Original Investigation

Hydromorphone Compared With Diacetylmorphine for Long-term Opioid Dependence
A Randomized Clinical Trial

Eugenia Oviedo-Joekes, PhD; Daphne Guh, MSc; Suzanne Brissette, MD; Kirsten Marchand, BSc; Scott MacDonald, MD; Kurt Lock, BA; Scott Harrison, MA; Amin Janmohamed, MSc; Aslam H. Anis, PhD; Michael Krausz, MD; David C. Marsh, MD; Martin T. Schechter, MD

IMPORTANCE Diacetylmorphine hydrochloride (the active ingredient in heroin), delivered under supervision, is effective for the treatment of severe opioid use disorder. However, owing to political and regulatory barriers, it is not available in many settings around the world, which limits the options for many long-term street opioid injectors not attracted into or retained in available treatments.

OBJECTIVE To test if injectable hydromorphone hydrochloride is noninferior to injectable diacetylmorphine in reducing illicit heroin use for chronic injection opioid users after 6 months of intervention.

DESIGN, SETTING, AND PARTICIPANTS The Study to Assess Longer-term Opioid Medication Effectiveness (SALOME) was a phase 3, double-blind, noninferiority trial. The study randomized 202 long-term street opioid injectors in Vancouver, British Columbia, Canada. Eligible participants were recruited between December 19, 2011, and December 18, 2013. Both intent-to-treat (ITT) and per-protocol (PP) analyses were conducted.

INTERVENTIONS Participants were randomly assigned to receive injectable diacetylmorphine or hydromorphone (up to 3 times daily) for 6 months under supervision.

MAIN OUTCOMES AND MEASURES Primary and coprimary efficacy outcomes were self-reported days of street heroin use (primary), days of any street-acquired opioids in the prior 30 days (noninferiority margin, 4 days), and the proportion of urinalyses positive for street heroin markers (margin, 10% of the observed rate in the diacetylmorphine group). The mean differences between diacetylmorphine and hydromorphone for the ITT and PP analyses were reported.

RESULTS The study included 202 participants; 100 randomized to receive hydromorphone and 102 to diacetylmorphine. Their mean (SD) age was 44.33 (9.63) years, and 30.7% (62 of 202) were women. Noninferiority of hydromorphone was confirmed in the PP analysis (−1.44; 90% CI, −3.22 to 0.27) for street heroin use, although the margin of 4 days was not excluded in the ITT analysis (−2.34; 90% CI, −4.14 to −0.52). Noninferiority was confirmed for any street opioids in the ITT analysis (−0.85; 90% CI, −2.97 to 1.25) and the PP analysis (−0.15; 90% CI, −2.09 to 1.76), as well as for the urinalyses (0.09; 90% CI, −0.02 to 0.19 for the ITT analysis and 0.13; 90% CI, 0.02-0.24 for the PP analysis). There were 29 SAEs considered to have some relationship with the injection medication, 5 in the hydromorphone group and 24 in the diacetylmorphine group (rate ratio, 0.21; 95% CI, 0.06-0.69). Seizures and overdoses accounted for 25 of the 29 related SAEs.

CONCLUSIONS AND RELEVANCE This study provides evidence to suggest noninferiority of injectable hydromorphone relative to diacetylmorphine for long-term opioid dependence. In jurisdictions where diacetylmorphine is currently not available or for patients in whom it is contraindicated or unsuccessful, hydromorphone could be offered as an alternative.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01447212

JAMA Psychiatry. 2016;73(5):447-455. doi:10.1001/jamapsychiatry.2016.0109
Published online April 6, 2016.

Editorial page 437

Supplemental content at jamapsychiatry.com

CME Quiz at jamanetworkcme.com and CME Questions page 540

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Eugenia Oviedo-Joekes, PhD, Centre for Health Evaluation and Outcome Sciences, Providence Health Care, St Paul's Hospital, Room 575, 1081 Burrard St, Vancouver, BC V6Z 1Y6, Canada (eugenia@cheos.ubc.ca).

Dependence on opioids, including heroin, continues to exact a heavy toll on people and communities around the world. Oral maintenance treatment, such as methadone hydrochloride and buprenorphine hydrochloride, has been shown to be effective for many affected individuals, increasing patient retention and decreasing drug use, infectious disease transmission, and illegal activity.[1,2] However, in contexts where oral maintenance treatment is available, an important minority of individuals with severe opioid use disorder are not attracted into or retained in such treatments, so that alternative approaches are urgently required.[3,4]

For this subgroup, 6 randomized trials have now shown that injectable diacetylmorphine hydrochloride (the active ingredient in heroin), delivered under supervision, is both more clinically effective[5-11] and cost-effective[12,13] than oral methadone. The Cochrane Collaboration has confirmed the superiority of diacetylmorphine in this subpopulation.[14] Supervised, medically prescribed diacetylmorphine is now being used with success in a number of countries in Europe (eg, Germany, the Netherlands, Switzerland, and Denmark), where it accounts for approximately 5% to 8% of all those enrolled in substitution treatments.[4] However, there are many countries around the world where diacetylmorphine is not available owing to regulatory or political reasons,[15] which limits the interventions available and thus access to care for many individuals with long-term use of street opioid injection not effectively reached by current approaches.

In the prior Canadian trial,[7] our group randomized a small number of participants to receive injectable hydromorphone hydrochloride (a medication licensed for analgesia but not opioid maintenance) instead of diacetylmorphine on a double-blind basis to test for heroin metabolites in urine. Surprisingly, these participants were unable to detect that they were receiving hydromorphone. Moreover, hydromorphone appeared as effective as diacetylmorphine, although the study was not powered to test this hypothesis.[16] These findings suggest that hydromorphone may offer the same benefits as diacetylmorphine, an intervention that has been demonstrated to be effective but is currently denied to patients owing to political and regulatory barriers in many settings. While noninferiority trials pose methodological challenges, they are designed to test treatments that offer ancillary advantages over those that have shown to be effective in previous superiority investigations.[17] The Study to Assess Longer-term Opioid Medication Effectiveness (SALOME) was designed to test whether injectable hydromorphone is noninferior to injectable diacetylmorphine for long-term opioid dependence.

Key Points

Question Is injectable hydromorphone hydrochloride as effective as injectable diacetylmorphine hydrochloride (ie, pharmaceutical heroin) for the treatment of long-term severe opioid use disorder?

Findings In this 6-month randomized clinical trial of injectable hydromorphone relative to diacetylmorphine, noninferiority was demonstrated for days of street heroin use in the per-protocol analysis but not in the intent-to-treat analysis. Noninferiority was also demonstrated for total days of any street opioid use in both analyses and hydromorphone had significantly fewer related adverse events.

Meaning In jurisdictions where diacetylmorphine is currently unavailable or in patients in whom it is contraindicated or unsuccessful, hydromorphone could be offered as an alternative.

Methods

Participants and Setting

Eligible participants, recruited between December 19, 2011, and December 18, 2013, were men and women 19 years and older with long-term opioid dependence[18] and residing in the greater Vancouver area, British Columbia, Canada. Screening procedures and baseline characteristics have been published previously[19,20] (eAppendix 1 in Supplement 1).

Study Design

The SALOME was a phase 3, double-blind, noninferiority trial that randomized participants to receive either injectable diacetylmorphine or injectable hydromorphone for 6 months. The full study protocol can be found in Supplement 2. The original sample size planned was 322, with 2 proposed sites (Vancouver, British Columbia, and Montréal, Québec, Canada). However, the Montréal site was unable to participate. As a result, the planned power of 0.95 was revised to 0.90 and the sample size to 202 participants[21] (eAppendix 2 in Supplement 1).

Oversight

The study was conducted in Vancouver. All participants provided written informed consent before administration of any medication or data collection. The SALOME followed good clinical practice guidelines and was approved by the Providence Health Care/University of British Columbia Research Ethics Board. An independent Data and Safety Monitoring Board advised the investigators on patient safety and trial conduct based on masked data (eAppendix 3 in Supplement 1).

Randomization

Variable block size randomization was used with prepared tables from the Data Centre at St Paul's Hospital in Vancouver. Only the study pharmacists (including one of us [A.J.]) could see participants' intervention assignment to prepare the medications. Randomization was stratified by sex, and couples were randomized together to the same arm.

Intervention

A total of 102 participants were randomly assigned to receive injectable diacetylmorphine and 100 to receive injectable hydromorphone. Identical coded, pharmacologically equivalent multidose vials and prefilled syringes were prepared by the pharmacy, allowing masked dose adjustment by physicians and nurses. Doses were presented in diacetylmorphine equivalents, with a 2:1 ratio of diacetylmorphine to hydromorphone.[22]

Injectable diacetylmorphine and hydromorphone were self-administered under supervision of registered nurses at the study site. Medications were not allowed to be removed from the injection room. Participants could receive up to

3 doses per day, up to 400 mg per dose, and up to 1000 mg per day. Intravenous injection was only allowed in the upper extremities. Intramuscular injections were also allowed in thighs and gluteals. At any time, in consultation with the study physician (S.M. and other nonauthors), participants could add oral methadone to their care (eAppendix 4 in Supplement 1). Participants had access to registered nurses, addiction counselors, social workers, physicians, and allied health professionals on site.

Outcome Measures

Assessments and research urine samples were obtained at baseline (before randomization and allocation to study medications) and at 3 and 6 months. Questionnaires were administered by experienced members of the research team (K.M. and K.L.), who operated independently of the clinical team (S.M. and other nonauthors) at a separate site.[19] The clinical team did not have access to any research data (eAppendix 5 in Supplement 1).

The primary outcome measure was street heroin use, defined as the number of days of use in the prior 30 days by means of self-report, in keeping with previous trials.[6-8] Coprimary outcomes were the number of days of using any street-acquired opioids (including heroin) in the prior 30 days and the proportion of urinalyses positive for street heroin markers in the urine sample provided at the 6-month assessment. Secondary outcomes included the proportion of participants receiving injectable medications at least 28 days in the prior 30 days (based on clinical records), physical and mental health symptoms based on the Maudsley Addiction Profile,[23] and self-reported number of days involved in illegal activities and of crack cocaine use. To test the success of the masking, participants were asked which medication they thought they had been receiving, allowing for one of 5 choices (definitely or possibly for each medication and unsure).

Urine specimens were collected from participants at each research visit. Samples were analyzed for the detection of the following opioid alkaloid impurities present in illicit but not pharmaceutical heroin: papaverine hydrochloride, noscapine, acetylcodeine, desmethylmeconine, desmethylpapaverine, and didesmethylpapaverine[24] (eAppendix 6 in Supplement 1). All study participants were assessed for adverse events (AEs), drug reactions, or changes in health status during each visit to the clinic by trained registered nurses (eAppendix 7 in Supplement 1).

Statistical Analysis

The effect of injectable diacetylmorphine on street heroin use has been remarkably consistent in trials testing efficacy to date.[5-8] To derive the noninferiority margin Δ, we conducted a Delphi process in which investigators of the main European trials[5,8-11] were asked what margin they would tolerate to accept hydromorphone as noninferior to diacetylmorphine. Based on their consensus, Δ was set at 4 days for both heroin use and total use of any street-acquired opioids. Noninferiority was assessed by the CI comparison approach and determined by examining the CI around the difference between diacetylmorphine and hydromorphone. If the lower bound of the 1-tailed 95% CI (ie, 100[1 − α]%), corresponding to a 2-tailed 90% CI (ie, 100[1 − 2α]%), excluded the margin (4 days), noninferiority was concluded, with a significance level of .05. For the proportion of urinalyses positive for street heroin markers, a margin of 10% of the observed rate in the diacetylmorphine group was used based on a recent noninferiority study[25] testing treatment with morphine for opioid dependence. Secondary outcomes and differences between groups are described using the means (95% CIs).

For those outcomes that were also measured at baseline, analysis of covariance was used to adjust for baseline values (eAppendix 8 in Supplement 1). All statistical analyses were performed using a software program (SAS, version 9.4; SAS Institute Inc).

Outcome data are given for intent-to-treat (ITT) and per-protocol (PP) analyses. Because participants were allowed to reinitiate study medications at any time during the 6-month period, the PP population was defined as those receiving injectable medications at least 20 days in the month before the 6-month assessment. The ITT analysis includes all randomized participants, regardless of retention in treatment. While ITT is clearly preferred in superiority trials, in the context of noninferiority trials, it increases the likelihood of falsely concluding noninferiority when such a conclusion is not justified. For this reason, regulators have put greater emphasis in the past on PP analyses in noninferiority trials, although other researchers have suggested that both are required.[17,26] Missing values were imputed using multiple imputation, except when data were missing owing to death (2 participants), thus avoiding assigning a score to a deceased participant[27] (see eAppendix 4 in Supplement 1 for the sensitivity analysis).

Success of the masking was measured using the blinding index by James et al,[28] which is sensitive to the degree of disagreement between randomization arm and guesses of allocation to study medications. This index ranges from 0 to 1, representing completely correct and incorrect guessing, respectively, with 0.5 representing complete random guessing.

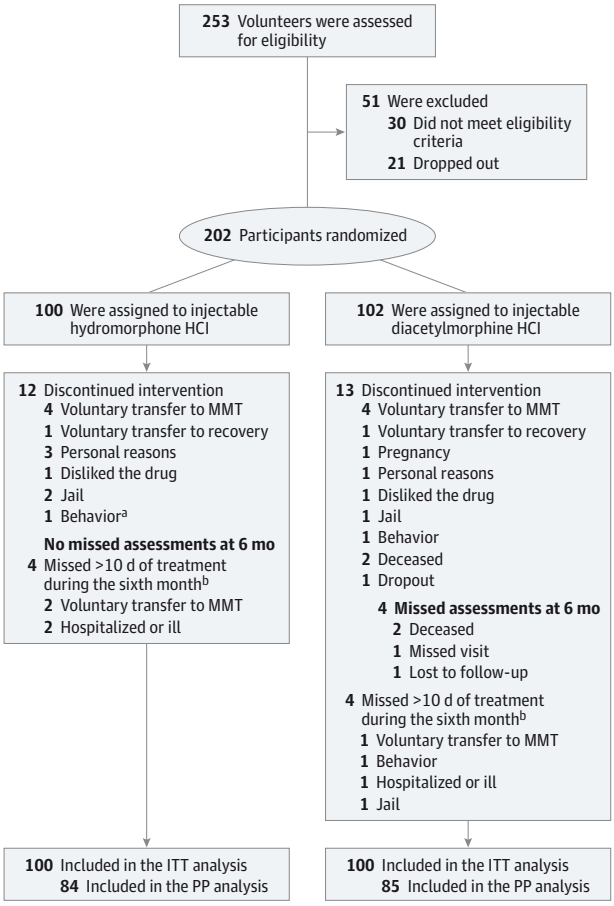
The AEs and serious AEs (SAEs) were compared between the intervention groups as binary outcomes (ie, having ≥1 event) and continuous outcomes (ie, number of events). For binary outcomes, relative risks and 95% CIs were calculated. For continuous outcomes, event rate ratios and 95% CIs were estimated by the negative binomial regression model to account for overdispersion.

Results

Participants

A total of 253 volunteers started the screening process (**Figure 1**), and 202 were randomized and received at least 1 dose of the study medications. The ITT analysis included 100 participants per group (2 deaths occurred in the diacetylmorphine group), and the PP analysis included 84 and 85 participants in the hydromorphone and diacetylmorphine groups, respectively. Baseline characteristics were similar between groups, as well as dropout rates. The sample represented the

Figure 1. Study Group Assignment and Retention Throughout the Trial



HCl indicates hydrochloride; ITT, intent to treat (included all randomized participants [using multiple imputation in case of missing assessments, except when data were missing owing to death]); MMT, methadone maintenance treatment; and PP, per-protocol (included all participants receiving treatment with injectables ≥20 days in the prior month of the main outcome assessment [the 6-month visit]).

[a] Refers to not respecting the clinic rules (eg, threats, verbal aggression).

[b] Among those who did not discontinue the intervention.

Table 1. Characteristics of the Study Participants Before Randomization

Baseline Characteristic[a]	Hydromorphone Hydrochloride (n = 100)	Diacetylmorphine Hydrochloride (n = 102)
Sociodemographics		
Age, mean (SD), y	45.17 (10.19)	43.50 (9.03)
Sex, No. (%)		
Male	67 (67.0)	73 (71.6)
Female[b]	33 (33.0)	29 (28.4)
Aboriginal ancestry, No. (%)[c]	32 (32.0)	30 (29.4)
Any nonstable or street housing in the prior month, No. (%)[d]	60 (60.0)	65 (63.7)
Drug use and illegal activities, mean (SD)		
Years injecting street heroin	15.56 (9.45)	15.34 (9.29)
Days of illegal activities in the prior month	12.78 (13.58)	15.50 (3.77)
Days of use of street drugs in the prior month		
Street opioids[e]	27.28 (4.79)	28.61 (3.40)
Street heroin	25.16 (7.50)	25.60 (8.47)
Crack cocaine smoked	11.25 (12.97)	9.41 (12.46)
Health, mean (SD)		
MAP physical health score[f]	11.82 (8.57)	12.50 (7.48)
MAP psychological health score[f]	9.24 (9.64)	9.56 (8.29)
Times attempted MMT in the prior 5 y[g]	2.84 (2.05)	2.77 (2.14)

Abbreviations: MAP, Maudsley Addiction Profile[23]; MMT, methadone maintenance treatment.

[a] There were no significant between-group differences, except for total days using street opioids (P = .02, by 2-sample t test). Percentages may not add up to 100 because of rounding.

[b] Includes 3 participants who self-identified as transgendered women.

[c] Self-identified as aboriginal ancestry, including Métis, First Nations, and Inuit.

[d] Nonstable housing includes single-resident occupancy hotel rooms with restrictions or "couch surfing." Street housing is defined as living outdoors, in vehicles, or in public places, such as train stations.

[e] Includes street use of heroin, morphine, hydromorphone, and speedball (combined street opioids and stimulants). Noninjection use of street opioids was reported a mean (SD) of 0.59 (2.59) days, with no significant differences by group.

[f] Maudsley Addiction Profile scores range from 0 to 40. Higher scores indicate poorer physical or psychological health.

[g] Based on provincial pharmacy records from 1995 to the date of randomization. An attempt was defined as a continuous period of MMT in which there was no interruption in doses of more than 30 days. All participants had at least 1 methadone attempt since 1995. These records do not include methadone dispensed in the correctional or acute care systems or in settings outside of British Columbia.

target population, including individuals who have injected heroin and other street-acquired opioids for many years, individuals who are currently engaged in illicit activities with daily use of street opioids, and individuals who had multiple attempts at methadone maintenance in the prior 5 years (**Table 1**).

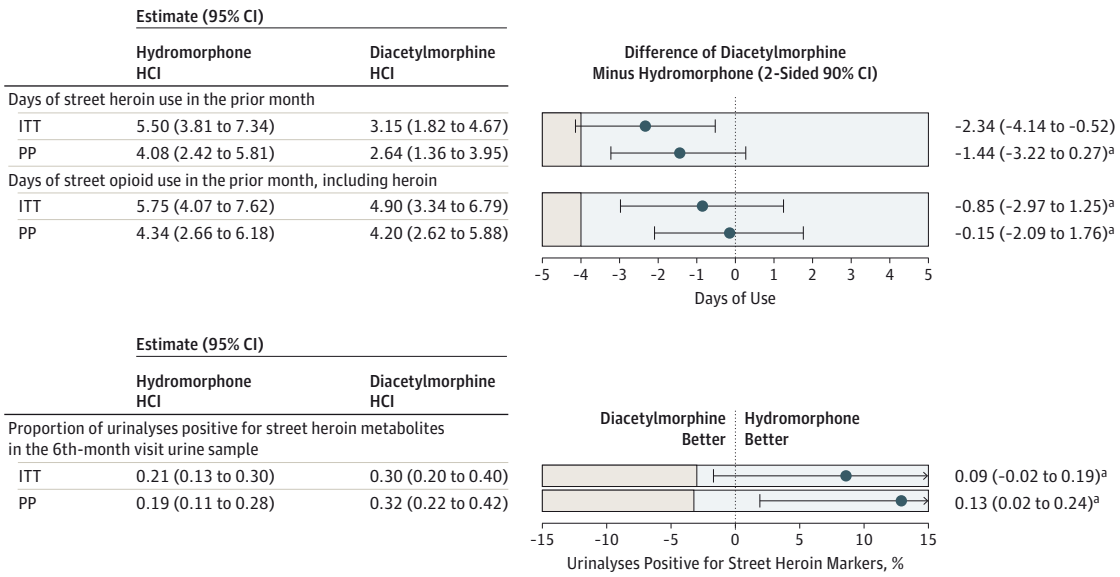
Masking

In the hydromorphone group, 48 of 99 (48.5%) participants thought that they were receiving diacetylmorphine or were unsure. In the diacetylmorphine group, 63 of 98 (64.3%) participants thought that they were receiving hydromorphone or were unsure. The blinding index was 0.56 (P = 0.96; bootstrap 95% CI, 0.50-0.63), indicating successful masking, with a response pattern close to that expected by random guessing.

Efficacy Variables

Figure 2 shows primary efficacy results for the 2-sided 90% CI. With respect to total days of street heroin use, the mean differences between groups (diacetylmorphine minus hydromorphone), adjusted by baseline values, were −2.34 (90% CI, −4.14 to −0.52) in the ITT analysis and −1.44 (90% CI, −3.22 to 0.27) in the PP analysis. The lower bound did not exclude the preestablished 4-day margin in the ITT analysis but did so in the PP analysis. Regarding total days of any street-acquired opioids, the adjusted mean differences between groups were −0.85 (90% CI, −2.97 to 1.25) in the ITT analysis and −0.15 (90% CI, −2.09 to 1.76) in the PP analysis. In both analyses, the lower

Figure 2. Primary Efficacy Outcomes According to the Analysis Population at 6 Months



HCl indicates hydrochloride; ITT, intent to treat (included all randomized participants [using multiple imputation in case of missing assessments, except when data were missing due to death]); PP, per protocol (included all participants receiving treatment with injectables ≥20 days in the prior month of the main outcome assessment [the 6-month visit]). Street opioid use includes illicit use of heroin, morphine, hydromorphone, and speedball (combined street opioids and stimulants). The CI comparison approach is used, in which noninferiority was concluded when the lower bound of the 2-sided 90% CI (corresponding to a 1-sided 95% CI) lies within the noninferiority zone, represented by the shaded area that is defined by the margin. For days of street heroin and opioid use, the margin was −4 days. For the proportion of urinalyses positive for street heroin markers, the margin was −10% of the value for diacetylmorphine (ie, −0.03 for ITT and −0.032 for PP). For days of street heroin and opioid use, baseline values were adjusted.

[a] Indicates that noninferiority was concluded.

Table 2. Group Differences in Secondary Outcomes According to the Analysis Population at 6 Months[a]

Secondary Outcome in the Prior Month	Value (95% CI) Hydromorphone Hydrochloride	Diacetylmorphine Hydrochloride	Difference of Diacetylmorphine Minus Hydromorphone
Proportion of participants receiving study medications ≥28 d			
ITT	0.77 (0.69 to 0.85)	0.80 (0.72 to 0.88)	0.03 (−0.08 to 0.14)
PP	0.92 (0.86 to 0.98)	0.94 (0.89 to 0.99)	0.02 (−0.05 to 0.10)
MAP physical health score[b]			
ITT	11.70 (10.28 to 13.13)	11.71 (10.23 to 13.19)	0.00 (−2.02 to 2.03)
PP	12.12 (10.62 to 13.61)	11.98 (10.45 to 13.51)	−0.13 (−2.25 to 1.98)
MAP psychological health score[b]			
ITT	9.08 (7.58 to 10.58)	8.13 (6.55 to 9.71)	−0.95 (−3.09 to 1.19)
PP	9.51 (7.90 to 11.13)	8.11 (6.50 to 9.72)	−1.40 (−3.65 to 0.85)
Days of illegal activities			
ITT	3.76 (2.14 to 5.66)	2.78 (1.65 to 4.21)	−0.98 (−3.11 to 1.04)
PP	3.73 (1.73 to 5.65)	2.78 (1.35 to 4.14)	−1.06 (−3.46 to 1.14)
Days of crack cocaine use			
ITT	7.09 (5.04 to 9.72)	4.78 (3.17 to 7.02)	−2.31 (−4.73 to −0.21)
PP	6.43 (4.03 to 9.47)	4.87 (2.91 to 7.53)	−1.56 (−3.94 to 0.41)

Abbreviations: ITT, intent to treat; MAP, Maudsley Addiction Profile[23];PP, per protocol.

[a] Based on the 95% CI (bootstrapped for illegal activities and crack cocaine use), the interventions did not differ significantly from each other, except with respect to days of crack cocaine use in the ITT analysis. The means are adjusted by baseline values.

[b] Maudsley Addiction Profile scores range from 0 to 40. Higher scores indicate poorer physical or psychological health.

bound excluded the 4-day margin. For the proportion of urinalyses positive for street heroin markers, the mean differences between groups were 0.09 (90% CI, −0.02 to 0.19) in the ITT analysis and 0.13 (90% CI, 0.02-0.24) in the PP analysis. The lower bounds excluded the 10% relative margins of −0.03 and −0.03 for ITT and PP, respectively. **Table 2** lists secondary outcomes, indicating that the interventions did not differ from each other overall.

Safety

There were 206 related AEs in 48 participants in the hydromorphone group and 353 related AEs in 80 participants in

Table 3. Summary Exposure to the Tested Medications, AEs, and SAEs Among the Study Participants[a]

Variable	Total (N = 202)	Total (Mean) or No. (%)		Hydromorphone vs Diacetylmorphine Relative Risk or Rate Ratio (95% CI)
		Hydromorphone Hydrochloride (n = 100)	Diacetylmorphine Hydrochloride (n = 102)	
Days receiving injectable medications, mean (SD)	165.51 (48.98)	166.53 (44.96)	164.52 (52.83)	NA
Injections received, mean (SD)[b]	423.02 (147.39)	410.27 (140.21)	435.53 (153.76)	NA
Diacetylmorphine equivalent dose received, mean (SD), mg[c]	NA	522.36 (208.04)	506.41 (205.49)	NA
AEs				
Total AEs	1375	596 (5.96)	779 (7.64)	0.78 (0.60-1.01)
Total AEs with some relationship to the treatment	559	206 (2.06)	353 (3.46)	0.60 (0.39-0.90)
Participants with AEs	189	94 (94.0)	95 (93.1)	1.01 (0.94-1.08)
Participants with related AEs	128	48 (48.0)	80 (78.4)	0.61 (0.49-0.77)
Most common related AEs				
Drowsiness	187	36 (0.36)	151 (1.48)	0.24 (0.14-0.43)
Minor or moderate histamine reactions[d]	178	111 (1.11)	67 (0.66)	1.69 (0.69-4.11)
SAEs				
Total SAEs	47	14 (0.14)	33 (0.32)	0.43 (0.20-0.93)
Total SAEs with some relationship to the treatment, all resolved with no sequelae	29	5 (0.05)	24 (0.24)	0.21 (0.06-0.69)
Participants with SAEs	33	11 (11.0)	22 (21.6)	0.51 (0.26-1.00)
Participants with related SAEs	18	3 (3.0)	15 (14.7)	0.20 (0.06-0.68)
Deaths, none related to study medications	2	0 (0.00)	2 (0.02)	NA
Most common related SAEs				
Seizures[e]	11	0 (0.00)	11 (0.11)	NA
Opioid overdoses[f]	14	3 (0.03)	11 (0.11)	0.28 (0.07-1.17)

Abbreviations: AEs, adverse events; NA, not applicable; SAEs, serious adverse events.

[a] Data are total (mean) for variables on number of events or No. (%) for variables on participants with events. Relative risks and rate ratios are unadjusted and are presented with 95% CIs. The 95% CIs that do not contain 1 are significant at α = .05. Relative risks and rate ratios are presented for binary and continuous variables, respectively. Rate ratios and CIs are not presented for deaths and seizures because the value in one of the groups is 0. Days receiving injectable medications, injections received, and diacetylmorphine equivalent dose received are not statistically different between groups ($P > .20$, by 2-sample t test). Relative risks and rate ratios compare the risk of the outcome (presence of or number of events) between groups.

[b] Participants could receive up to 3 injections per day.

[c] The mean dose excludes the first month to adjust for titration and individual adjustment. There was a 1:2 ratio of diacetylmorphine to hydromorphone.

[d] Minor histamine reactions include localized itchiness and raised blotchiness at the injection site. Moderate allergic reactions include localized itchiness, raised blotchiness at the injection site plus facial flushing, feeling pins and needles, and generalized urticarial.

[e] Eleven seizures occurred in 4 participants. One participant who had a history of seizures had 4 seizures, 2 participants had 3 seizures each, and one participant had one seizure.

[f] Three overdoses in the hydromorphone group occurred in 2 participants, and 11 overdoses in the diacetylmorphine group occurred in 9 participants.

the diacetylmorphine group (**Table 3**). An unadjusted rate ratio comparing the rate of related AEs and an unadjusted relative risk comparing the presence of related AEs showed that the hydromorphone group had a significantly lower risk compared with the diacetylmorphine group (rate ratio, 0.60; 95% CI, 0.39-0.90 and relative risk, 0.61; 95% CI, 0.49-0.77, respectively). Regarding drowsiness, there was a significantly protective rate ratio of 0.24 (95% CI, 0.14-0.43) in the hydromorphone group relative to the diacetylmorphine group.

There were 29 SAEs considered to have some relationship with the injection medication, 5 in the hydromorphone group and 24 in the diacetylmorphine group (rate ratio, 0.21; 95% CI, 0.06-0.69) (Table 3). Seizures and overdoses accounted for 25 of the 29 related SAEs: there were 3 overdoses in the hydromorphone group compared with 11 overdoses in the diacetylmorphine group (rate ratio, 0.28; 95% CI, 0.07-1.17). All 11 seizures occurred in 4 participants in the diacetylmorphine group. Two participants died during the study period, and neither death was related to the study treatment.

Discussion

Although the primary outcome did not show noninferiority in the ITT analysis, noninferiority was demonstrated in the PP analysis and in both PP and ITT analyses of the coprimary outcomes. The observed treatment effect of injectable diacetylmorphine was consistent with prior clinical trials that have reported use of street heroin at 6 months approximately 3 to 5 days in the prior 30 days.[6-8] Also, treatment

retention was as high (>80%) as in previous studies[3,14] investigating diacetylmorphine and virtually identical between groups, and secondary outcomes did not differ between groups as well. Taken together, these results suggest that injectable hydromorphone is as effective as injectable diacetylmorphine for long-term injection street opioid users not currently benefiting from available treatments.

The AEs that occurred in this trial were expected according to the profile of the study medications and the injectable route of administration. However, there were some differences between intervention groups in the rate and presence of AEs and SAEs, independent of diacetylmorphine dose equivalency and total number of injections (both of which were similar between groups). Overall, there were fewer related AEs and SAEs in the hydromorphone group than in the diacetylmorphine group. The 2 most common SAEs related to the study medications were opioid overdoses and seizures, with no seizures reported in the hydromorphone arm. Prior investigations have reported an association between hydromorphone use and seizures among patients receiving palliative care.[29] However, differences in study populations and the finding that all seizures occurred in a small number of participants receiving diacetylmorphine (n = 4) precludes us from drawing conclusions about the safety profile of hydromorphone regarding seizures. There were also significantly fewer reports of drowsiness and overdoses with hydromorphone compared with diacetylmorphine. While studies[30-32] indicate that hydromorphone might have similar analgesic effects as other opioids, there are minor and inconsistent differences regarding AEs. It has been proposed that the manner in which hydromorphone is metabolized is an important differentiating characteristic of this opioid.[33] At any rate, it is well established that opioid use presents important interindividual variability among patients.[34] This variation reinforces the need to provide a patient-centered approach that offers a choice of opioids, as is the standard of practice in other clinical areas, such as palliative care.[34]

Noninferiority trials are conducted on the tacit assumption that the new treatment would exhibit efficacy in a placebo-controlled trial if such a trial was to be conducted. Intervention with injectable diacetylmorphine has been shown to be effective for the small subgroup of opioid-dependent individuals who are not benefiting sufficiently from available therapies and continue injecting street opioids.[3] The results of the present study suggest that hydromorphone is as safe and effective as diacetylmorphine for this subgroup. Owing to the noninferiority nature of the study, we can only assume that hydromorphone would exhibit the same effectiveness as diacetylmorphine compared with oral methadone if it would have been tested in a superiority study.[17] It is important to note that in the present study hydromorphone provided similar benefits to diacetylmorphine and that diacetylmorphine provided benefits similar to those achieved in trials where it was demonstrated to be superior to methadone maintenance for long-term injection street opioid users not currently benefiting from available treatments. Therefore, our findings suggest that hydromorphone is as effective as diacetylmorphine and, as a licensed analgesic, offers a clear ancillary advantage in jurisdictions that would permit its use for maintenance treatment. Both of these attributes are required to establish noninferiority.[17]

Our study had some limitations. The choice of a margin poses a well-known challenge in noninferiority trials.[26,35] In such trials, one tests whether an experimental intervention offering some advantage (eg, lower cost, lower toxicity, or less invasive) is not unacceptably less effective than the reference intervention. The margin is meant to represent the limit of lowered effectiveness in order for the experimental intervention to be used in place of the reference intervention. A limitation of this trial is that the margin of 4 days was set by clinicians with experience in countries where diacetylmorphine has been incorporated into the addiction treatment system. As such, this margin may have been conservative (too small). As noted earlier, in many countries the reference intervention (diacetylmorphine) is not presently available for political or regulatory reasons. In those settings, the experimental intervention (hydromorphone) has a significant advantage as a currently accessible medication. While hydromorphone is currently licensed for analgesia and not yet for opioid maintenance, this barrier is not insurmountable. Therefore, a larger margin might be deemed acceptable in such settings. As such, clinicians and decision makers should interpret the present results in the context of their own jurisdictions.

Two efficacy outcomes were based on self-report of street heroin use and total use of street-acquired opioids in the prior 30 days. Reliability of self-reported street drug use has been demonstrated when interviews are conducted by people with no control or power over treatment decisions,[36] as in the present study. In addition, noninferiority was confirmed by urinalysis, which we recognize was a single sample. Urine collections at more frequent intervals would have provided more comprehensive data concerning street heroin markers. By necessity, this trial was double-blinded to compare treatment outcomes without expectation bias. Therefore, each participant knew that his or her chance of receiving diacetylmorphine was 50%. For the use of hydromorphone to be effective in real-world circumstances, it must be able to attract and retain patients alone on an open-label basis. However, given the success of the masking and the overall equal effectiveness of the study medications, this requirement seems unlikely to be a significant obstacle for most patients, particularly where diacetylmorphine is not available.

Conclusions

The results of our study suggest that hydromorphone is as effective as diacetylmorphine for this subgroup of individuals with severe opioid use disorder. In jurisdictions where diacetylmorphine is currently not available or in patients in whom it is contraindicated or unsuccessful, hydromorphone provides a licensed alternative, once its use for maintenance treatment of opioid use disorder is permitted.

ARTICLE INFORMATION

Submitted for Publication: November 10, 2015; final revision received January 11, 2016; accepted January 13, 2016.

Published Online: April 6, 2016. doi:10.1001/jamapsychiatry.2016.0109.

Author Affiliations: Centre for Health Evaluation and Outcome Sciences, Providence Health Care, St Paul's Hospital, Vancouver, British Columbia, Canada (Oviedo-Joekes, Guh, Marchand, Lock, Janmohamed, Anis, Krausz, Schechter); School of Population and Public Health, Faculty of Medicine, University of British Columbia, Vancouver, Canada (Oviedo-Joekes, Marchand, Anis, Schechter); Centre de Recherche du Centre Hospitalier de l'Université de Montréal, Montréal, Québec, Canada (Brissette); Providence Crosstown Clinic, Providence Health Care, Vancouver, British Columbia, Canada (MacDonald, Harrison); Department of Psychiatry, University of British Columbia, Vancouver, Canada (Krausz); Northern Ontario School of Medicine, Sudbury, Canada (Marsh).

Author Contributions: Dr Oviedo-Joekes (principal investigator) and Ms Guh take full responsibility for the integrity of the data and the accuracy of the data analysis. All authors are accountable for all aspects of the accuracy and integrity of this work.
Study concept and design: Oviedo-Joekes, Brissette, Janmohamed, Anis, Krausz, Marsh, Schechter.
Acquisition, analysis, or interpretation of data: Marchand, MacDonald, Lock, Harrison.
Drafting of the manuscript: Oviedo-Joekes, Schechter.
Critical revision of the manuscript for important intellectual content: All authors.
Administrative, technical, or material support: Marchand, MacDonald, Lock, Harrison.
Statistical analysis: Guh.

Conflict of Interest Disclosures: None reported.

Funding/Support: The Study to Assess Longer-term Opioid Medication Effectiveness (SALOME) was funded through operating grant MCT-103817 from the Canadian Institutes of Health Research in partnership with Providence Health Care (PHC), with additional financial support from the InnerChange Foundation, Providence Health Care Research Institute, St Paul's Hospital Foundation, and Vancouver Coastal Health. Further financial support was provided by the Michael Smith Foundation for Health Research Career Award and the Canada Institutes of Health Research New Investigator Award (Dr Oviedo-Joekes) and the Canada Research Chairs Program (Dr Schechter).

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: First and foremost, we acknowledge the contribution and commitment of the study participants, who made it possible to continue advancing this research, while overcoming its many challenges. We also thank the following people and teams for their direct contributions to the study: Salima Jutha (clinical trial coordinator); Shirley Chai (programming of research and clinical databases); Christopher McPartlin (peer worker); Justin Karasick and the Providence Health Care (PHC) communications team; Julie Foreman and the Providence Crosstown Clinic and Pharmacy team; Julie Kille and the PHC urban health team (clinical operations and program support); and Kristin Westland and the many staff at the Centre for Health Evaluation and Outcome Sciences (administrative and technical support). We acknowledge the support and commitment of Dianne Doyle, David Byres, Patricia Daly, Shaf Hussain, Zulie Sachedina, and the senior leadership teams at PHC and Vancouver Coastal Health; Cheryl Bishop (PHC corporate director for acute care); Providence Health Care Research Ethics Board; and Kenneth Tupper (Director, Problematic Substance Use Prevention, BC Ministry of Health). We thank the British Columbia Ministry of Health and Health Canada's many divisions, directors, and staff for helping us comply timely with all regulatory requirements. We would like to thank the community health care providers that supported the study participants to transition in and out from the clinical trial. We would like to also thank Drs William Schreiber and Walter Martz and colleagues at the Provincial Toxicology Centre and BRI Biopharmaceutical Research Inc for the development of toxicological, stability, and sterility test methods. We acknowledge the commitment and leadership of our many partners in the community: Russell Maynard and the Portland Hotel Society Community Service and the Safe Injection Site; Dean Wilson and the Drug Users Resource Center; Ann Livingston and the Vancouver Area Network of Drug Users; and the SALOME Community Advisory Board. We thank the Data and Safety Monitoring Board (Janet Raboud, David Roy, and Michael Lester) for their invaluable expertise and commitment to the patients. Finally, we wish to acknowledge all past and present SALOME investigators and research team.

REFERENCES

1. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev*. 2014;2:CD002207.

2. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev*. 2009;2009(3):CD002209.

3. Strang J, Groshkova T, Uchtenhagen A, et al. Heroin on trial: systematic review and meta-analysis of randomised trials of diamorphine-prescribing as treatment for refractory heroin addiction. *Br J Psychiatry*. 2015;207(1):5-14.

4. Strang J, Groshkova T, Metrebian N, Strang J, Groshkova T, Metrebian N. *New Heroin-Assisted Treatment: Recent Evidence and Current Practices of Supervised Injectable Heroin Treatment in Europe and Beyond*. Lisbon, Portugal: European Monitoring Centre for Drugs and Drug Addiction; 2012.

5. March JC, Oviedo-Joekes E, Perea-Milla E, Carrasco F; PEPSA team. Controlled trial of prescribed heroin in the treatment of opioid addiction. *J Subst Abuse Treat*. 2006;31(2):203-211.

6. Demaret I, Quertemont E, Litran G, et al. Efficacy of heroin-assisted treatment in Belgium: a randomised controlled trial. *Eur Addict Res*. 2015;21(4):179-187.

7. Oviedo-Joekes E, Brissette S, Marsh DC, et al. Diacetylmorphine versus methadone for the treatment of opioid addiction. *N Engl J Med*. 2009;361(8):777-786.

8. Haasen C, Verthein U, Degkwitz P, Berger J, Krausz M, Naber D. Heroin-assisted treatment for opioid dependence: randomised controlled trial. *Br J Psychiatry*. 2007;191(191):55-62.

9. van den Brink W, Hendriks VM, Blanken P, Koeter MW, van Zwieten BJ, van Ree JM. Medical prescription of heroin to treatment resistant heroin addicts: two randomised controlled trials. [published correction appears in BMJ. 2003;3217(7417):724]. *BMJ*. 2003;327(7410):310.

10. Strang J, Metrebian N, Lintzeris N, et al. Supervised injectable heroin or injectable methadone versus optimised oral methadone as treatment for chronic heroin addicts in England after persistent failure in orthodox treatment (RIOTT): a randomised trial. *Lancet*. 2010;375(9729):1885-1895.

11. Perneger TV, Giner F, del Rio M, Mino A. Randomised trial of heroin maintenance programme for addicts who fail in conventional drug treatments. *BMJ*. 1998;317(7150):13-18.

12. Dijkgraaf MG, van der Zanden BP, de Borgie CA, Blanken P, van Ree JM, van den Brink W. Cost utility analysis of co-prescribed heroin compared with methadone maintenance treatment in heroin addicts in two randomised trials. *BMJ*. 2005;330(7503):1297.

13. Nosyk B, Guh DP, Bansback NJ, et al. Cost-effectiveness of diacetylmorphine versus methadone for chronic opioid dependence refractory to treatment. *CMAJ*. 2012;184(6):E317-E328. doi:10.1503/cmaj.110669.

14. Ferri M, Davoli M, Perucci CA. Heroin maintenance for chronic heroin-dependent individuals. *Cochrane Database Syst Rev*. 2011;(12):CD003410.

15. Fletcher J. Canada in breach of ethical standards for clinical trials. *CMAJ*. 2014;186(1):11.

16. Oviedo-Joekes E, Guh D, Brissette S, et al. Double-blind injectable hydromorphone versus diacetylmorphine for the treatment of opioid dependence: a pilot study. *J Subst Abuse Treat*. 2010;38(4):408-411.

17. Kaul S, Diamond GA. Good enough: a primer on the analysis and interpretation of noninferiority trials. *Ann Intern Med*. 2006;145(1):62-69.

18. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 1994.

19. Oviedo-Joekes E, Marchand K, Lock K, MacDonald S, Guh D, Schechter MT. The SALOME study: recruitment experiences in a clinical trial offering injectable diacetylmorphine and hydromorphone for opioid dependency. *Subst Abuse Treat Prev Policy*. 2015;10:3.

20. Oviedo-Joekes E, Marchand K, Guh D, et al. History of treatment access and drug use among participants in a trial testing injectable opioids under supervision for long-term heroin injectors. *J Addict Med Ther*. 2015;3(1):1015-1026.

21. Laster LL, Johnson MF. Non-inferiority trials: the 'at least as good as' criterion. *Stat Med*. 2003;22(2):187-200.

22. Oviedo-Joekes E, Marsh DC, Guh D, Brissette S, Schechter MT. Potency ratio of hydromorphone and diacetylmorphine in substitution treatment for long-term opioid dependency. *J Opioid Manag*. 2011;7(5):371-376.

23. Marsden J, Gossop M, Stewart D, et al. The Maudsley Addiction Profile (MAP): a brief instrument for assessing treatment outcome. *Addiction*. 1998;93(12):1857-1867.

24. Paterson S, Lintzeris N, Mitchell TB, Cordero R, Nestor L, Strang J. Validation of techniques to detect illicit heroin use in patients prescribed pharmaceutical heroin for the management of opioid dependence. *Addiction*. 2005;100(12):1832-1839.

25. Beck T, Haasen C, Verthein U, et al. Maintenance treatment for opioid dependence with slow-release oral morphine: a randomized cross-over, non-inferiority study versus methadone. *Addiction*. 2014;109(4):617-626.

26. D'Agostino RB Sr, Massaro JM, Sullivan LM. Non-inferiority trials: design concepts and issues: the encounters of academic consultants in statistics. *Stat Med*. 2003;22(2):169-186.

27. Biering K, Hjollund NH, Frydenberg M. Using multiple imputation to deal with missing data and attrition in longitudinal studies with repeated measures of patient-reported outcomes. *Clin Epidemiol*. 2015;7:91-106.

28. James KE, Bloch DA, Lee KK, Kraemer HC, Fuller RK. An index for assessing blindness in a multi-centre clinical trial: disulfiram for alcohol cessation--a VA cooperative study. *Stat Med*. 1996;15(13):1421-1434.

29. Kullgren J, Le V, Wheeler W. Incidence of hydromorphone-induced neuroexcitation in hospice patients. *J Palliat Med*. 2013;16(10):1205-1209.

30. Pigni A, Brunelli C, Caraceni A. The role of hydromorphone in cancer pain treatment: a systematic review. *Palliat Med*. 2011;25(5):471-477.

31. Hong D, Flood P, Diaz G. The side effects of morphine and hydromorphone patient-controlled analgesia. *Anesth Analg*. 2008;107(4):1384-1389.

32. Chang AK, Bijur PE, Meyer RH, Kenny MK, Solorzano C, Gallagher EJ. Safety and efficacy of hydromorphone as an analgesic alternative to morphine in acute pain: a randomized clinical trial. *Ann Emerg Med*. 2006;48(2):164-172.

33. Gregory TB. Hydromorphone: evolving to meet the challenges of today's health care environment. *Clin Ther*. 2013;35(12):2007-2027.

34. Drewes AM, Jensen RD, Nielsen LM, et al. Differences between opioids: pharmacological, experimental, clinical and economical perspectives. *Br J Clin Pharmacol*. 2013;75(1):60-78.

35. Piaggio G, Elbourne DR, Pocock SJ, Evans SJ, Altman DG; CONSORT Group. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *JAMA*. 2012;308(24):2594-2604.

36. Darke S. Self-report among injecting drug users: a review. *Drug Alcohol Depend*. 1998;51(3):253-263.