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

Published online April 6, 2016.

Copyright 2016 American Medical Association. All rights reserved.

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. 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.

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 and cost-effective than oral methadone. The Cochrane Collaboration has confirmed the superiority of diacetylmorphine in this subgroup. 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. However, there are many countries around the world where diacetylmorphine is not available owing to regulatory or political reasons, 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, 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. 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. 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.

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 and residing in the greater Vancouver area, British Columbia, Canada. Screening procedures and baseline characteristics have been published previously (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 (eAppendix 2 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.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.

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

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.
Hydromorphone vs Diacetylmorphine for Long-term Opioid Dependence

Original Investigation  Research

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...
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
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 margin 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 hydromorphine group and 353 related AEs in 80 participants in
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
Hydromorphone vs Diacetylmorphine for Long-term Opioid Dependence

Original Investigation Research

May 2016 Volume 73, Number 5

453

Copyright 2016 American Medical Association. All rights reserved.

Downloaded From: on 01/11/2019

Retention was as high (>80%) as in previous studies 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. 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 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. At any rate, it is well established that opioid use presents important interindividual variability among patients. 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.

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. 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. 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.

Our study had some limitations. The choice of a margin poses a well-known challenge in noninferiority trials. 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, 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.
Hydromorphone vs Diacetylmorphine for Long-term Opioid Dependence

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

Published Online: April 6, 2016.

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, JannMohamed, Anis, Krausz, Schechter); School of Population and Public Health, Faculty of Medicine, University of British Columbia, Vancouver, Canada (Oviedo-Joekes, Marshand, 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, JannMohamed, Anis, Krausz, March, 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, Zule 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


