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Cost-effectiveness of hydromorphone for severe opioid use disorder: findings from the SALOME randomized clinical trial

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ABSTRACT

Background and aims Previous research has found diacetylmorphine, delivered under supervision, to be cost-effective in the treatment of severe opioid use disorder, but diacetylmorphine is not available in many settings. The Study to Assess Long-term Opioid Maintenance Effectiveness (SALOME) randomized controlled trial provided evidence that injectable hydromorphone is non-inferior to diacetylmorphine. The current study aimed to compare the cost-effectiveness of hydromorphone directly with diacetylmorphine and indirectly with methadone maintenance treatment. **Design** A within-trial analysis was conducted using the patient level data from the 6-month, double-blind, non-inferiority SALOME trial. A life-time analysis extrapolated costs and outcomes using a decision analytical cohort model. The model incorporated data from a previous trial to include an indirect comparison to methadone maintenance. **Setting** A supervised clinic in Vancouver, British Columbia, Canada. **Participants** A total of 202 long-term street opioid injectors who had at least two attempts at treatment, including one with methadone (or other substitution), were randomized to hydromorphone (n = 100) or diacetylmorphine (n = 102). **Measurements** We measured the utilization of drugs, visits to health professionals, hospitalizations, criminal activity, mortality and quality of life. This enabled us to estimate incremental costs, quality-adjusted life years (QALYs) and cost-effectiveness ratios from a societal perspective. Sensitivity analyses considered different sources of evidence, assumptions and perspectives. **Findings** The within-trial analysis found hydromorphone provided similar QALYs to diacetylmorphine [0.377, 95% confidence interval (CI) = 0.361–0.393 versus 0.375, 95% CI = 0.357–0.391], but accumulated marginally greater costs [$49 830 ($28 401–73 637) versus $34 320 ($21 780–55 998)]. The life-time analysis suggested that both diacetylmorphine and hydromorphone provide more benefits than methadone [8.4 (7.4–9.5) and 8.3 (7.2–9.5) versus 7.4 (6.5–8.3) QALYs] at lower cost [$1.01 million ($0.6–1.59 million) and $1.02 million ($0.72–1.51 million) versus $1.15 million ($0.71–1.84 million)]. **Conclusions** In patients with severe opioid use disorder enrolled into the SALOME trial, injectable hydromorphone provided similar outcomes to injectable diacetylmorphine. Modelling outcomes during a patient's life-time suggested that injectable hydromorphone might provide greater benefit than methadone alone and may be cost-saving, with drug costs being offset by costs saved from reduced involvement in criminal activity.

Keywords Cost-effectiveness, economics, injectable diacetylmorphine, injectable hydromorphone, methadone maintenance therapy, opioid dependence.

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INTRODUCTION

Opioid dependence has an enormous burden on individuals and society. Maintenance treatment such as methadone and buprenorphine can be effective for many individuals, in terms of improving physical and psychological health, decreasing drug use, infectious disease transmission and illegal activity [1–3]. However, a subpopulation of

individuals with severe opioid use disorder are not attracted or maintained in oral maintenance treatment, and so alternative approaches are required urgently [4,5]. The North American Opiate Medication Initiative (NAOMI) [5], along with five European randomized controlled trials, have found that injectable diacetylmorphine (DAM) (pharmaceutical heroin), delivered under supervision, to be more clinically effective than oral methadone in patients with severe opioid use disorder [6–12]. Previous studies in Canada and Europe have found that DAM is cost-saving compared to oral methadone in this patient group through its ability to reduce criminal activity [13–15]. Despite this, medically prescribed DAM is not available in Canada without special access due to regulatory and political reasons [16]. In the quest to find a more politically acceptable alternative to DAM, the Study to Assess Long-term Opioid Maintenance Effectiveness (SALOME) trial was conducted to test if injectable hydromorphone (HDM) was non-inferior to injectable DAM as a second-line treatment for severe opioid use disorder [17,18]. HDM is currently licensed for moderate to severe pain treatment but at smaller doses than utilized in the SALOME trial for treatment of opiate dependence. While HDM is not currently licensed for the treatment of opioid maintenance, the regulatory and political barriers for this extension are far less in comparison to DAM.

The objective of this study was to consider the economic implications of HDM in patients with severe opioid use disorder. We first compare the patient-level cost and cost-effectiveness of injectable HDM relative to DAM using the results of the SALOME trial. We also extrapolate outcomes from the SALOME trial to estimate the long-term cost-effectiveness of a policy of HDM versus DAM versus methadone for individuals with severe opioid use disorder. This secondary analysis addresses policy questions not addressed by the SALOME trial alone, and combines evidence from multiple sources.

METHODS

Overview

The aim of the analysis was to determine the incremental cost-effectiveness ratios (ICERs) of different maintenance strategies including injectable HDM and DAM and oral methadone in individuals with severe opioid use disorder who continued injecting illicit opioids, despite other treatment options being available. The methods employed are consistent with published methodological guidelines for undertaking economic evaluations [19,20] by considering all societal costs in 2015 dollars and outcomes in terms of quality-adjusted life years (QALYs). For the base-case analysis, a cohort of adults with severe opioid use disorder with demographic and other clinical characteristics similar to the SALOME trial population is assumed. We employed two forms of analysis, a within-trial analysis for which we have comprehensive data from trial participants on injectable HDM and DAM but for only a 6-month time horizon, and a life-time analysis, which employed a decision analytical model that uses assumptions and external data, including patient-level NAOMI data, to extrapolate costs and QALYs to a 50-year time horizon and compared to oral methadone.

Strategies

The within-trial analysis considers strategies from the SALOME study, a 6-month, Phase III, double-blind, non-inferiority trial in which 202 patients with severe opioid use disorder in Vancouver (Canada) were assigned randomly to either injectable HDM (average daily dose = 261 mg) or DAM [18]. The trial found that self-reported days of street heroin use was non-inferior for the per protocol analysis −1.44 days different; 90% confidence interval (CI) = −3.22, 0.27 (marginally different for the ITT analysis −2.34, 90% CI = − 4.14, −0.52), as well as days of non-prescribed opioid use and urinalysis positive to illicit heroin markers [both non-inferior per protocol and intention-to-treat (ITT)]. Other end-points (number of days engaged in illegal activities, treatment retention, physical and mental health) were similar (except crack cocaine use, that was higher in the HDM arm), while there were lower rates of adverse events and serious adverse events in the HDM arm than in the DAM arm.

The life-time analysis follows patients through time on treatment, relapse, treatment abstinence and death. The analysis also includes data from the NAOMI trial, which found DAM to be superior to oral methadone maintenance. Using DAM as the common comparator, we compared HDM indirectly to methadone maintenance.

Analysis

Within-trial analysis

We included the 202 individuals who were randomized in the SALOME trial (n = 100 and 102 for HDM and DAM, respectively) to estimate their economic outcomes. Cumulative costs and QALYs were calculated for each treatment strategy assuming an ITT. Cumulative costs were adjusted for baseline crime and resource utilization costs and QALYs were adjusted for baseline utility values to account for differences between treatment groups. Missing data was estimated using multiple imputations. Bootstrapped confidence intervals were estimated.

Life-time analyses

For the life-time analyses, we extrapolated the findings from the SALOME and NAOMI studies during the

projected life-time of individuals. An existing semi-Markov cohort model was further developed for the purposes of the analysis [13]. The model is described further in the Supporting information and depicted in Fig. 1. Briefly, the health states in the model included treatment [HDM, DAM or methadone maintenance treatment (MMT)], relapse (defined by opioid use outside of treatment), abstinence from any opioids and death. Individuals in the model belonged to one of three cohorts (HDM, DAM or MMT), and all patients entered the model in a treatment state. A new treatment cycle was defined as one beginning each time a patient re-entered treatment following relapse. Transitions between health states could occur every 30 days.

The probabilities of retention in each treatment were based on data from the SALOME and NAOMI trials, and data from an 11-year population study of methadone recipients in British Columbia [21]. In scenario analyses we considered the influence of combining evidence from other trials using a mixed treatment comparison (Supporting information). Transitions to death were based on age- and sex-adjusted mortality rates from the general Canadian population [22]. The estimates of mortality were then multiplied by standardized mortality ratios for different health states [23,24] As there is no study available on mortality among opioid users treated with HDM, we assumed the mortality rate in the HDM state to be the same as in the DAM state. The probability of HIV seroconversion was a function of treatment status, frequency of heroin injection and unprotected sexual contact [25,26]. Seroconversion could occur at any stage in the model and was independent of transitioning between states of treatment, relapse and abstinence. Parameters are described in Table 1 and described further below and in the Supporting information. All statistical analyses and modelling were performed using SAS version 9.4 and R version 3.2.0.

Resource use and costs

During the trial, utilization of drugs, non-protocol visits to health professionals, other health-care resources, including hospitalizations, and criminal involvement and charges were collected routinely. Drug costs were estimated based on the dosages reported in the study. All costs were calculated by multiplying resource use by respective unit costs, adjusted to 2015 dollars and discounted at 5% per year.

Fully allocated treatment costs of methadone and DAM, including costs of medication, human resources and overheads, were sourced from the SALOME trial. As neither medication is licensed for opioid maintenance, we use the Active Pharmaceutical Ingredient (API) price and associated costs of production, but vary this in the sensitivity analysis. Costs of drug treatment for HIV infection were estimated based on the estimated proportion of infected patients receiving treatment.

We included the costs of involvement in violent and property crime, and criminal charges for any crime. The costs related to criminal activity included costs borne by the criminal justice system as well as out-of-pocket costs resulting from criminal victimization. We used self-reported criminal involvement, but this was limited to property and violent crimes and did not include the possession or dealing of drugs, disorderly conduct, sex work, major driving violations or broken conditions imposed by the legal system. Data from provincial court records were

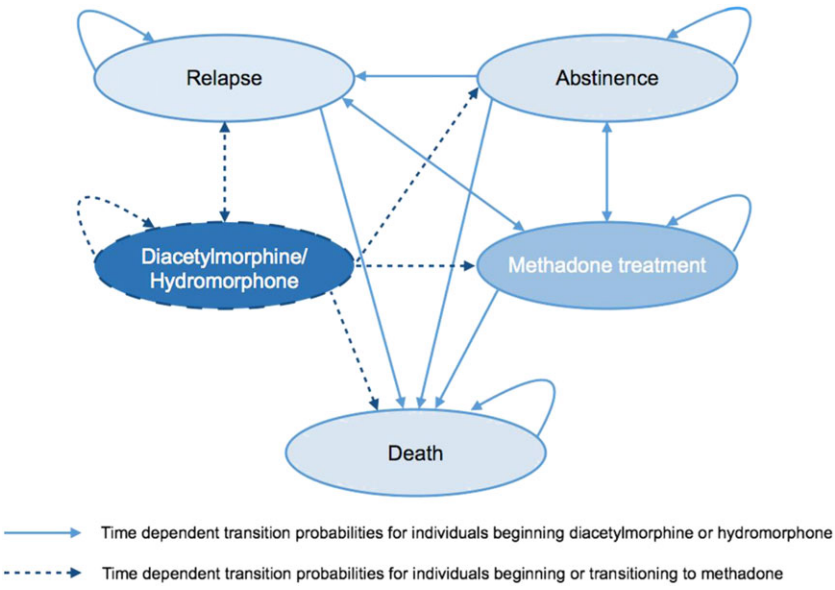

Figure 1 Model diagram [Colour figure can be viewed at wileyonlinelibrary.com]

Table 1 Model parameter estimates.

Parameter	*Estimate*	*Distribution*	*Source*
State transition probabilities			
MMT state			
Remain in MMT state[a]	(λ = 0.114, γ = 0.643)	Weibull	BC MMTOS
Multiplier: episode 4, model est. (SE)	0.923 (0.033)	Normal	Nosyk *et al.* 2009 [21]
Multiplier: episode 5, model est. (SE)	0.965 (0.042)	Normal	
Multiplier: episode 6, model est. (SE)	0.952 (0.041)	Normal	
Transition to relapse state, %	95.88	Beta (3748,	BC MMTOS
Transition to abstinence state, %	4.12	161)	
DAM state			
Remain in DAM state[a]	(λ = 0.090, γ = 0.503)	Weibull	SALOME/NAOMI
Multiplier: episode 4,[b] model est. (SE)	0.923 (0.033)	Normal	Nosyk *et al.* 2009 [21]
Multiplier: episode 5, model est. (SE)	0.965 (0.042)	Normal	
Multiplier: episode 6, model est. (SE)	0.952 (0.041)	Normal	
Transition to relapse state,[c] %	36.96	Dirichlet (407,	Rehm *et al.* 2001 [28]
Transition to abstinence state, %	22.38	224, 370)	
Transition to MMT state, %	40.66		
HDM state			
Remain in HDM state[a]	(λ = 0.051, γ = 0.473)	Weibull	SALOME/NAOMI
Multiplier: episode 4,[b] model est. (SE)	0.923 (0.033)	Normal	Nosyk *et al.* 2009 [21]
Multiplier: episode 5, model est. (SE)	0.965 (0.042)	Normal	
Multiplier: episode 6, model est. (SE)	0.952 (0.041)	Normal	
Transition to relapse state,[c] %	36.96	Dirichlet (407, 224, 370)	Rehm *et al.* 2001 [28]
Transition to abstinence state, %	22.38		
Transition to MMT state, %	40.66		
Relapse state			
Remain in relapse state[a]	(λ = 0.091, γ = 0.672)	Weibull	BC MMTOS
Multiplier: episode 4, model est. (SE)	1.220 (0.048)	Normal	Nosyk *et al.* 2009 [21]
Multiplier: Episode 5, model est. (SE)	1.350 (0.060)	Normal	
Multiplier: episode 6, model est. (SE)	1.442 (0.056)	Normal	
Transition to treatment state	1	Fixed	
Abstinence state			
Remain in abstinence state[a]	(λ = 0.089, γ = 0.797)	Weibull	Termorshuizen *et al.* 2005 [29]
Transition to relapse state	1	Fixed	
Transition to mortality[d]			
Abstinence state: HIV^-	See Supporting information, Table S4	Fixed	Stats Canada [22]
Abstinence state: HIV^+, HR (95% CI)	Female: 2.2 (1.6–3.0) Male: 1.4 (1.1–1.7)	Normal	Lewden *et al.* 2012 [23]
MMT state: SMR (95% CI)	Female: 12.2 (10.3–14.4) Male: 8.7 (8.0–9.4)	Normal	Arendt *et al.* 2011 [30]
MMT state relative to relapse state: AHR (95% CI)	Female: 0.24 (0.17, 0.33) Male: 0.29 (0.23, 0.35)	Normal	Evans *et al.* 2015 [24]
DAM/HDM state: SMR (95% CI)	Female 17.2 (10.0–29.6) Male 8.4 (6.1–11.6)	Normal	Rehm *et al.* 2005 [31]
HIV seroconversion[e]			
Probability in treatment, α (β)	0.0028 (0.0010)	Beta	Bayoumi *et al.* 2008 [25], Nosyk *et al.* 2012 [13]
Probability in relapse, α (β)	0.0364 (0.0146)	Beta	
Probability in abstinence, α (β)	0.0007 (0.0001)	Beta	
Utilities[f]			
MMT state, mean	0.775	MVN	SALOME/NAOMI
DAM state, mean	0.793	MVN	SALOME/NAOMI
HDM state, mean	0.747	MVN	SALOME/NAOMI
Relapse state, mean	0.726	MVN	SALOME/NAOMI

(***Continues***)

Table 1. (Continued)

Parameter	*Estimate*	*Distribution*	*Source*
Abstinence state: HIV^-	See Supporting information, Table S15	Beta	Bansback *et al.* 2012 [32]
Abstinence state: HIV^+, α (β)	0.756 (0.19)	Beta	Anis *et al.* 2009 [33]
Monthly costs[g]			
Drug treatment:			
Methadone, mean, $	359.19	Normal	NAOMI, BC PNET
DAM, mean, $	1836.15	Normal	SALOME
HDM, mean, $	1855.35	Normal	SALOME
HIV, $	865.69	Fixed	Nosyk *et al.* 2014 [34], Wood *et al.* 2003 [35]
MMT state			
Health resource use,[h] mean, $	125.89	MVN	SALOME/NAOMI
Criminal involvement,[h] mean, $	7126.88	MVN	SALOME/NAOMI
Criminal charges,[h] mean, $	279.22	MVN	SALOME/NAOMI
DAM state			
Health resource use,[h] mean, $	250.40	MVN	SALOME/NAOMI
Criminal involvement,[h] mean, $	4461.87	MVN	SALOME/NAOMI
Criminal charges,[h] mean, $	186.99	MVN	SALOME/NAOMI
HDM state			
Health resource use,[h] mean, $	383.09	MVN	SALOME/NAOMI
Criminal involvement,[h] mean, $	4475.57	MVN	SALOME/NAOMI
Criminal charges,[h] mean, $	249.12	MVN	SALOME/NAOMI
Relapse state			
Health resource use,[h] mean, $	985.99	MVN	SALOME/NAOMI
Criminal involvement,[h] mean, $	10 286.59	MVN	SALOME/NAOMI
Criminal charges,[h] mean, $	600.02	MVN	SALOME/NAOMI

MMT = methadone maintenance treatment; BC MMTOS = British Columbia Methadone Maintenance Treatment Outcome Study; DAM = diacetylmorphine; SALOME = Study to Assess Long-term Opioid Maintenance Effectiveness; NAOMI = North American Opiate Medication Initiative; HDM = hydromorphone; HR = hazard ratio; SMR = standardized mortality ratio; AHR = adjusted hazard ratio; BC PNET = BC PharmaNet database; MVN = multivariate normal; SE = standard error; CI = confidence interval. [a]Parameter estimates provided for the time-to-discontinuation of each health state represent the shape (γ) and scale (λ) parameters of the Weibull distribution. From estimated survival functions, at 6 months, the probability of remaining in MMT was approximately 70%; 80% in DAM, 89% in HDM, 74% in relapse and 69% in abstinence. [b]Change in duration of successive DAM/HDM episodes assumed equivalent to MMT. [c]Included transition to MMT (n = 379) and other treatment (n = 28) among all non-missing participants alive at the end of follow-up (n = 1001). [d]Gender-specific estimates used in the model are shown in the Supporting information, Table S5. [e]See NAOMI cost-effectiveness paper, Nosyk *et al.* 2012 [13] [f]Calculations shown in the Supporting information, Tables S11–S13. [g]Calculations shown in the Supporting information, Tables S6–S12. [h]For all costs of health resource use, criminal involvement and criminal charges, trial-based data on utilization/frequency of events was multiplied by unit costs from Krebs *et al.* detailed in the Supporting information, section S2.2. Presented state-specific costs are estimated mean values, given mean age and HIV and gender mix of participants in the SALOME and NAOMI studies.

extracted for each trial participant and used to represent the frequency of criminal charges [27].

For the life-time analysis, we classified participants in SALOME and NAOMI trials as being in treatment (HDM, DAM or MMT) or in relapse within each month. Estimates of costs related to each health state were derived from generalized linear mixed-effects regression models that controlled for age, sex and HIV status to account for heterogeneity of participants, and allowed for changes in costs over time. We used treatment-specific regression models (HDM versus DAM versus MMT) to estimate costs and explored pooling HDM and DAM estimates in a sensitivity analysis.

Patients accumulated costs as a result of opioid substitution treatment, drug treatments for HIV infection, other health-care use, self-reported criminal activity and criminal charges within each 30-day period in the simulation model. The frequency of other health resource use and the frequency of crime without criminal charges (i.e. self-reported criminal involvement of property and violent crimes) were based on data from the SALOME trial.

Health-related quality of life

Health-related quality of life is incorporated in terms of utility values on a scale from 0 (equivalent to death) to 1 (full health), combined with life years to generate QALYs, and discounted at 5%. The European Quality of Life–5 Dimensions (EQ-5D) was measured in the SALOME trial and we utilized Canadian societal utility values for this instrument [32]. We calculated health utility value estimates for the MMT treatment, DAM treatment, HDM treatment and

relapse states from trial data using generalized linear mixed-effects regression (Supporting information, Section 2.3). We again explored pooling HDM and DAM estimates in a sensitivity analysis.

Uncertainty analysis

We use a probabilistic analysis to estimate means and 95% CIs of total costs, QALYs and ICERs to reflect the underlying parameter uncertainty. For the within-trial analysis, we used the percentile method based on bootstrap replicates [36]. For the life-time analysis we combined bootstrap samples from SALOME/NAOMI derived parameters with samples from probability distributions assigned to non-SALOME/NAOMI-derived parameters and conducted 5000 Monte Carlo simulations [37]. To explore the sensitivity of results to specific parameter uncertainty, alternative assumptions and sources of data we conducted a series of scenario analyses.

RESULTS

Within-trial analysis

The 6-month benefits for the two strategies were very similar, with HDM providing 0.002 additional QALYs (95% CI = –0.018 to 0.023) in comparison to DAM (Table 2). The total costs of HDM were $15 510 higher than DAM, but the confidence interval overlapped zero (95% CI = –9955 to 43 706). While the costs of drug treatment were similar, the costs of involvement in property and violent crime were slightly higher ($32 201, 95% CI = 11695–57 239 versus $19 992, 95% CI = 6557–40 410) for HDM compared to DAM. The ICER for HDM versus DAM was subsequently high due to the small incremental QALYs. However, as the incremental benefits and costs overlapped, there was a 16% probability that HDM would provide more benefit at less cost than DAM.

Life-time analysis

Base case

The model results suggest that the DAM and HDM strategies provide 2–3 additional years of life compared to the methadone strategy (18.4 and 17.5 versus 14.9 years). For the DAM strategy patients were estimated to spend, on average, 14.4 of their 17.5 years of life in treatment (1.4 of these years in methadone), 2.5 years in relapse and 0.6 years in abstinence. For the HDM group, patients were estimated to spend 16.8 of their 18.4 years of life in treatment, 1.3 years in relapse and 0.3 years in abstinence. For the methadone group, patients were estimated to spend 9 of their 14.9 years of life on treatment, 5.5 years in relapse and 0.2 years in abstinence.

When combining life years with quality of life, the model suggests that the DAM and HDM strategies provide similar benefits (8.4 QALYs, 95% CI = 7.4–9.5 and 8.3 QALYs, 95% CI = 7.2–9.5, respectively). This is 1.1–0.9 additional QALYs in comparison to the methadone strategy (7.4 QALYs, 95% CI = 6.5–8.3). In terms of costs, methadone was the most expensive strategy, costing $1.15 million (95% CI = $0.71–1.84 million) during the life-time. Of this, 90% of the cost was attributable to involvement in property and violent crime and less than 3% attributable to treatment. DAM and HDM has similar costs ($1.01 million, 95% CI = $0.68–1.59 million and

Table 2 Within-trial analysis results.

	Hydromorphone	*Diacetylmorphine*
By arm		
Costs of drug treatment, mean (95% CI), $	10 780 (10 179, 11 358)	10 352 (9668, 10 964)
Costs of resource utilization	5770 (4040, 7833)	5034 (3737, 7140)
Costs of HIV treatment	779 (416, 1143)	764 (407, 1120)
Costs of in-patient care	3063 (1477, 4964)	2210 (1080, 4194)
Costs of out-patient care	1928 (1616, 2262)	2060 (1737, 2455)
Cost of crime, mean (95% CI), $	32 201 (11 695, 57 239)	19 992 (6557, 40 410)
Costs of involvement in property and violent crime	30 543 (10 546, 54 717)	18 739 (5586, 39 073)
Costs of criminal charges	1658 (558, 3127)	1253 (424, 2321)
Total costs,[a] mean (95% CI), $	49 830 (28 401, 73 637)	34 320 (21 780, 55 998)
Total QALYs,[b] mean (95% CI)	0.377 (0.361, 0.393)	0.375 (0.357, 0.391)
Hydromorphone versus diacetylmorphine		
Incremental adjusted costs, mean (95% CI), $	15 510 (−9955, 43 706)	
Incremental adjusted QALYs, mean (95% CI)	0.00232 (−0.01777, 0.02288)	
ICER	6 683 925 (dominates, dominated)	

QALY = quality adjusted life years; ICER = incremental cost-effectiveness ratio; CI = confidence interval. [a]Adjusted for baseline costs of resource utilization and property and violent crime. [b]Adjusted for baseline utility scores.

$1.02 million, 95% CI = $0.72–$1.51 million). DAM and HDM are therefore both considered to dominate methadone, providing more benefit at less cost. Even when considering the parameter uncertainty, DAM and HDM had a 75 and 67% probability of dominating methadone.

To explain further the impact of each treatment on crime, we estimated patients on the DAM and HDM strategies would have a similar decrease in criminal charges for property crime compared to methadone (0.3 versus 0.5 charges related to property crime per person-year) and have five fewer involvements with property crimes per person-year (9.6 and 8.8 compared to 15.0 involvements per person-year), based on the average life-time crime cost derived from the model.

Scenario analysis

The results were consistent in nearly all scenarios, with the exception to the price of medication and the perspective taken (Table 3). If the list price on the formulary for HDM is used (note that the list price is for pain management, which is prescribed typically at doses far lower than the average daily dose of 261 mg per day), HDM is no longer cost-saving, and instead has an ICER versus methadone of $173 k/QALY (total cost of HDM increases to $1.31 million during a life-time). If involvement in property and

Table 3 Base case and scenario analyses.

	ICER (95% CI)/probability treatment dominates		
Scenario	*Diacetylmorphine versus methadone*	*Hydromorphone versus methadone*	*Hydromorphone versus diacetylmorphine*
Base case (retention: from SALOME/NAOMI trials, cost and utilities: treatment-specific, drug cost: API price, perspective: societal)	Ds (Ds, 306.8)/75%	Ds (Ds, 883.7)/67%	Dd (Ds, Dd)/17%
Costs and utilities: pooled	23.5 (Ds, 200.8)/37%	24.5 (Ds, 210.2)/36%	27.7 (Ds, Dd)/32%
Retention: from MTC	Ds (Ds, 300.4)/74%	Ds (Ds, 749.7)/68%	Dd (Ds, Dd)/5%
Retention: from MTC, costs and utilities: pooled	20.6 (Ds, 203.7)/38%	22.5 (Ds, 207.7)/37%	34.3 (Ds, 339.9)/33%
Perspective: MoH	132.3 (87.5, 278.1)/0%	200.7 (116.9, 1400.4)/0%	Dd (20.5, Dd)/0%
Age (years) = 30	Ds (Ds, 342.0)/79%	Ds (Ds, 1632.0)/70%	36.0 (Ds, Dd)/12%
Age = 50	Ds (Ds, 279.8)/68%	Ds (Ds, 611.0)/59%	Dd (Ds, Dd / 21%
Crime cost 20% lower	Ds (Ds, 277.9)/70%	Ds (Ds, 764.4)/60%	Dd (Ds, Dd)/16%
Crime cost 20% higher	Ds (Ds, 340.2)/78%	Ds (Ds, 980.0)/71%	Dd (Ds, Dd)/18%
Resource utilization cost 20% lower	Ds (Ds, 309.3)/75%	Ds (Ds, 885.4)/67%	Dd (Ds, Dd)/17%
Resource utilization cost 20% higher	Ds (Ds, 306.0)/75%	Ds (Ds, 880.1)/67%	Dd (Ds, Dd)/17%
Addiction treatment cost 20% lower	Ds (Ds, 276.1)/79%	Ds (Ds, 802.0)/71%	Dd (Ds, Dd)/18%
Addiction treatment cost 20% higher	Ds (Ds, 343.4)/70%	Ds (Ds, 935.3 /61%	Dd (Ds, Dd)/17%
Discount rate = 3%	Ds (Ds, 291.0)/72%	Ds (Ds, 684.8)/63%	Dd (Ds, Dd)/20%
Discount rate = 0%	Ds (Ds, 266.7)/66%	Ds (Ds, 472.5)/57%	Dd (Ds, Dd)/23%
Frailty terms = 1	Ds (Ds, 268.9)/76%	Ds (Ds, 604.3)/67%	Dd (Ds, Dd)/20%
Conservative extrapolation for discontinuation curves (exponential)	Ds (Ds, 385.9)/82%	Ds (Ds, 1152.0)/73%	113.5 (Ds, Dd)/29%
Conservative extrapolation for hydromorphone and diacetylmorphine only (exponential)	Ds (Ds, 834.8)/81%	Ds (Ds, 4831.1)/71%	113.5 (Ds, Dd)/29%
Probability of HIV seroconversion: set to zero	Ds (Ds, 306.8)/75%	Ds (Ds, 883.7)/67%	Dd (Ds, Dd)/17%
Diacetylmorphine drug cost: most recent purchase price, hydromorphone drug cost: list price	Ds (Ds, 315.2)/74%	172.7 (Ds, 1647.6/26%	Dd (Ds, Dd)/5%
Diacetylmorphine drug cost: most recent purchase price, hydromorphone drug cost: 20% of list price	Ds (Ds, 315.2)/74%	Ds (Ds, 901.6)/66%	Dd (Ds, Dd)/18%

Ds = dominates: the treatment provides more or equal benefit [quality-adjusted life years (QALYs)] at less cost to the comparator. Dd = dominated: the treatment provides equal or less benefit (QALYs) at more cost to the comparator. MoH = Ministry of Health; MTC = mixed treatment comparison (see Supporting information); CI = confidence interval; API = active pharmaceutical ingredient; ICER = incremental cost-effectiveness ratio; SALOME = Study to Assess Long-term Opioid Maintenance Effectiveness; NAOMI = North American Opiate Medication Initiative.

violent crime costs are not included, neither DAM nor HDM are cost-saving, with ICERs versus methadone of $132 k/QALY and $201 k/QALY, respectively. Using more conservative assumptions around the longer-term retention in DAM and HDM treatment reduced the QALYs, but also reduced drug costs, and so the ICERs remained cost-saving.

DISCUSSION

This study considers the economic arguments for HDM substitution therapy for opioid maintenance informing wider policymaking, where spending on pharmaceuticals has to be considered against alternative spending opportunities. The results demonstrate that both HDM and DAM provide similar costs and benefits using the API prices in the trial. In comparison to methadone, the costs saved through reduced involvement in violent and property-related criminal activity and hospitalization outweigh the costs of both HDM and DAM, and provide more benefit. Our findings suggest therefore, that HDM could be an attractive use of health-care resources from the societal perspective, if prices for HDM can be negotiated effectively to reflect its value.

While the effectiveness and the cost-effectiveness of DAM for opioid maintenance have been demonstrated previously, the motivation for undertaking the SALOME trial was dictated by the social connotations, political reality and the resistance of government bureaucracy to legalize and allow DAM as the approved therapy for methadone refractory opioid-dependent patients. The SALOME trial demonstrated the non-inferiority of HDM, a legally approved drug for pain management, to DAM, finding similar impacts on treatment retention, involvement in violent and property-related criminal activity and associated resources use. This, to our knowledge the first cost-effectiveness study of HDM substitution therapy for opioid maintenance, provides economic evidence for its use.

There are limitations to our study. First, we were not able to include costs relating to the possession or dealing of drugs, disorderly conduct, sex work, major driving violations or broken conditions imposed by the legal system which have a huge burden on society. Measuring these costs is challenging, but would probably further improve the cost savings from the provision of HDM (and DAM) substantially. Secondly, we relied upon extrapolations beyond the trial data on transitions between treatment states, which required a number of assumptions. We considered various scenario analyses on these extrapolations, including lower retention in treatment, and found that all were relatively insensitive to our assumptions. Thirdly, other oral opioids such as buprenorphine or slow-release morphine are an important option to improve the effectiveness of opioid agonist treatment by adapting it to the needs of the patients [1,38]. Lack of accessibility to other oral opioids besides methadone, as it was in Canada during enrolment into our clinical trials, could have potentially influenced the generalizability of the rates of retention used in the model. Fourthly, our life-time analysis assumed only one state for relapse, when in reality there are some people who relapse but remain engaged with care, for whom benefits may be greater than those who do not. We did not have sufficient evidence to separate this health state. Fifthly, our findings from the within-trial analysis, that the unadjusted involvement in property and violent criminal activity was higher in the HDM versus DAM strategy, is based only on a few individuals and we do not have a hypothesis that this would be higher in reality. In our life-time model, where the cost of involvement in property and violent crime was adjusted for age and gender, the HDM and DAM strategies were similar. Finally, our comparison between HDM and methadone was achievable only through an indirect comparison. While such comparisons are becoming an increasingly adopted methodology, they are more susceptible to bias [39].

While this study provides the economic evidence for adding injectable HDM as part of the therapeutic options for opioid use disorder, resistance in many regions obstruct the expansion and scale-up of this treatment, not just to this particular option but to opioid agonist treatment in general [40]. Although political arguments against injectable opioid agonist treatment (e.g. potential for diversion, safety, undermining of other therapies, etc.) have been addressed by several randomized controlled trials and years of practice [4,41–43], policymakers remain reluctant to support its implementation or expansion. Much of that resistance stems from beliefs that the goal of any treatment should be abstinence of all opioids and from the stigma associated with opioid use disorder and related concerns about how public funds are allocated [44,45]. Despite the evidence of effectiveness and cost-effectiveness of injectable opioid agonist treatment, it is undeniable that a shift in drug policy that embraces evidence-based approaches is needed in order to overcome implementation barriers.

In conclusion, our study finds that injectable HDM treatment is less costly and more beneficial than methadone treatment during a life-time predominantly through reducing the costs of involvement in violent and property criminal activity. In jurisdictions where DAM treatment is not available, not providing HDM treatment would add to the societal costs.

Trial registration

clinicaltrials.gov Identifier: NCT01447212.

Declaration of interests

None.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

Appendix S1 model description, calculation of model parameters, and supplementary information on the results of the sensitivity analyses.
Table S1 Results of Weibull and exponential regression models for time to discontinuation in primary model states.
Table S2 External estimates of transition to alternate health states following discontinuation in treatment [hydromorphone (HDM), diacetylmorphine (DAM), methadone maintenance treatment (MMT), multiple personality disorder (MPD)], relapse, abstinence.[a]
Table S3 Results of proportional hazards random intercept regression to estimate duration in successive treatment and relapse episodes from British Columbia Methadone Maintenance Treatment Outcome Study (BC MMTOS).
Table S4 Base annual probability of mortality (abstinence state, HIV-negative).
Table S5 Estimated mortality risks for model health states.
Table S6 Parameters and calculation of study treatment costs.
Table S7 Parameters and calculation of HIV drug treatment costs.
Table S8 Health resource utilization: Study to Assess Long-term Opioid Maintenance Effectiveness (SALOME) and North American Opiate Medication Initiative (NAOMI) trials.
Table S9 Unit costs of health resource utilization and crime.
Table S10 Self-reported property theft and violent crime rates and police charges: Study to Assess Long-term Opioid Maintenance Effectiveness (SALOME) and North American Opiate Medication Initiative (NAOMI) trials.
Table S11 Results of generalized least squares regression to estimate the costs of health resource utilization, criminal involvement, criminal charges and health utility from Study to Assess Long-term Opioid Maintenance Effectiveness (SALOME) and North American Opiate Medication Initiative (NAOMI) data set: treatment-specific estimates.
Table S12 Results of generalized least-squares regression to estimate the costs of health resource utilization, criminal involvement, criminal charges and health utility from Study to Assess Long-term Opioid Maintenance Effectiveness (SALOME) and North American Opiate Medication Initiative (NAOMI) data set: pooled estimates.
Table S13 Reported general-population European Quality of Life–5 Dimensions (EQ-5D) estimates.[33]
Table S14 Complete results of sensitivity analyses.
Figure S1 Internal validation.

