treatment provision. Requiring patients to pay out-of-pocket would likely severely limit participant uptake; requirements for insurance to cover HAT costs would need to be negotiated and may prove intractable; and the likely governmental funders of HAT, health and healthcare agencies, are not the agencies where the bulk of savings are accrued.

1. ummary of Findings

Based on evidence from ten RCTs, our review found that, for individuals with chronic heroin use disorder who have not responded to conventional medication treatments, HAT co-prescribed with flexible doses of oral methadone offers significant benefits over oral methadone with respect to improving treatment retention, although there are several nuances in interpreting these results with respect to both the HAT trials in particular as well as to the treatment of opioid use disorder more broadly (see Vogel et al. (2017) for discussion). For individuals with chronic treatment-refractory heroin use disorder, co-prescribed HAT also seems to offer significant benefits relative to oral methadone alone in terms of reducing illicit heroin use and criminal activity. More limited evidence shows that co-prescribed HAT may have some benefits over oral methadone alone for improving physical health and mental health; and the treatments do not seem to significantly differ with respect to influencing other substance use, social functioning, and mortality. RCTs have also consistently shown a higher risk of medication-related serious adverse events for individuals receiving HAT relative to individuals receiving oral methadone; however, at least within the trial context, the higher risk of serious adverse events does not translate to higher risk of mortality.

These findings are based on a review of the results of ten RCTs that have been implemented across seven countries. While the RCTs have varied somewhat in how both the experimental and control conditions have been implemented, our summary findings are largely reflective of comparisons between supervised injectable heroin treatment (plus optional oral methadone) and oral methadone treatment. Importantly, given participant eligibility requirements, the evidence base reviewed should also largely be interpreted as one that informs the comparative effectiveness of HAT for treatment of heroin use disorder among a patient population that has previously attempted but not responded to oral methadone treatment. Findings are thus not intended to provide evidence regarding the use of HAT as a first-line treatment option. These conclusions also may not generalize to comparisons of supervised injectable heroin with other medication treatments (e.g., buprenorphine); or to the effectiveness of HAT delivered through other routes of administration (e.g., oral heroin). Furthermore, the supervised nature of HAT delivery mandated in nearly all identified RCTs means we cannot disentangle to what extent the relative benefits from HAT are accrued because of the medication itself or because of the structured routine that coming to the facility to receive study medication entails. In addition, while the experimental design of the reviewed studies bolsters a causal interpretation of the findings, the reliance on RCT evidence also potentially limits the generalizability of our conclusions. Still the evidence for the effectiveness of HAT relative to oral methadone treatment is markedly consistent across RCTs regarding the primary outcomes of treatment retention and illicit heroin use.

Our review of community-level and economic outcomes identified a much smaller set of studies. We identified five descriptive or quasi-experimental studies that evaluated the potential community-level impacts of HAT. Overall, these studies do not suggest large impacts of HAT implementation on the broader community, although the empirical strategies used in prior research largely rely on community-level changes induced by HAT RCT implementation as opposed to wider integration of HAT into the standard healthcare system as has been done in Switzerland and Denmark. Additionally, community-level concerns have a clear impact on the feasibility of implementing HAT. Therefore, it would be beneficial for future research to employ causal inference methods to evaluate the impact of HAT in countries where it has been implemented and for future trials to consider embedding evaluation of community-level outcomes within their research design.

Finally, the literature shows that the programmatic costs of supervised injectable treatments greatly exceed the programmatic costs of oral methadone treatment, but that the higher programmatic costs are more than offset by greater cost savings from crime damages and criminal justice involvement. However, the costs associated with damages to victims of crime perpetrated by study participants were generally calculated using estimates of the average cost of certain crime types that were derived outside of the study context. The validity of these estimates thus hinges on a number of assumptions, which merit further consideration within the context of these trials. Additionally, further research evaluating how the costs and cost-effectiveness of HAT may vary as a function of scale or the setting in which it is implemented could help shed more light on economic outcomes associated with HAT implementation outside the trial context.

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Table A.1. Overview of Heroin-Assisted Treatment Randomized Controlled Trials

Trial	Setting (timeframe)	Treatment (T)	Control (C)
Early UK	Single clinic in London (1972–1975)	Unsupervised injectable heroin	Oral methadone treatment (MT)
Swiss trial	Single clinic in Geneva, Switzerland (1995–1996)	Supervised injectable heroin (SIH) plus optional oral MT	Any other conventional drug treatment
Dutch injectable trial	8 treatment units in 6 cities in Netherlands (1998–01)	SIH + optional oral MT	Oral MT
Dutch inhalable trial	8 treatment units in 6 cities in Netherlands (1998–01)	**T1**: SIH + optional oral MT **T2**: Oral MT for 6mo then inhalable heroin + optional oral MT for 6mo	Oral MT
Spain PEPSA	1 hospital in Granada, Spain (2001–2004)	SIH + oral MT	Oral MT
German study	Seven cities in Germany (2002–2004)	SIH + optional oral MT plus: **T1**: psychoeducation, counseling **T2**: case management, motivational interviewing	Oral T plus: **C1**: education **C2**: case management
Canada NAOMI	3 cities in Canada (2005-2008)	**T1**: SIH + optional oral MT **T2**: Supervised injectable hydro-morphone + optional oral MT	Oral MT
UK RIOTT	Three sites in England (2005-2008)	**T1**: SIH + optional oral MT **T2**: Supervised injectable MT + optional oral MT	Optimized oral MT
TADAM	Liège, Belgium (2011-2013)	Supervised injectable or inhalable heroin + optional oral MT	Oral MT
SALOME	Vancouver, Canada (2011-2013)	SIH + optional oral MT	Supervised injectable hydromorphone + optional oral MT

Table A.4. Details of Treatment Conditions in Heroin-Assisted Treatment Randomized Controlled Trials

Trial	Additional Services
Early UK	Counseling by clinic psychiatrists; hospital admission and referral to a therapeutic community available as normal
Swiss trial	All HAT participants were offered HIV prevention, social & legal support, primary care, and psychological counseling; control group participants were not precluded from receiving additional services but were not offered such services explicitly through the program
Two Dutch trials	Offered psychosocial services, including individual counseling, group counseling, housing and budget assistance, participation in work projects and standard medical and psychiatric treatment
Spain PEPSA	All received clinical, social, legal support, and psychological services
German study	Psychosocial care with (attempted) weekly contacts mandatory
Canada NAOMI	All patients offered a comprehensive range of primary care and psycho-social services
UK RIOTT	All assigned a case worker, medical reviews, and access to psychological services. Other health or social services available.
TADAM	All offered psychosocial services
SALOME	Access to a pre-specified range of primary care services and a psychosocial support worker who offered individual counselling and case management services.

Table A.5. Measurement Methods for Illicit Drug Use and Criminal Activities in Heroin-Assisted Treatment Trials

Experimental v Control		
Study: Follow-up	**Illicit drug use meacure**	**Measurement**
Unsupervised injectable heroin v oral methadone		
Early UK trial: 12 months	Daily average illicit opiate use over past 12 months	Self-report; Urinalysis
	Non-opiate illicit substance use	Self-report; Urinalysis
	Crime as source of income over past year	Self-report
	Number of arrests over past year	Official record
	Incarceration/imprisonment	Official record
Supervised injectable heroin (+ oral methadone) v other drug treatment		
Swiss trial: 6 months	Daily use of street heroin	Self-report (ASI)
	Daily use alcohol, tobacco, or other drugs	Self-report (ASI)
	Charged in past 6 months	Self-report
	Commercial sex in past 6 months	Self-report
Supervised injectable heroin (+ oral methadone) v oral methadone		
Dutch trial: 12 months	Average days illicit heroin use during past month	Self-report; urinalysis
	Average days illicit activities during past month	Self-report
Spain PEPSA: 9 months	Days street heroin use in past month	Self-report (ASI)
	Days per month involved in illegal activities	Self-report (ASI)
German trial: 12 months	>50% negative specimens for street heroin and no increase in cocaine use in the past month	Urine/hair analysis; self-report
	Criminal activity	Self-report (ASI); official records
NAOMI: 12 months	Use of street heroin at least one day of past month	Self-report (ASI)
	Days use of illicit drugs in past month	Self-report (ASI)
	Illegal activities	Self-report (ASI)
UK RIOTT: 6 months	>50% negative specimens for street heroin, past 12 weeks	Urinalysis
	Criminal offenses	Self-report (ASI)
Supervised injectable heroin or methadone (+ oral methadone) v oral methadone		
UK RIOTT: 6 months	>50% negative specimens for street heroin, past 12 weeks	Urinalysis
	Criminal offenses	Self-report (ASI)
Supervised injectable or inhalable heroin (+ oral methadone) v oral methadone		
Belgium TADAM: 12 months	Days illicit heroin use in past month	Self-report (ASI); urinalysis
	Days cocaine use in past month	Self-report (ASI); urinalysis
	Days benzodiazepine use in past month	Self-report (ASI)
	# acts committed or experienced as victim, past-month	Self-report; official record
Supervised inhalable heroin (+ oral methadone) v oral methadone		
Dutch trial: 12	Average days illicit heroin use during past month	Self-report; urinalysis