Safety profile of injectable hydromorphone and diacetylmorphine for long-term severe opioid use disorder

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Disclosure Statement

- I have no affiliation (financial or otherwise) with a pharmaceutical, medical device or communications organization.

Background

- Opioid use disorder is a chronic relapsing condition. Medically assisted treatment with long-acting oral opioid agonists (e.g. methadone, buprenorphine, SROM) **works**, however not for everyone, and not all the time. **Diverse treatment options are needed**.

- There are several opioids licensed for analgesia; however few countries offer opioids beyond methadone and buprenorphine for OST.

- Robust evidence from several randomized controlled trials (RCTs) in Canada and Europe has shown injectable opioid agonist treatment (iOAT) with diacetylmorphine (i.e., pharmaceutical grade heroin) and hydromorphone (i.e., Dilaudid®) to be effective and cost-effective.

- Despite opioids being quite similar, there are important inter-individual differences that could have an impact on patient safety as well as treatment retention (e.g., dose thresholds, side effects). Expanding the list of opioids for OST could reduce some of the barriers related to individual variations in the medication response.

Aim of the presentation

- The aim of this presentation is to examine the safety profile of injectable hydromorphone and diacetylmorphine by analyzing rates of adverse events (AEs) in the SALOME study and exploring if they were associated with dose and patterns of treatment attendance.

SALOME
Study to Assess Longer-term Opioid Medication Effectiveness

- In a ***non-inferiority***, **double-blind,** randomized clinical trial (RCT), injectable hydromorphone was demonstrated to be as effective as injectable diacetylmorphine for the treatment of long term severe opioid use disorder:
  - Participants in both treatments achieved similar reductions in street opioid use, illegal activities, health outcomes and retention to treatment
  - Participants did not correctly guess their treatment allocation beyond what would be expected by chance.

E. Oviedo-Joekes, et al. *JAMA Psychiatry* (2016), 73(5): 1-9.
E. Oviedo-Joekes, et al. Addiction Research & Theory (2017), 25: 263-272.

AEs & SAEs

- AE: Any adverse health event, drug reaction, laboratory finding or change in health status occurring during the trial, whether it is suspected to be drug related or not
- SAE: AE that results in:
  - Life-threatening event
  - Hospitalization or prolongation of hospitalization
  - Persistent or significant disability or incapacity
  - Congenital anomaly or birth defect
  - Death

Recording of AEs

- AEs were mostly recorded by the clinic staff at every treatment dispensation visit during the pre-injection assessment and post-injection assessment periods
- AEs could also be reported by the research staff
- Once reported, AEs were evaluated as to their severity, relationship to the study medication and their expectedness (as per the drug profile).
- Coded using the Medical Dictionary for Regulatory Activities (MedDRA)

Relationship of AE to study medication

Relationship	Comments
Definitely	**Previously known toxicity** of agent; or an event that follows a **reasonable temporal sequence from administration of the drug**; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is **not explained by any other reasonable hypothesis**.
Probably	An event that follows a **reasonable temporal sequence** from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is **unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions**.
Possibly	An event that follows a **reasonable temporal sequence** from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that **could readily have been produced by a number of other factors**.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

Summary of related adverse events and serious adverse events (SALOME)

Outcomes	Total (n=202)	HDM (n=100)	DAM (n=102)	HDM vs. DAM
By number of related events	N (%)	N (%)	N (%)	Adjusted RR (95% CI)
Any category of related AE *	559 2.77 ± 4.87	206 2.06 ± 5.62	353 3.46 ± 3.92	0.63 (0.40, 0.97)
Related Immediate post-injection reaction or Injection site pruritus [a]	190 0.94 ± 3.81	113 1.13 ± 5.01	77 0.75 ± 2.05	1.10 (0.42, 2.88)
Related Somnolence [b]***	187 0.93 ± 1.87	36 0.36 ± 1.24	151 1.48 ± 2.21	0.27 (0.15, 0.49)
Any category of related SAE *	29 0.14 ± 0.55	5 0.05 ± 0.33	24 0.24 ± 0.69	0.21 (0.06, 0.72)
Related SAE opioid overdose [c]	14 0.07 ± 0.32	3 0.03 ± 0.22	11 0.11 ± 0.40	0.28 (0.06, 1.22)

HDM= hydromorphone; DAM= diacetylmorphine; RR= relative rate; 95% CI = 95% Confidence Interval; M= mean; SD= standard deviation; AE = adverse event; SAE = serious adverse event
Data presented are the mean (SD) number of events and the adjusted relative rate (95% CI) of events for HDM compared to DAM. Rate ratios (negative binomial regression) are adjusted by age, gender, dose received, and number of sessions.
*p<0.05; ** p<0.01; ***p<0.001
(a) Includes related allergic conditions or severe itching at the site of injection; (b) Includes related drowsiness; (c) Includes related SAE opioid overdoses, where naloxone was the required intervention.

E. Oviedo-Joekes, et al. *Drug and Alcohol Dependence* (2017), 176: 55-62.

Summary of related adverse events and serious adverse events (SALOME)

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

HDM= hydromorphone; DAM= diacetylmorphine; OR= odds ratio; 95% CI = 95% Confidence Interval; M= mean; SD= standard deviation; AE = adverse event; SAE = serious adverse event
Data presented are the mean (SD) number of events and the adjusted relative rate (95% CI) of events for HDM compared to DAM. Rate ratios (negative binomial regression) are adjusted by age, gender, dose received, and number of sessions.
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E. Oviedo-Joekes, et al. *Drug and Alcohol Dependence* (2017), 176: 55-62.

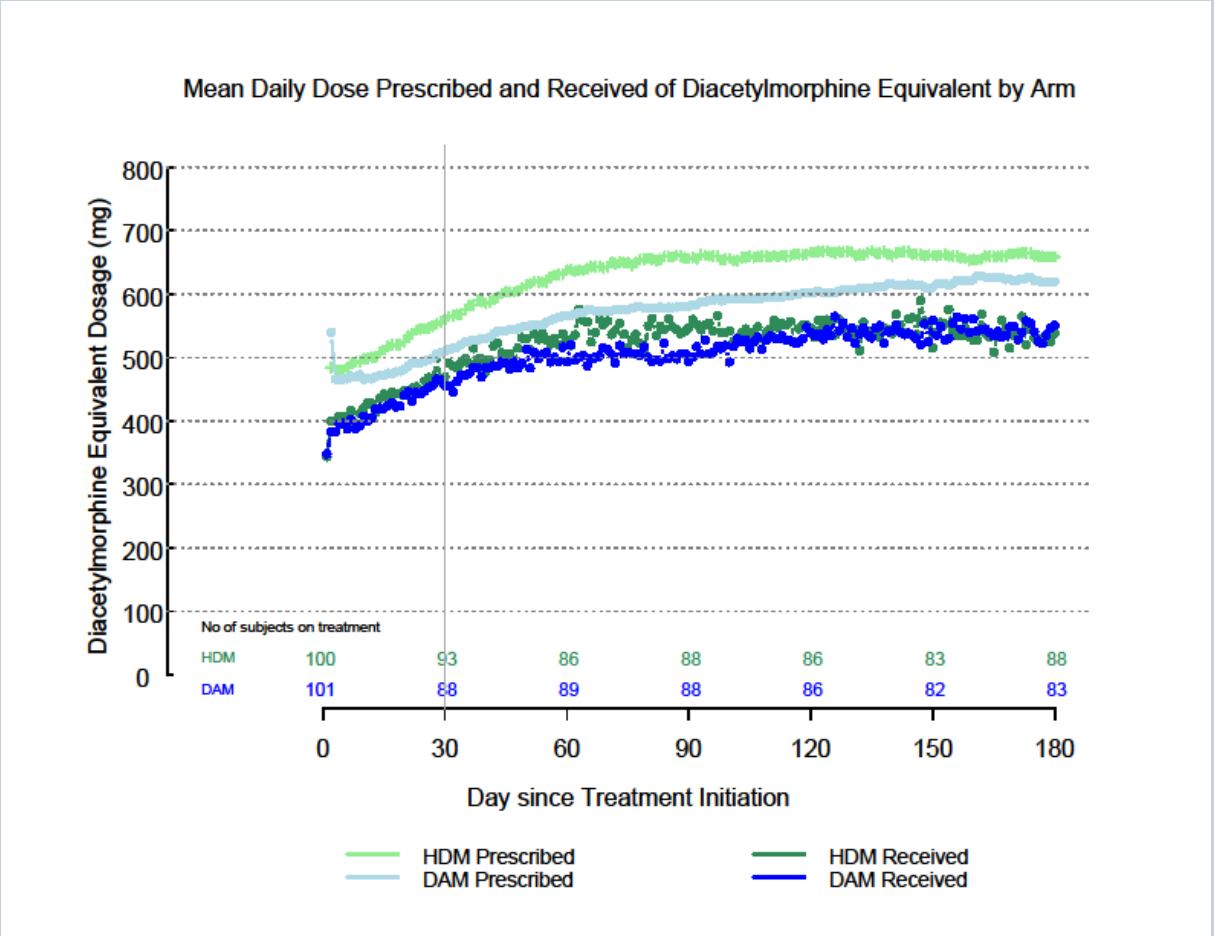
Total days receiving hydromorphone and diacetylmorphine and adverse events

AE Related Group		With an S/AE		Without an S/AE
By number of participants	N	Median days in treatment (IQR)	N	Median days in treatment (IQR)
Hydromorphone [a]				
Any category of AE	48	176.0 (162.5, 179.0)	52	175.0 (158.0, 180.0)
Immediate post-injection reaction or Injection site pruritus [b]	16	175.5 (164.0, 180.0)	84	175.0 (158.5, 180.0)
Somnolence or Opioid Overdose [c]	17	177.0 (159.0, 179.0)	83	175.0 (161.0, 180.0)
Diacetylmorphine [a]				
Any category of AE	80	177.5 (170.5, 180.0)	22	174.0 (125.0, 180.0)
Immediate post-injection reaction or Injection site pruritus [b]	28	178.5 (169.0, 180.0)	74	176.0 (168.5, 180.0)
Somnolence or Opioid Overdose [d]	60	177.5 (170.5, 180.0)	42	176.0 (161.0, 180.0)

AE = adverse event; SAE = serious adverse event; S/AE = serious adverse or adverse event; IQR= interquartile range. Data shown are the median (IQR) days of treatment among participants who had at least one S/AE listed and among participants without the S/AEs listed. (a) Differences between S/AE groups were non-significant (p>0.2 Wilcoxon rank sum test). (b) Includes related allergic conditions or severe itching at the site of injection. (c) MedDRA Preferred Terms Somnolence and Lower Level Term Opioid Overdose, both AE (n=1) and SAE (3 events in 2 participants, requiring intervention with naloxone). (d) MedDRA Preferred Terms Somnolence and Lower Level Term Opioid Overdose both AE (12 events in 8 participants) and SAE (11 events in 9 participants, requiring intervention with naloxone).

E. Oviedo-Joekes, et al. *Drug and Alcohol Dependence* (2017), 176: 55-62.

Mean daily dose by arm in the SALOME study

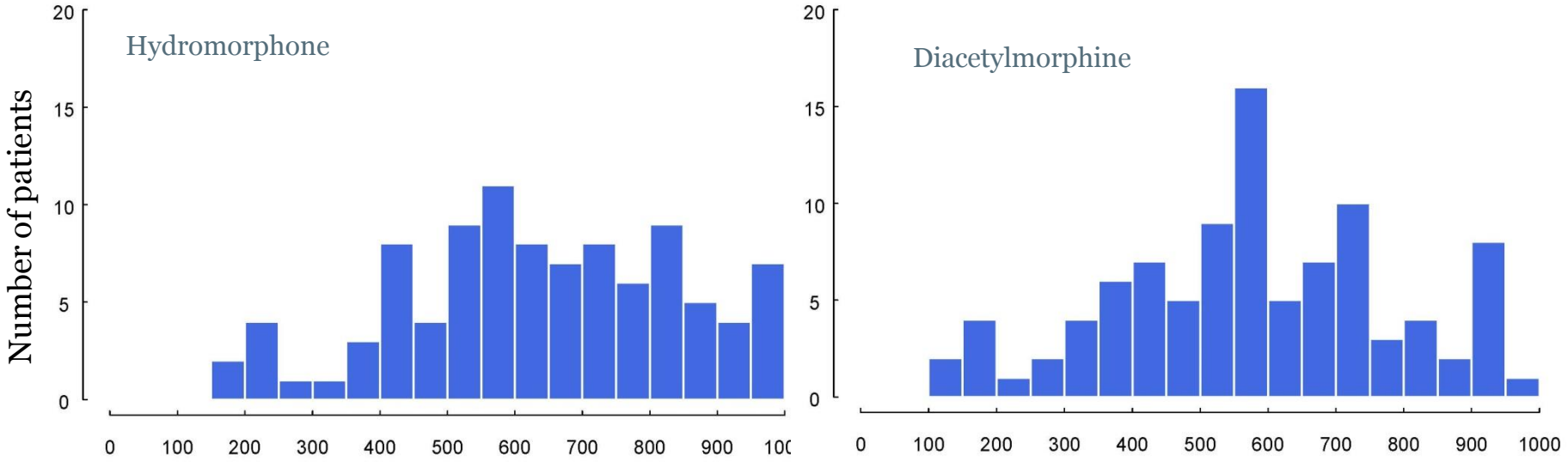


Average daily-total dose received:

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).

High inter-individual variability



Average daily dose prescribed in diacetylmorphine equivalent milligrams

100 mg hydromorphone = 200 mg diacetylmorphine

Summary of Results

- All related AEs and SAEs were expected (immediate post-injection reactions or injection site pruritus and somnolence)
- In the total 88,451 injections, the most common related SAEs were opioid overdoses (n=14) and seizures (n=11), all successfully treated on site without hospitalization.
- Hydromorphone had significantly less related AEs and SAEs compared to diacetylmorphine
- Related AEs were not associated with treatment retention or dose.
- Participants can reach an optimal individualized dose with short-acting injectable opioids, without requiring continuous increments.
- Limitations: The effect of confounding factors related to the comorbidities presented by the participants was difficult to analyse due to the small subsample of other events and the overall profile of the participants.

CONCLUSIONS

- When injectable hydromorphone and diacetylmorphine are individually dosed and monitored, their opioid-related side effects, including potential fatal overdoses, are safely mitigated and treated by health care providers.
- Related adverse events did not lead to more missed treatment days and the dose prescribed does not seem to play a direct or sole role.

THANK YOU!!!