How Can Injectable Hydromorphone and Pharmaceutical-Grade Heroin be Used to Treat Opioid Use Disorder?

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November 22nd, 2017
Provincial System Support Program (PSSP)

- Supports *Ontario’s Comprehensive Mental Health and Addictions Strategy*, through system interventions.

- Capacity and expertise in:
  - Knowledge exchange
  - Information management
  - Implementation
  - Coaching
  - Equity and engagement
  - Evaluation
Evidence Exchange Network

Includes CAMH Health Promotion Resource Centre and Opioid Resource Hub
Evidence

Research

Practice

Cultural knowledge

Lived experience
Coming up...

Dr. Eugenia Oviedo-Joekes  

Dr. Martin Schechter
How Can Injectable Hydromorphone and Diacetylmorphine (i.e. heroin) be Used to Treat Opioid Use Disorder?

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EUGENIA OVIEDO-JOEKES
Acknowledgements

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- Research team
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  - Providence Health Care, Providence Health Care Research Institute, St. Paul’s Hospital Foundation
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  - Canadian Institutes of Health Research
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  - University of British Columbia
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  - Canada Research Chairs Program
  - BC Ministry of Health
- Also:
  - Health Canada and its many divisions
  - PHC/UBC Research Ethic Board
  - Data and Safety Monitoring Board
  - Community Advisory Board
Presenters’ Disclosure

- Martin T. Schechter and Eugenia Oviedo-Joekees have no conflicts of interest to declare.
A Tale of Two Medications

Diacetylmorphine (Heroin™)  
(\textbf{DAM})

Hydromorphone (Dilaudid™)  
(\textbf{HDM})
Background

- Opioid dependence is a chronic relapsing condition.

- Substitution treatment with long-acting oral opioids (e.g. methadone, buprenorphine) works, however not for everyone, and not all the time. Diverse treatment options are needed.

- Clinical evidence from Canada and European studies showed that medically prescribed injectable DAM (diacetylmorphine, the active ingredient in heroin), is an effective, feasible and safe treatment approach.

- Positive findings have not in general persuaded policy makers to support DAM, nor to roll-out the treatment more widely to bring those not doing well with first-line treatments into care.
A Bit of History

- UK addiction system offers injectable diacetylmorphine (DAM) (and injectable methadone) as part of the continuum of care.
- UK issued restrictions in the 1960’s due to concerns about safety (diversion).
- Switzerland started offering injectable DAM in the 1990’s, under supervision, as a public health response to the heroin crisis.
- The ‘Swiss’ model was more appealing and palatable for many, and several countries followed this initiative.
North American Opiate Medication Initiative (NAOMI) Trial

Sample n=251

Randomization

Control Group
n= 111
Oral Methadone

Experimental Group
n=115
Injectable DAM

Experimental Group
n=25
Injectable HDM

Double blind

12 months evaluation

Treatment efficacy
Between groups comparison

18 & 24 months follow-up

Validation of reported illicit heroin use
Within group comparison
NAOMI Results, Primary Outcomes

 RR = 1.62; p<0.001; 95% CI= 1.35-1.95
 RR = 1.40; p=0.004; 95% CI= 1.11-1.77

Diacetylmorphine versus Methadone for the Treatment of Opioid Addiction

Eugenia Oviedo-Joekes, Ph.D., Suzanne Brissette, M.D., David C. Marsh, M.D., Pierre Lauzon, M.D., Daphne Guh, M.Sc., Aslam Anis, Ph.D., and Martin T. Schechter, M.D., Ph.D.
Heroin maintenance for chronic heroin-dependent individuals (Review)

Ferri M, Davoli M, Perucci CA

THE COCHRANE COLLABORATION

2011
Eight randomized clinical trials involving 2007 patients.

Patient profile in RCTs:
- those not benefiting from oral MMT (or suboxone)
- i.e. continued use of street opioids whether retained in oral treatment or not

Outcomes:
- retention in treatment
- reduction in street opioid use, illicit activities
- possible reduction in mortality
The available evidence suggests an added value of heroin prescribed alongside flexible doses of methadone for long-term, treatment refractory, opioid users, to reach a decrease in the use of illicit substances, involvement in criminal activity and incarceration, possible reduction in mortality; and an increase in retention in treatment.

NAOMI Trial

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NAOMI Results, Hydromorphone

Street heroin use

<table>
<thead>
<tr>
<th></th>
<th>HDM (25)</th>
<th>DAM (115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Retention</td>
<td>22 (88%)</td>
<td>101 (87.8%)</td>
</tr>
<tr>
<td>Treatment Response</td>
<td>16 (64%)</td>
<td>77 (67%)</td>
</tr>
</tbody>
</table>

Participants did not appear to distinguish whether they were receiving DAM or HDM

BUT N = only 25

After the NAOMI Trial

- NAOMI: injectable DAM was more effective than oral methadone for long-term injecting opioid use disorder
- Providence Health Care kept the Vancouver site open, providing oral methadone to NAOMI patients.
Tested the non-inferiority of hydromorphone compared to diacetylmorphine for long-term opioid dependence in a double-blind Randomized Clinical Trial.

- Non-inferiority trials are designed to test treatments that offer ancillary advantages over those that have shown to be effective in previous superiority studies.

- Ancillary advantage of hydromorphone: is currently licensed for analgesia (DAM is not licenced in Canada and many other countries).
Medication is dispensed and self-administered by injection under supervision.

The supervision ensures safety of the patients (e.g., overdoses) and the community (e.g., secure the medication).

For some, injectable diacetylmorphine and hydromorphone seem to provide enough motivation to attend and comply with much needed structured treatment.

Daily visits allow nurses, staff and patients to build relationships.

The supervised model of cares provides a tremendous opportunity to offer comprehensive care.
Participants’ Profile

“Long-term injection opioid users who are not sufficiently benefiting from available therapies”

- Opioid Dependence as confirmed by DSM IV diagnostic criteria.
- 19 years of age or older.
- At least 5 years of opioid use.
- Injecting opioids regularly in the past year and past month.
- At least two episodes of opioid addiction treatment (methadone maintenance, detoxification, residential care, etc), including one or more episodes of substitution treatment.
- Poor physical, psychological, mental or psychosocial functioning.
Cumulative Recruitment into The SALOME Trial

1- National shortage of hydromorphone; 2- Physical issues at the study site; 3- Change in provincial drug records

253 Volunteers were assessed for eligibility

202 Participants randomized

51 Were excluded
30 Did not meet eligibility criteria
21 Dropped out

100 Injectable Hydromorphone

12 Discontinued Intervention
4 Voluntary transfer to MMT; 1 Voluntary transfer to recovery; 3 Personal reasons; 1 Disliked the drug; 2 Jail; 1 Behavior

No missed assessments at 6 months

4 Missed more than 10 days of treatment during the 6th month
2 Voluntary transfer to MMT; 2 Hospitalized or ill

102 Injectable Diacetylmorphine

13 Discontinued Intervention
4 Voluntary transfer to MMT; 1 Voluntary transfer to recovery; 1 Pregnancy; 1 Personal reasons; 1 Disliked the drug; 1 Jail; 1 Behavior; 2 Deceased; 1 Drop-out

4 Missed assessments at 6 months
2 Deceased; 1 Missed visit; 1 Lost to follow-up

4 Missed more than 10 days of treatment during the 6th month
1 Voluntary transfer to MMT; 1 Behavior; 1 Hospitalized or ill; 1 Jail

100 Included in the ITT analysis
84 Included in PP analysis

100 Included in the ITT analysis
85 Included in PP analysis
Primary Efficacy Outcomes According to Analysis Population at Six Months

**Difference: DAM minus HDM (two-sided 90% CI)**

**Days of street heroin use in the prior month**
- **ITT**: DAM = 5.50 (3.81 to 7.34), HDM = 4.08 (2.42 to 5.81), **Difference**: -2.34 (-4.14 to -0.52)
- **PP**: DAM = 3.15 (1.82 to 4.67), HDM = 2.64 (1.36 to 3.95), **Difference**: -1.44 (-3.22 to 0.27)*

**Days of street opioid use in the prior month, including heroin**
- **ITT**: DAM = 5.75 (4.07 to 7.62), HDM = 4.90 (3.34 to 6.79), **Difference**: -0.85 (-2.97 to 1.25)*
- **PP**: DAM = 4.34 (2.66 to 6.18), HDM = 4.20 (2.62 to 5.88), **Difference**: -0.15 (-2.09 to 1.76)*

**Proportion of urinalyses positive for street heroin metabolites in the 6th month visit urine sample**
- **ITT**: DAM = 0.21 (0.13 to 0.30), HDM = 0.30 (0.20 to 0.40), **Difference**: 0.09 (-0.02 to 0.19)*
- **PP**: DAM = 0.19 (0.11 to 0.28), HDM = 0.32 (0.22 to 0.42), **Difference**: 0.13 (0.02 to 0.24)*

HDM = hydromorphone, injectable; DAM = diacetylmorphine, injectable; CI = confidence intervals; ITT = Intention to Treat, included all participants randomized, using multiple imputation in case of missing data, except when data were missing due to death. PP = Per Protocol, included all participants receiving treatment with injectables at least 20 days in the month prior to the 6th 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 non-inferiority was concluded when the lower bound of the 1-sided 95% CI (corresponding to a two-sided 90% CI) lies within the non-inferiority zone represented by the shaded area 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 DAM (i.e. -0.03 for ITT and -0.32 for PP). For days of street heroin and opioid use, baseline values were adjusted. Asterisks indicate where non-inferiority was concluded.
Total Street Acquired Opioid Use

ITT: intention to treat; PP: Per protocol; HDM: hydromorphone; DAM: diacetylmorphine
Time to First 30-Day SALOME Treatment Interruption

Probability of Survival

Events in Next Period / Subjects Currently at Risk:

<table>
<thead>
<tr>
<th></th>
<th>PP: HDM</th>
<th>PP: DAM</th>
<th>ITT: HDM</th>
<th>ITT: DAM</th>
</tr>
</thead>
<tbody>
<tr>
<td>0/84</td>
<td>1/84</td>
<td>0/83</td>
<td>0/83</td>
<td>0/83</td>
</tr>
<tr>
<td>2/85</td>
<td>0/83</td>
<td>0/83</td>
<td>0/83</td>
<td>0/83</td>
</tr>
<tr>
<td>4/100</td>
<td>4/96</td>
<td>2/92</td>
<td>1/90</td>
<td>1/89</td>
</tr>
<tr>
<td>10/102</td>
<td>2/92</td>
<td>2/90</td>
<td>1/88</td>
<td>1/87</td>
</tr>
</tbody>
</table>

Days from Treatment Initiation

ITT: intention to treat; PP: Per protocol; HDM: hydromorphone; DAM: diacetylmorphine
The SALOME Trial

JAMA Psychiatry

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

TRIAL REGISTRATION  clinicaltrials.gov Identifier: NCT01447212

Published online April 6, 2016.
SALOME Highlights

- Participants significantly improved, by decreasing their street opioid use, being retained in treatment, and reducing their involvement in illegal activities.
- Adverse events related to the medications were safely mitigated.
- **Injectable diacetylmorphine (again...) and hydromorphone** could be offered as an alternative treatment within the supervised model of care.
- The positive findings have not in general persuaded policy makers to support many existing programs, nor to roll-out the treatment more widely to bring into care those not doing well with first-line treatments (e.g., methadone, buprenorphine).
Dosing and Safety

- Over years of experiences in Europe and Canada, there are safe and effective protocols for initial titration, maintenance and conversion into oral treatments.

- Maximum dose allowed per day:
  - Diacetylmorphine: 400 mg per dose and 1,000 mg per day.
  - Hydromorphone: 200 mg per dose and 500 mg per day.

- Averages are approximately half of the maximum daily dose allowed in the Canadian and European trials.

- Safe and effective titration in 3 days.

- High inter-individual variability.

- Doses remain stable over time.
Titration

- Doses are titrated over a 3 day period under close nursing supervision.
- At any time during the titration period, a physician or nurse may order a lower dose or more gradual titration based on participant response and safety concerns.
- The participant itself can also request a lower dose or a more gradual titration process, such as only upping by 15 mg, not taking a second dose, etc.
- In consultation with their prescribing physician, doses and frequency of doses can be adjusted.
- Dose increases must be well tolerated in order to continue.
- Nurses are able to lower prepared doses based on clinical assessment or patient preference.
High Inter-individual Variability

**Average daily dose prescribed in diacetylmorphine equivalent milligrams**

100 mg hydromorphone = 200 mg diacetylmorphine
The potency ratio of HDM: DAM for agonist maintenance treatment is 1:2
Mean Daily Dose by Arm in the SALOME Study

Average daily-total dose received:

HDM = 261.18 mg (SD=104.02; range= 44.18 to 497.85).

DAM = 506.41 mg (SD=205.49; range = 51.00 to 933.15).
Safety

- Adverse events related to medically prescribed injectable hydromorphone and diacetylmorphine administered under supervision, are safely mitigated and treated by health care providers.

- In the seven RCTs conducted in Europe and Canada, no deaths have been deemed definitively related to the study medication.
NAOMI/SALOMÈ Adverse Events

- 197,662 treatment injections
- Common expected side effects:
  - Drowsiness (oversedations)
  - Local histamine reaction (itchiness, pins and needles)
- SAEs:
  - 18 episodes of seizures (none with hydromorphone)
    - Occurred mostly in patients with previous history of seizures
  - 27 episodes of overdoses (SAEs)
    - All reversed with naloxone
    - No hospitalizations
### Summary of Related Adverse Events and Serious Adverse Events (SALOME)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Total (n=202)</th>
<th>HDM (n=100)</th>
<th>DAM (n=102)</th>
<th>HDM vs. DAM</th>
</tr>
</thead>
<tbody>
<tr>
<td>By participants with a related event</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>Adjusted OR (95% CI)</td>
</tr>
<tr>
<td>Any category of related AE ***</td>
<td>128 (63.4)</td>
<td>48 (48.0)</td>
<td>80 (78.4)</td>
<td>0.26 (0.14, 0.49)</td>
</tr>
<tr>
<td>Related Immediate post-injection reaction or Injection site pruritus *</td>
<td>46 (21.8)</td>
<td>16 (16.0)</td>
<td>30 (29.4)</td>
<td>0.38 (0.18, 0.79)</td>
</tr>
<tr>
<td>Related Somnolence ***</td>
<td>70 (34.7)</td>
<td>16 (16.0)</td>
<td>54 (52.9)</td>
<td>0.19 (0.10, 0.39)</td>
</tr>
<tr>
<td>Any category of related SAE **</td>
<td>18 (8.9)</td>
<td>3 (3.0)</td>
<td>15 (14.7)</td>
<td>0.16 (0.04, 0.60)</td>
</tr>
<tr>
<td>Related SAE opioid overdose*</td>
<td>11 (5.4)</td>
<td>2 (2.0)</td>
<td>9 (8.8)</td>
<td>0.17 (0.03, 0.86)</td>
</tr>
</tbody>
</table>

Odds ratios (logistic regression) are adjusted by age, gender, dose received, and number of sessions.

*p<0.05; **p<0.01; ***p<0.001
Do patients prefer Diacetylmorphine over Hydromorphone?

- In SALOME, at baseline, participants were asked what they prefer:
  - 83.2% indicated that they wished to be randomized to injectable diacetylmorphine.
- When asked if injectable diacetylmorphine was NOT available:
  - 82.2% responded they would start injectable hydromorphone.
Participants did not correctly guess their treatment allocation beyond what would be expected by random guessing.

- James 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.

<table>
<thead>
<tr>
<th>Guessed</th>
<th>Randomized to diacetylmorphine (n=98)</th>
<th>Randomized to hydromorphone (n=100)</th>
<th>Total (n=198)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diacetylmorphine</td>
<td>35 (35.7%)</td>
<td>29 (29%)</td>
<td>65 (32.%)</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>44 (44.9%)</td>
<td>51 (51%)</td>
<td>95 (48%)</td>
</tr>
<tr>
<td>Unsure</td>
<td>19 (19.4%)</td>
<td>20 (20%)</td>
<td>39 (19.7%)</td>
</tr>
</tbody>
</table>
No differences in the study’s primary outcomes by treatment guess:

<table>
<thead>
<tr>
<th>Outcome Variable</th>
<th>Guessed Diacetylmorphine n=64</th>
<th>Guessed Hydromorphone n=95</th>
<th>Unsure n=39</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days of street heroin use in the prior month</td>
<td>4.33 ± 7.94</td>
<td>4.58 ± 8.82</td>
<td>3.33 ± 6.10</td>
</tr>
<tr>
<td>Days any street opioid use in the prior month</td>
<td>5.47 ± 9.02</td>
<td>5.36 ± 9.24</td>
<td>4.74 ± 7.55</td>
</tr>
<tr>
<td>Positive for street heroin metabolites</td>
<td>15 (23.8%)</td>
<td>24 (26.4%)</td>
<td>10 (25.6%)</td>
</tr>
<tr>
<td>Retention (at least 28 days in prior month)</td>
<td>54 (84.4%)</td>
<td>76 (80.0%)</td>
<td>27 (69.2%)</td>
</tr>
</tbody>
</table>
Aren’t These Treatments too Expensive?

- Dutch findings:
  - program costs more than MMT
  - but decreased crime, enforcement, medical costs
  - overall savings: 12,793 euros (per patient per year)

- NAOMI Cost-effectiveness Evaluation
  - about $23 per day for DAM treatment
  - dominant over MMT – better outcomes, lower cost

- SALOME Cost-effectiveness Evaluation
  - DAM and HDM equivalent in cost-effectiveness
Moving Forward...

- Consider integrating injectable treatment into available services:
  - Existing **Community Health Clinic** or **Harm Reduction site** could integrate injectable opioid agonist treatment within the range of treatments and programs offered.
  - Hospitals may integrate injectable treatment by opening a dedicated space for the self administration of medication, **capitalizing on existing infrastructure** and programs.

- Patients’ eligibility:
  - While injectables are meant to be a second line treatment, appropriateness of treatment with injectables should be determined **jointly** between the patient and the prescribing physician, with the intention of **meeting patients where they are at**.
There is consistent, high quality evidence that treatment with injectable diacetylmorphine and hydromorphone works.

There is an important minority of patients facing structural and individual vulnerabilities that are in need to access injectable treatment.

In the midst of an opioid overdose epidemic, injectable options are timely to reach people who inject street opioids and are not attracted to other treatments.

Thank you!!!
Please fill out our evaluation at: https://www.surveymonkey.com/r/HBC6YZC

To learn about upcoming events, visit the EENet Opioid Resource Hub at https://www.porticonetwork.ca/web/opioid-resource-hub/home