# Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Oviedo-Joekes E, Brissette S, Marsh DC, et al. Diacetylmorphine versus methadone for the treatment of opioid addiction. N Engl J Med 2009;361:777-86.

# A Randomized Trial of Diacetylmorphine vs. Methadone for Treatment-Refractory Opioid Addiction

## Additional information

### Blinding of hydromorphone (HDM) and diacetylmorphine (DAM)

Identical pre-filled syringes of the injection drugs were provided to the treatment clinic by the pharmacies. Pharmacologically equivalent doses of DAM and HDM were prescribed over a dose range based on Swiss clinical practices [1], allowing blinded dose adjustment by study physicians. A potency of hydromorphone to diacetylmorphine of 1:3 was utilized.

*Evaluation of the Blinding*

Participants completed a research interview at 12 months that included the following question for those receiving injected medication: What type of injectable opiate do you think you were receiving at the NAOMI clinic? The question was in Likert format with 5 options: Heroin Definitely; Heroin Possibly; Not sure; Dilaudid® Possibly; Dilaudid® Definitely. In the hydromorphone arm, 23 of the 25 participants completed this questionnaire. As stated in the paper, none of them responded 'Dilaudid® definitely'. Also, 67.6% and 69.6% in the DAM and HDM groups respectively responded they were receiving heroin possibly or definitely.

**Interventions:**

Patients in both arms of the trial were offered a comprehensive range of psycho-social and primary care services. Each participant was assigned a psychosocial support worker whose duties were to establish a relationship with the patient, assess the individual's situation and psychological and social needs, and suggest appropriate services. In keeping with Health Canada Best Practices documents for MMT, all services were delivered in a patient-centred fashion [2]. The multidisciplinary clinical teams at each clinic met weekly to review and revise individualized care plans.

Study treatments were provided for 12 months followed by a 3-month period during which participants still being treated with injection drugs were tapered and transitioned to conventional therapies such as methadone. Those on MMT alone at 12 months were transferred to an existing methadone program or another treatment modality of their choice. The 12-month study visit at which the primary outcome measures were assessed was conducted before any tapering or transition began.

This study followed Good Clinical Practice Guidelines[3] and the Declaration of Helsinki.[4] It received ethical approval by the review ethics boards of the University of Montreal and the University of British Columbia. Given that initially more sites were planned, the study also received ethical approval from the University of Toronto, the New York Academy of Medicine and Johns Hopkins University. All participants received clear information about the study and provided informed consent prior to any study procedures being performed.

**Randomization**

Treatment was assigned by means of a central telephone randomization system at the Data Centre at St. Paul's Hospital (Vancouver). The randomization ratio was diacetylmorphine 45%, methadone 45% and hydromorphone 10%. A computer-generated randomization list of variable permuted blocks of 2, 4,

and 6 was used for treatment allocation. Randomization was stratified by center and by previous methadone treatments (2 or less and 3 or more) before randomization. After the participants were deemed eligible and provided consent, both the research office and the clinic were informed whether the allocation was to MMT or to injection medication. The Data Centre in Vancouver also provided participant assignments electronically to hospital pharmacies preparing drugs at each site. Only the pharmacies were aware of allocations to DAM vs HDM. Participants randomized into the trial were instructed to go to the treatment clinic on the following Monday morning to begin treatment at which time they first learned of their treatment allocation.

**Data analysis:**

For secondary analysis, missing values were replaced using last observation carried forward.

**CONSORT Flow Chart**

A total of 1588 people were in contact with the study and went through the initial pre-screening process (1053 in Vancouver and 535 in Montreal). Of these, 1007 (63.4%) were pre-screened out as ineligible and 581 were invited to the research office to begin the full screening process. Of these individuals, 229 (39.4%) were found to be ineligible and 101 (17.4%) dropped out during the screening process. The remaining 251 volunteers met the eligibility criteria and provided informed consent and were randomized into the study. Random assignments were as follows: oral methadone 111 (44.2%); injected diacetylmorphine 115 (45.8%); injected hydromorphone 25 (10.0%). For the 251 randomized participants, it was not possible to obtain 12 month retention data for 6 participants (2.5%) and response data for 11 participants (4.4%).

Participants randomized to DAM and HDM were able to switch to MMT. There were two main ways to switch from DAM and HDM to MMT: voluntary and involuntary. The first group represents patients who after being stabilized with the injection medication and in consultation with the physician, elected to switch to MMT and started this treatment at the clinic. The second group includes those patients who were discontinued from the injected medications for behavioural reasons and offered MMT at the clinic. Any participant in the injection arm caught attempting to divert injection medication out of the clinic was withdrawn from injection medication as were patients in either arm who demonstrated repeat aggressive behaviour (threat, intimidation).

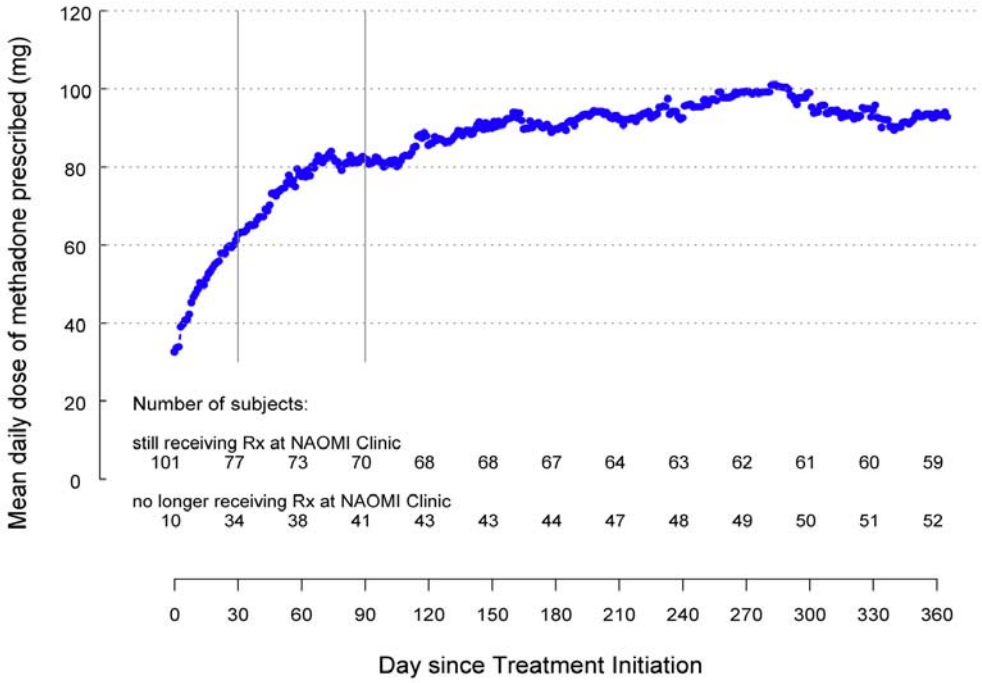
**Methadone Protocol**

For MMT treatment, we followed the recommendations issued by the College of Physicians and Surgeons of each of the provinces concerned as to proper dosage, recommended urine testing and patient drug management (take home doses). In Quebec, methadone was dispensed through the network of participating community pharmacists who directly supervised its administration. In British Columbia, the methadone was dispensed during the week from the treatment clinic and on the weekends by a community pharmacy. The methadone was diluted in a solution to mask the drug's bitter taste, to discourage the practice of injecting the drug and to prevent the risk of diversion.

Patients in the methadone arm received an initial dose between 15 to 40 mg on days 1 to 3. Afterwards, if the individual so wished and there were no clinical contraindications, the dose could be increased from 5 mg to 10 mg once or twice a week to a maximum dose of 60 mg. Once the 60 mg level was reached, doses could be increased from 10 mg to 15 mg each week or two, if the patient so wished, and if there were no clinical contraindications. Since we were aiming to offer optimal therapy, the doses could be increased as long as the patient continued taking non-prescribed opiates three or more times a week, did not show signs of overmedication and was taking the prescribed methadone on a daily basis.

As per the British Columbia College of Physicians and Surgeons guidelines, there was no pre-set maximum dose of methadone in the trial.

**Methadone Dose Results**




**Urine Assay**

Several tests were performed for detection of opioids and opiates at the research visits at 0, 3, 6, 9 and 12 month. For detecting each opioid (natural or synthetic) as positive or negative separately high-performance liquid chromatography (HPLC) test were used. The presence of 6-monoacetylmorphine (6-MAM) in urine test confirms the use of heroin since this metabolite is unique for diacetylmorphine.

The substances tested were: tranquilizers (benzodiazepines; barbiturates; diphenhydramine), opioids (opiates; methadone; methadone, EDDP; monoacetylmorphine (6-MAM); morphine; codeine; oxycodone; hydrocodone; hydromorphone), stimulants (cocaine; cocaine, benzoylecognine;

methamphetamine and amphetamines), hallucinogens (MDMA, MDA ecstasy; phencyclidine; ketamine) and ranitidine.

Among participants randomized to MMT, there were a total of 71 visits at which no use of illicit heroin was reported in the prior 30 days (among 32 different participants). Of the 71 corresponding urine samples, none tested positive for 6-MAM and 6 (8.5%) tested positive for morphine without self-reported use of the latter drug.

The sub-group that received HDM in a double-blind basis with DAM also allowed a comparison of 6-MAM and morphine positive test with the MMT group. A total of 369 (83.1% of the expected 444) urine samples were obtained in the MMT arm and 94 (94.0% of the expected 100) in the HDM arm. Participants in the HDM group showed a significant less proportion of positive tests for 6-MAM (6.4% vs. 22.5%; $p<0.001$) and morphine (13.8% vs. 57.5%; $p<0.001$) compared to the MMT group.

**Definition of Legal Score in the ASI:**

Five questions are used in the ASI to determine this score:
A. Are you presently awaiting charges, trial, or sentencing?
B. How many days in the past 30 have you engaged in illegal activity for profit?
C. How serious do you feel your present legal problems are?
D. How important to you now is counseling or referral for these legal problems?
E. How much money did you receive from illegal sources in the past 30 days?

**Assessment of Adverse Events:**

All study participants were assessed for adverse events, drug reactions or changes in health status during all visits to the clinic by clinic nurses, coordinators, physicians and/or other clinic workers. To ensure that administration of the medication was safe, participants who received injection medication were assessed at every clinic visit during a 15 minute pre- and 30 minute post-injection assessment period. Participants receiving methadone did not have pre- or post-assessment and had the option of picking up their daily dosage at the study clinic or at a community pharmacy. Severe adverse events

(SAEs) were analyzed to 15 months of treatment initiation to include the 12 months of active treatment and the 3 months of treatment possibly received during the transition period.

## Reference List


1. OFSP. Manuel Traitement avec prescription d'héroine. Directives, recommandations, informations. Berne. Swiss: Office Fédéral de la Santé Publique, 2004.

2. Health Canada. Best practices in methadone maintenance treatment. Ontario, Canada.: Minister of Public Works and Government Services Canada, 2002.

3. ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice. EMEA, 2002.

4. World Medical Assembly. Declaration of Helsinki: Interpreting and implementing ethical principles in biomedical research. 18th World Medical Assembly, Helsinki Finland June 1964 amended by the 29th World Medical Assembly Tokyo Japan October 1975 and the 35th World Medical Assembly Venice Italy October 1983. 41st WMA General Assembly Hong Kong September 1989. 48th WMA General Assembly Somerset West Republic of South Africa October 1996. 52nd WMA General Assembly Edinburgh Scotland October 2000.