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NORTH AMERICAN OPIATE MEDICATION INITIATIVE

FOR IMMEDIATE RELEASE

Results show that North America's first heroin therapy study keeps patients in treatment, improves their health and reduces illegal activity

VANCOUVER, BC, October 17, 2008 – Researchers from the North American Opiate Medication Initiative (NAOMI Study) today released final data on the primary outcomes from the three-year randomized controlled clinical trial.

"Our data show remarkable retention rates and significant improvements in illicit heroin use, illegal activity and health for participants receiving injection assisted therapy, as well as those assigned to optimized methadone maintenance," says Dr. Martin Schechter, NAOMI's Principal Investigator, Centre for Health Evaluation and Outcome Sciences and Professor and Director, University of British Columbia School of Population and Public Health. "Prior to NAOMI, all of the study participants had not benefited from repeated standard addiction treatments. Society had basically written them off as impossible to treat."

The data, which was collected from 251 participants at sites in Vancouver and Montreal, demonstrate that a combination of optimized methadone maintenance therapy (MMT) and heroin assisted treatment (HAT) can attract and retain the most difficult-to-reach and the hardest-to-treat individuals who have not been well served by the existing treatment system.

Key findings at the 12-month point of the treatment-phase of the study showed that HAT and MMT achieved high retention rates: 88 per cent and 54 per cent respectively. Illicit heroin use fell by almost 70 per cent. The proportion of participants involved in illegal activity fell by almost half from just over 70 per cent to approximately 36 per cent. Similarly, the number of days of illegal activity and the amount spent on drugs both decreased by almost half. In fact, participants once spending on average $1,500 per month on drugs reported spending between $300-$500 per month by the end of the treatment phase. Marked improvements were also seen in participants' medical status with scores improving by 27 per cent.

Of particular note amongst the findings, participants receiving hydromorphone (Dilaudid™) instead of heroin on a double-blind basis (neither they nor the researchers knew) did not distinguish this drug from heroin. Moreover, hydromorphone – an opiate licensed for the relief of pain - appeared to be equally effective as heroin, although the study was not designed to test this conclusively. According to the NAOMI Study Investigators, further research could help to confirm these observations, allowing hydromorphone assisted therapy to be made more widely available.

While a comprehensive health economics study is pending, researchers have already determined that the cost of continued treatment is much less than that of relapse.

"We now have evidence to show that heroin-assisted therapy is a safe and effective treatment for people with chronic heroin addiction who have not benefited from previous treatments. A combination of optimal therapies – as delivered in the NAOMI clinics - can attract those most severely addicted to heroin, keep them in treatment and more importantly, help to improve their social and medical conditions," explains Schechter.

A summary report of the findings and background information on the study are available at: www.naomistudy.ca.

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Funding provided by the Canadian Institutes of Health Research.

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Over the coming weeks, NAOMI Study researchers will be presenting results at the following conferences: Premier colloque francophone sur le traitement de la dépendance aux opioïdes, (Opening Plenary, October 23) in Montreal, Quebec and the Canadian Society of Addiction Medicine Annual Scientific Meeting (Session IX-B, November 1) in Vancouver, BC.

Background

The NAOMI study tested whether heroin-assisted therapy or methadone therapy is better for improving the health and quality of life of long-time opiate users. Eligible participants were randomly assigned to receive a 12-15-month course of medically prescribed injection opioids (heroin or hydromorphone) or oral methadone therapies. Following a slow, but steady recruitment of volunteers who met the study's rigorous inclusion criteria, NAOMI fully enrolled 251 participants (192 in Vancouver and 59 in Montreal) by March of 2007. The treatment phase of the study was completed in June 2008. Researchers will continue to gather and analyze data until NAOMI's expected closure date in mid-2009. Funded by the Canadian Institutes of Health Research, and approved by Health Canada, NAOMI enrolled and treated participants in Vancouver and Montreal since 2005.

Individuals were considered eligible for the NAOMI study if they:

- Had been addicted to heroin, dilaudid or another opiate for five years;
- Had been injecting heroin for the past year;
- Had tried addiction treatment twice in the past including methadone maintenance;
- Were 25 or older; and,
- In the case of the Vancouver site, were a member of the Downtown Vancouver community and had been for an extended period of time.

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STATUS REPORT
October 2008

The North American Opiate Medication Initiative (NAOMI Study) is a CIHR-funded scientific clinical trial that examines innovative ways to treat addiction as a medical condition. The NAOMI study should not be confused with supervised injection sites.

The NAOMI study aims to determine whether the provision of medically supervised injectable, pharmaceutical-grade heroin benefits people suffering from chronic opiate addictions who have not benefited from other treatments. Participants were randomized between two arms of the study: The injection arm and the oral methadone arm, which served as the control. Studies such as the NAOMI trial are critical to investigating further treatment options for people who live with heroin addiction. Ultimately, the evidence gained through the study will be added to a larger pool of information that policy and decision makers can use to make decisions that are evidence-based.

There have been similar studies done in other jurisdictions, including Switzerland, Germany, Spain and the Netherlands, that indicate that chronic heroin addicts who participated in a trial where they received controlled doses of heroin under supervised care, along with drug treatment, showed improvements in physical and mental health, reduced their illicit drug use, participated in less crime, stayed in treatment longer and improved their social functioning. The recently released results from the German study not only saw an improvement in the health status of heroin addicted people who received heroin under medical supervision, but also a reduction in crime rates and other socio-economic costs to society. The findings of the German study support the research results of the Netherlands, Spain, and Switzerland, as well as innovative and ongoing studies and programs in Britain. The intention of the NAOMI project is to evaluate the effectiveness and applicability of these experiences in a North American setting.

CIHR Funding
This study is in keeping with CIHR's mandate in the "creation of new knowledge and its translation into improved health for Canadians" – in this case, investigating whether heroin-assisted treatment can produce benefits for long-term, treatment-resistant opiate dependent individuals as well as public health. In 2002, the Clinical Trials Review Committee of the CIHR assessed the scientific merit of the NAOMI study and decided to fund this study on the basis of its outstanding scientific value.

As a result, the project received $8.1 million of funding from CIHR in 2002 and the current end date of funding for the study is in 2009. Researchers are expected to use existing funding to complete the study follow-up and data analysis. Renewals and additional funding do not appear to be required for the scope of the project as outlined in the research protocol.

The Research and Status Update
Participants were randomly assigned to three different groups: The control group who received oral methadone maintenance treatment, an experimental group who received prescription heroin and a small group who received injection hydromorphone (dilaudid), which is a medically available potent opioid. The hydromorphone group was used to help validate the reported use of illicit heroin beyond what is prescribed in the study. This was the double-blinded element of the study, as researchers, clinic staff, and participants did not know whether any given participant

was receiving heroin or hydromorphone. Data shows that of those who received dilaudid, all but one participant suspected that they were receiving heroin.

For all individuals in the study, addiction medicine physician specialists monitored their individual prescription throughout the study, and social workers assisted with access to community resources, including addiction treatment, housing and job training. Clinic staff guided all those ready towards treatments that would get them off drugs altogether. After the clinical portion of the study, participants receiving injection medication were aided through a three-month transition period, and then monitored by the research team for up to two years to determine the study's longer-term outcomes.

NAOMI was to originally run in three sites: Vancouver, Montreal and Toronto. However, it took place at two sites (Vancouver and Montreal) that have the largest heroin addicted populations in Canada. The Toronto clinic site that the research team was planning to use was occupied by another project, causing delays in construction and ultimately making it unavailable for the NAOMI study within an appropriate timeframe. As such, the Toronto site of the project could not be included.

Enrolment began early 2005 in Vancouver, followed six months later by Montreal. Overall, recruitment was steady, and gained momentum over time. NAOMI closed enrolment in Vancouver and Montreal in the spring of 2007 with 192 participants in Vancouver and 59 in Montreal – divided between the injection group and the oral methadone group. The last of the participants completed the treatment phase of the study in June 2008.

In 2006, the NAOMI team received final Health Canada and subsequent ethics approval to revise the sample size of the study to a target of 253 participants. This was on recommendation and approval from an independent Data Safety and Monitoring Board. Such a change is not uncommon in a scientific study. The final enrolment total of 251 allowed for an appropriate statistical significance that answers the researchers' questions.

To be eligible for the study, participants must have been 25 years or older, must have had chronic opiate addiction (at least 5 years of addiction) and must have tried opiate addiction treatment at least twice in the past without success. Thus, the study is aimed towards the most severely affected individuals who have not benefited from conventional treatment options.

Participants in the study received the injectable drug for a maximum of 15 months. The end of 12 months through to 15 months was included as a transition or weaning off phase. Participants were supported by social workers, physicians, nurses, and drug counselors to transition into the appropriate treatment of their choice whether it be methadone maintenance, abstinence or other available programs.

The research team released results of the primary outcomes on October 17, 2008. It can be stated that the injectable treatment appears to be extremely safe. It is also noteworthy that there have been neither security problems nor any evidence whatsoever of neighborhood disruption in either city. An important aspect of the study is a full health economic assessment of the incremental cost-effectiveness of medically prescribed heroin. The Dutch and German studies both suggested that the increased cost of heroin therapy was more than offset by the increased savings in health and criminal justice costs. The NAOMI study will formally assess whether this

therapy is cost-effective in the Canadian setting; however, these results will not be ready until early 2009.

Approval of the Trial
There are currently only two sites authorized in Canada for this clinical trial: Vancouver and Montreal.

Health Canada completed a review of the proposed physical security measures and procedures to be put in place by the researchers at the sites to ensure the safety of staff and participants. Researchers obtained approval by the Therapeutic Products Directorate in Health Canada to conduct the clinical trials with heroin.

Heroin Use in Canada:
In Canada, there are approximately 60,000 to 90,000 people addicted to illicit opiates such as heroin. Chronic, untreated opiate addiction is associated with overdose, infection risks and epidemics, loss of regular social functioning, drug-related crime and drug acquisition crime, and extensive costs to the public health, welfare and criminal justice systems. Research estimates that the societal costs of an untreated heroin addiction exceed $45,000 per person per year. While methadone maintenance therapy (MMT), the current standard of care, is effective in some cases, many long-term, higher risk patients do not respond to or benefit from this standard treatment.

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Reaching the Hardest to Reach – Treating the Hardest-to-Treat

Summary of the Primary Outcomes of the the North American Opiate Medication Initiative (NAOMI)

The NAOMI Study Team

October 17, 2008

STUDY TITLE

North American Opiate Medication Initiative (NAOMI): Multi-Centre, Randomized Controlled Trial of Heroin-Assisted Therapy for Treatment-Refractory Injection Opiate Users

BACKGROUND

Addiction to opiates, primarily heroin, remains an enormous public health challenge in Canada and many other settings. Despite important and timely expansions of access to conventional treatments, there are significant proportions of affected individuals, many with multiple co-morbidities, who remain outside the reach of the current treatment system and who contribute disproportionately to the health care costs, criminal justice costs and public disorder associated with drug addiction. A number of studies in Europe have shown that expansion of treatment options to include heroin maintenance therapy can have significant beneficial impacts on these individuals and address the open drug scenes and the public safety in the cities involved.

The North American Opiate Medication Initiative (NAOMI) is a two-centre, parallel, open-label randomized controlled trial (RCT) aimed at testing whether heroin assisted treatment (HAT) offers benefits over and above optimized methadone therapy in the treatment of individuals with chronic addiction who continue to use heroin despite having tried conventional treatments in the past.

The trial includes long-term follow-up of participants for a total of 24 months and this phase is still ongoing. The treatment phase was completed in June 2008; therefore the primary outcomes are now available. The research team will continue to gather and analyze data until full study closure in mid-2009.

HOST INSTITUTIONS

Vancouver: St. Paul's Hospital, 620B–1081 Burrard St., Vancouver, B.C., V6Z 1Y6
Montreal: Hôpital Saint-Luc du CHUM, 1058 rue Saint-Denis, Montréal, QC, H3X 3J4

The NAOMI trial received ethical approval from the Research Ethics Boards of both host institutions.

MEDICATIONS STUDIED

Injection Drugs: Injected diacetylmorphine (DAM) – this is the active ingredient in heroin.
Injected hydromorphone (HMO)

Active Comparator: Oral methadone

STUDY DESIGN

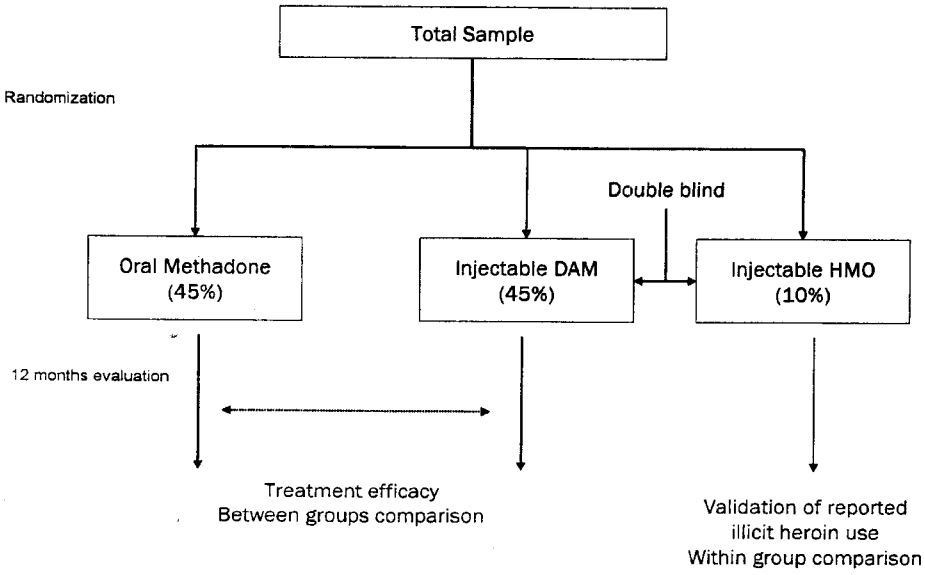
A two-centre, parallel, open-label randomized controlled trial (RCT). As seen in Figure 1, the investigational arm received assisted therapy with diacetylmorphine (DAM) (45%) or with hydromorphone (HMO) (10%). This was on a double blind basis implying the participants, the clinic nurses, the clinic doctors and the researchers did not know which of the two drugs any individual was receiving.

The control arm received optimized methadone maintenance therapy (45%) (MMT). Because MMT is given orally and not by injection, it was impossible to double-blind this comparison so that this component of the trial is open-label.

Optimized MMT and assisted therapy, as delivered within NAOMI, included the following characteristics:

- Interdisciplinary care (physician, nursing, social work and addiction counselors)
- Low patient-to-staff ratios
- Client-centered counseling including case management
- Outreach supports including accompaniment to specialty care
- Targeted primary care for common physical and psychiatric conditions
- Highly trained clinical team including all physicians certified in Addiction Medicine
- Linked dispensing of psychiatric, HIV and antimicrobial medications
- Average methadone doses at least 50% higher than the community average
- Effective pain management for acute or chronic pain
- On-call and weekend support to prevent missed doses in the event of missed appointments or unexpected release from correctional institution or hospital

Figure 1: NAOMI design



PRIMARY HYPOTHESES

1. Among chronic, opioid-dependent treatment-refractory injection drug users randomized to receive injected diacetylmorphine (combined with methadone if deemed appropriate), the proportion who accept and are retained in therapy at 12 months, who are in other treatments at 12 months or who are drug-free at 12 months, will be higher than those randomized to receive oral methadone alone.

2. Among such individuals randomized to receive injected diacetylmorphine (combined with methadone if deemed appropriate), the proportion who demonstrate reduced illicit drug use and criminal behaviour at 12 months, will be higher than those randomized to receive oral methadone alone.

PRIMARY OUTCOMES

Treatment Retention – Definition

A participant was defined as "retained at 12 months" if he or she met any of the following 4 criteria:

- was compliant with study medication (DAM, HMO and/or MMT) on at least 10 of 14 days prior to the 12-month date; or
- was confirmed to be enrolled in detoxification program at the 12-month date; or
- was confirmed to be enrolled in a drug-free program at the 12-month date; or
- was confirmed to be abstinent at the 12-month date.

Treatment Response – Definition

Illicit drug use and criminal justice involvement were measured by self-report as recorded by quarterly administration of the European Addiction Severity Index (EuropASI). At 12 months, all study participants regardless of the treatment arm to which they were randomized were defined as either a treatment "responder" or treatment "non-responder". We defined a "responder" as a subject who met <u>both</u> of the following criteria at the 12-month outcome assessment:

- demonstrated at least 20% improvement in the illicit drug use subscale or in the legal status (criminal justice involvement) subscale of the EuropASI, or in both relative to their baseline scores.
- demonstrated a deterioration of 10% or more **on at most one** of the remaining 7 EuropASI subscales relative to baseline.

TARGET POPULATION

Inclusion Criteria

To be eligible for the study, participants must have fulfilled the following entry criteria:

a. Opioid Dependence as confirmed by DSM-IV diagnostic criteria;
b. 25 years of age or older;
c. 5 years or more of opioid use;
d. Regular opioid injection use in the past month and in at least 8 months in the past 12 months (self reported; regular use – defined as injecting opioids for at least 4 days or more in a week); 50% or more of the injections during the prior year must have involved heroin);
e. Minimum of one-year residence in site/city location;
f. No enrolment in any other opioid substitution (e.g. methadone) program within the prior 6 months – enrolment is defined as participation in a community based program having received at least 45 milligrams of prescribed methadone per day on any consecutive 30 day period or more in the 6 months prior to date of randomization;
g. At least two previous episodes of opiate addiction treatment (methadone maintenance, detoxification, residential care, etc) during which, on at least one occasion, the patient received at least 60 mg of methadone daily for at least 30 days in a 40 day period;
h. Willingness and ability to adhere to study protocol and follow-up schedule as determined through the pre-randomization period;
i. Documentation of fulfillment of the above study criteria (prison records, treatment records, cohort study enrolment, urine sampling);
j. Provide written and informed consent.

Criteria (f) ensured that subjects had not been in methadone maintenance treatment or other substitution programs in the preceding 6 months. This was to prevent the situation of persons currently in treatment dropping out in order to meet the inclusion criteria. This led, however, to the exclusion of large numbers of potential participants.

Exclusion Criteria

Participants were not eligible for the trial if they did not meet the above criteria or if they met any of the following exclusion criteria:

a. Diagnosis of severe medical or psychiatric conditions that are contra-indicated for heroin treatment;
b. Pregnancy upon study entry;
c. On parole or with current justice system involvement that is likely to result in an extended period of incarceration (more than 4 months) during the study period (e.g. scheduled trial for an indictable offense, jail, etc);
d. Hydromorphone is a class C teratogen and should not be given to pregnant women.

All female subjects upon study entry were urged to engage only in protected sexual intercourse and provided consent to undergo monthly pregnancy tests during the course of the study;

e Serum bilirubin >2.5 x normal;

f. Stage II or greater hepatic encephalopathy;

g. Chronic respiratory disease resulting in resting respiratory rate >20/minute;

h. Bipolar Mood Disorder, Schizophrenia or other psychotic disorder with active psychotic symptoms, refractory to medical management, within the past 6 months;

i. Major Depression requiring electroconvulsive therapy within the past 12 months.

RESULTS

Screening and Recruitment

A total of 1587 people were in contact with the study and went through the initial pre-screening process (1053 in Vancouver and 534 in Montreal). Of these, 1006 (63.4%) were pre-screened out as ineligible and 581 entered into full screening. Of the latter 581 individuals, 229 (39.4%) were subsequently determined to be ineligible and 101 (17.4%) dropped out during the screening process. The remaining 251 volunteers provided informed consent and were randomized into the study.

Reasons for excluding patients were primarily related to the restrictive criteria involving previous addiction treatment attempts and recent or current MMT at the time of recruitment. Of the participants pre-screened as ineligible in Vancouver, 85.1% were due to not meeting the MMT inclusion/exclusion criteria either alone (60.9%) or in combination with other criteria (24.2%). For example, many potential candidates had not reached a dose of 60 mg and/or had not remained on methadone for at least one month in the past.

Due to these issues, recruitment into the study took longer than expected. However, it is worth noting that the delay in recruitment is not unique to NAOMI, but a difficulty in most of the trials aimed at hard-to-reach drug using populations. Like NAOMI, the German trial of heroin-assisted therapy had to be extended an additional year due to unexpected delays in recruitment.

A total of 251 clients met the eligibility criteria and provided informed consent including 59 (23.5%) in Montreal and 192 (76.5%) in Vancouver. Random assignments were as follows: oral methadone 111 (44.2%); injected diacetylmorphine 115 (45.8%); injected hydromorphone 25 (10.0%).

Characteristics of the NAOMI participants

Analysis of the baseline characteristics of participants in the NAOMI trial demonstrates successful recruitment of the target population: long-term, chronic opioid injectors with severe health and social problems and several previous addiction treatment attempts. In addition, almost all the participants were poly-drug users with cocaine being the second most popular drug of choice after heroin.

Socio-demographics: The mean age of the study group at recruitment was 39.7 years, 38.6% of the participants were female, and 23.9% defined themselves as Aboriginal (Table 1). A total of 72.9% declared that they were living in an unstable/precarious housing situation.

In the prior 3 years, most of the participants had been regularly unemployed (70.9%). The two most frequently cited sources of income were public assistance (76.1%) and illegal activity (67.3%). A total of 17.5% were involved in sex work.

Almost all of the participants (94.4%) had been charged at least once in their life for crimes of any nature and 81.7% had been convicted at some point. In the month prior to the baseline

assessment, participants spent a median of 15 days involved in illegal activities out of the prior 30 days and spent a median of $1500 on acquiring drugs in the same time period.

NAOMI participants reported an extensive history of regular drug use with heroin and cocaine being the most commonly used drugs (Table 2). Not surprisingly given the inclusion criteria, heroin was used on average more than 26 days of the prior 30 days. Cocaine was usually smoked as crack cocaine a mean of 13.4 days and injected as cocaine powder a mean of 5.1 days in the prior month. Speedballs, a combination of heroin and cocaine, were used a mean of 2.7 days the prior month. Participants injected on average around 4 to 5 times per day and reported a mean history of 16.5 years of drug injection prior to the study.

A total of 62.9% or participants were positive for hepatitis C (HCV) at baseline while 9.6% were HIV positive (Table 3). Almost one third of the sample (31.3%) had attempted suicide at least once in their life. In the month prior to randomization, 55% reported psychological problems though only 38.2% received psychological treatment in their life.

Participants had a median of 7 previous drug treatment attempts including a median of 3 previous methadone treatments episodes. The mean lifetime number of previous overdoses was 4.1.

In summary, the profile of the participants entering the NAOMI trial demonstrated that the trial reached some of the most chronic and marginalized heroin users in Vancouver and Montreal who were outside the treatment system and who continued to use heroin despite numerous previous treatment attempts.

Follow-up rates

Follow-up is a critical element in randomized controlled trials, and has been viewed as a concern when dealing with hard-to-reach groups such as injection drug users. However, despite the marginalized and transient nature of the study population, follow-up in NAOMI was excellent. Participants visited a separate research office for their research follow-up visits whether or not they were retained in treatment at the clinic. The independence of the research office, the commitment and dedication of the participants together with an experienced research staff that developed innovative ways of reaching out to participants (e.g. visiting jails, hospitals) resulted in extremely low rates of loss to follow-up for research purposes. Of 251 participants in NAOMI, only 11 individuals did not complete the 12-month primary outcome assessment yielding a research completion rate of 95.6%.

Table 1: Selected characteristics of the NAOMI participants

	Vancouver (n=192) % or mean	Montreal (n=59) % or mean	Total (n=251) % or mean
Age	40.9	35.6	39.7
Female Gender	38.5%	39.0%	38.6%
First Nation	31.3%	-	23.9%
Current housing			
stable housing	11.5%	78.0%	27.1
precarious housing	88.5%	22.0%	72.9
Generally unemployed in the past 3 years	74.0%	61.0%	70.9%
Received money in the prior 30 days for			
Public Assistance or Welfare	79.2%	66.1%	76.1%
Illegal Sources	70.3%	57.6%	67.3%
Sex work	18.8%	13.6%	17.5%
Charges in life for any crime	97.9%	83.1%	94.4%
Ever convicted in life	87.5%	62.7%	81.7%
Illegal activities, days in the prior 30 (median)	20	5	15
Money spent on drugs, prior month (median)	$1500	$1200	$1500

Table 2: Drug use among NAOMI participants

	Vancouver (n =192) mean	Montreal (n=59) mean	Total (n=251) mean
Days of Heroin use in prior 30 days	26.8	25.4	26.5
Days of Crack Cocaine in prior 30 days	16.9	2.3	13.4
Days of Cocaine Powder in prior 30 days	5.1	4.9	5.1
Days of Speedball use in prior 30 days	3.2	1.1	2.7
Number of times injecting drugs in a day	5.1	3.6	4.8
Years injecting drugs	17.4	13.4	16.5

Table 3: Selected health related events and behaviours

	Vancouver (n =192) mean or %	Montreal (n=59) mean or %	Total (n=251) mean or %
Hepatitis C Positive	66.1%	52.5%	62.9%
HIV Positive	9.9%	8.6%	9.6%
Ever attempted suicide	28.1%	40.7%	31.3%
Number of prior MMT (median)	3	3	3
Number of previous treatments (median)	7	7	7
Overdoses in life	3.5	5.9	4.1

The Primary Outcomes

Figure 2 and Tables 4 and 5 present the results of the primary analyses involving treatment retention and response in both graphic and tabular form. The retention and response rates were high in both groups, but significantly higher in the heroin (DAM) group than the MMT group, in keeping with the two primary hypotheses.

As seen below, the respective retention rates in the DAM and MMT groups were 87.8% and 54.1% respectively (Table 4). The difference between groups was statistically significant ($p<0.001$) with a Relative Risk (RR) of 1.62 (95% confidence interval = 1.35-1.95).

The treatment response rates were 67.0% and 47.7% in the DAM and MMT groups respectively (Table 5). This difference was statistically significant ($p=0.004$) with an RR of 1.40 (95% confidence interval = 1.11-1.77).

Figure 2: The Primary Outcomes by Type of Treatment

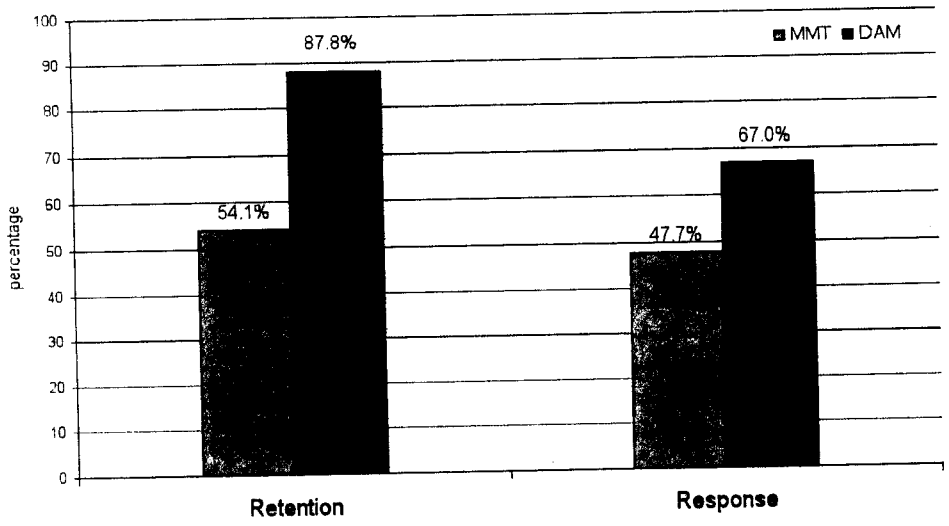


Table 4: Treatment Retention by group at 12 months

	MMT	DAM	Total	Relative Risk (95% CI)
Not Retained	51	14	65	
	45.9%	12.2%	28.8%	1.62 (1.35-1.95)*
Retained	60	101	161	
	54.1%	87.8%	71.2%	
Total	111	115	226	
	100.0%	100.0%	100.0%	

(*) p<0.001

Table 5: Treatment Response by group at 12 months

	MMT	DAM	Total	Relative Risk (95% CI)
Non-Responders	58	38	96	
	52.3%	33.0%	42.5%	1.40 (1.11-1.77)*
Responders	53	77	130	
	47.7%	67.0%	57.5%	
Total	111	115	226	
	100.0%	100.0%	100.0%	

(*) p=0.004

A related analysis concerns the proportion of participants in each group that were able to achieve both primary outcomes: retention and response. This is seen in Table 6 below.

In the DAM group, 63.5% of the participants achieved both primary outcomes compared to 35.1% in the oral group. This difference was statistically significant (p<0.001) with an RR of 1.81 (95% CI = 1.35-2.41).

Table 6: Response rate in both primary outcomes among groups at 12 months

	MMT	DAM	Total	Relative Risk (95% CI)
Non-Responders	72	42	114	
	64.9%	36.5%	50.4%	1.81 (1.35-2.41)*
Responders	39	73	112	
	35.1%	63.5%	49.6%	
Total	111	115	226	
	100.0%	100.0%	100.0%	

(*) p<0.001

Similarity of Heroin and Hydromorphone

Table 7 below presents the comparison of the treatment retention and response within the injection arm between the group that received heroin (DAM) and the group that received hydromorphone (HMO). The results were very similar.

Subjectively, the participants did not appear to be able to distinguish the effects of the two drugs. Despite long histories of heroin use, only 1 of 24 participants who were receiving HMO, thought (s)he was not receiving heroin.

Table 7: Response in both primary outcome measures in the injection group by type of opioid received on a double-blind basis (HMO vs DAM)

	HMO (25)	DAM (115)	Total
Treatment Retention Rate	22	101	123
	88.0%	87.8%	87.9%
Treatment Response Rate	16	77	93
	64.0%	67.0%	66.4%

Treatment Effect in Vancouver vs Montreal

We also tested to see if the effects were similar in Vancouver and Montreal. As seen in Table 8, the retention and response rates were very similar in both cities.

Table 8: Primary outcomes by site, by group at 12 months

	Treatment Retention		Treatment Response	
	Oral	Injection	Oral	Injection
Vancouver	45	95	40	72
	52.9%	88.8%	47.1%	67.3%
Montreal	15	28	13	21
	57.7%	84.8%	50.0%	63.6%
Total	60	123	53	93
	54.1%	87.9%	47.7%	66.4%

Trends in Responses over Time

Figure 3: Illicit heroin use among NAOMI participants

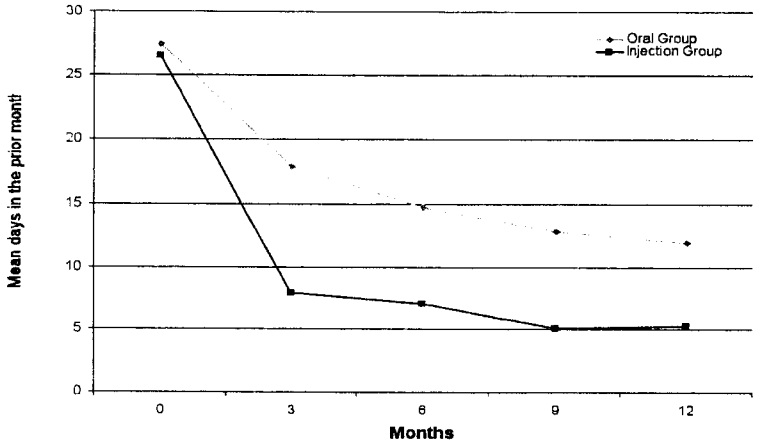
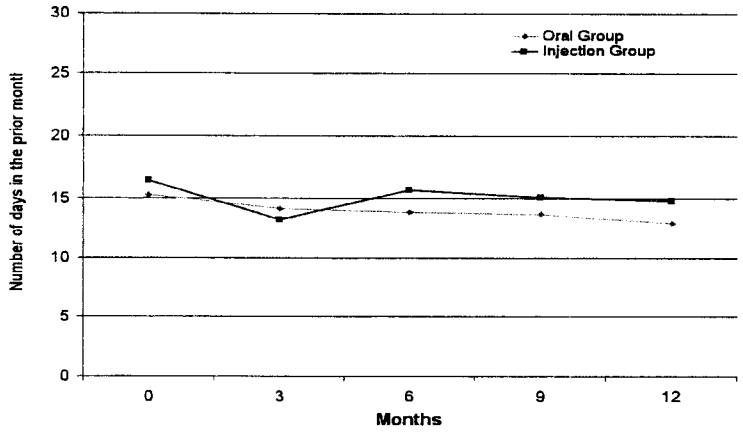


Figure 3 shows marked declines in illicit heroin use over time in both groups, significantly more so in the injection group.

Figure 4: Cocaine use among NAOMI participants



Cocaine use did not show a similar decline in either the oral or injection group (Figure 4).

Figure 5: Money spent on drugs in the prior 30 days

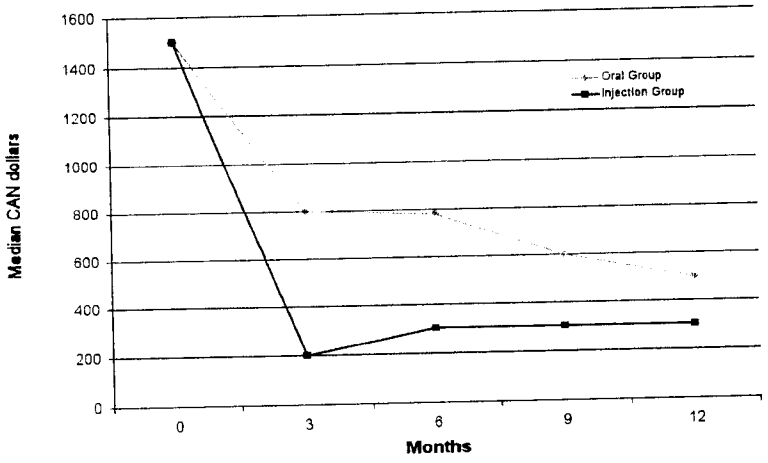
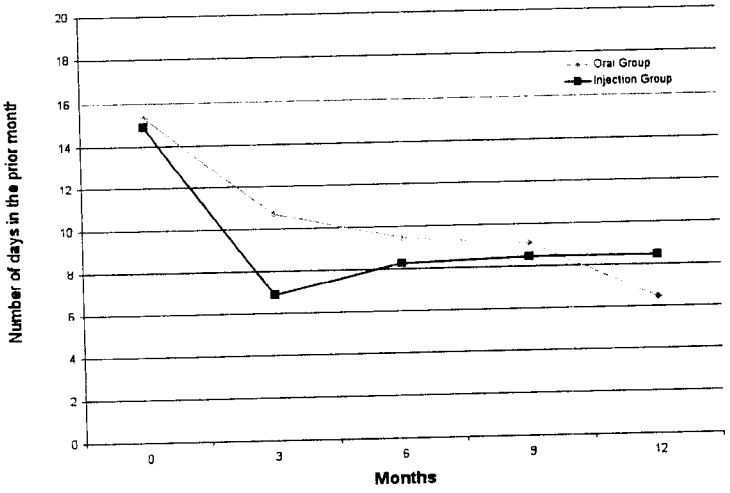


Figure 6: Days of illegal activity in the prior 30 days



Figures 5 and 6 show declines in the both the oral and injection arms with respect to money spent on drugs and days of illegal activity respectively in the prior 30 days.

Figure 7: MAP Physical health scores among NAOMI participants

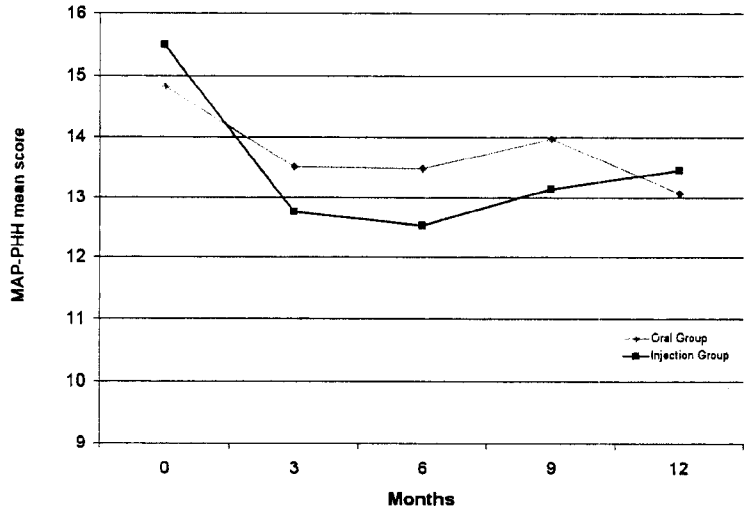
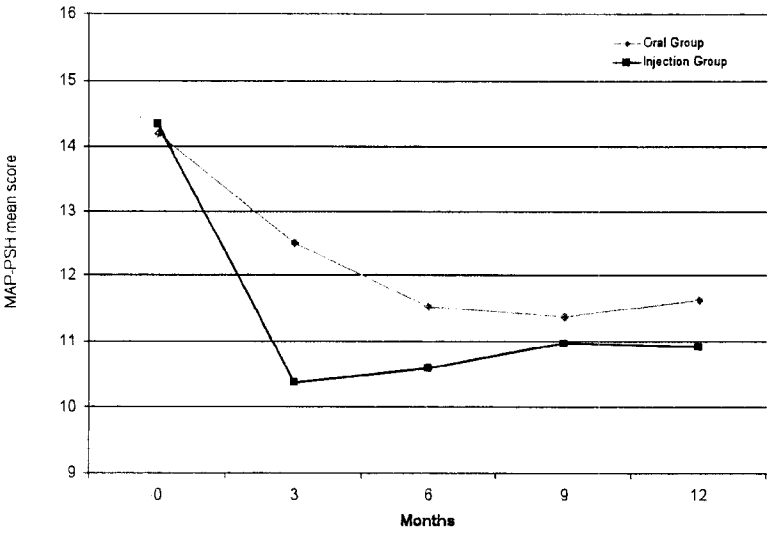


Figure 8: MAP Psychological health scores among NAOMI participants



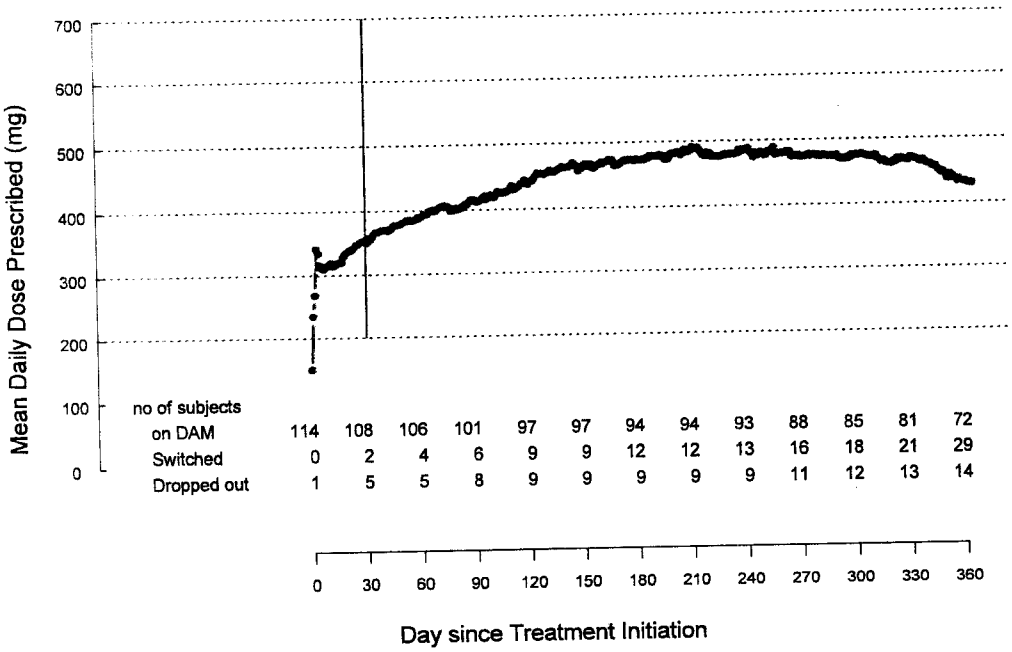
We used the Maudsley Addiction Profile (MAP) questionnaire as one of the secondary instruments in the trial. Figures 7 and 8 show the mean scores over time in the MAP physical health and psychological health scores respectively. A lower score indicates improved health. As seen in the Figures, there were marked improvements in both groups, particularly during the early phase of the treatment.

Dosage

As seen in Figure 9, the mean daily dose of heroin increased during the initial dose adjustment period as was expected. The average dose then stabilized at 450 to 500 mg. This was less than half the maximum allowed daily dose of 1000 mg. This does not support the suggestion that heroin users will become tolerant and require higher and higher doses.

The decline seen in the last month on the right side of Figure 9 is due to tapering of heroin doses for those participants who had entered the transition period.

Figure 9: Mean daily dose of heroin (DAM) prescribed



With respect to methadone dosage, for those who received DAM or HMO co-prescribed with methadone, the mean daily dose of methadone was 42.7 mg. For the control group who received methadone alone, the mean daily dose was 95.7 mg.

Safety

During the NAOMI study, a total of 109,171 injections of the study medications took place in the treatment clinics. Utilizing the experience gained in Europe and enacting sound safety protocols allowed the treatments to be administered very safely.

Adverse Events: Most of the adverse events in the injection arm were expected based on the European experience. More than half (54.7%) of the adverse events involved mild and moderate allergic-type reactions (localized itchiness, raised blotchiness at injection site, facial flushing, pins and needles, generalized hives), and only 0.4% (11) of these events were considered severe in intensity.

There were 167 adverse events considered as severe in intensity of which 106 were deemed to have some relationship with the injection medication (1 per 1029 injections). Besides the 11 cases of allergic reactions already mentioned, drowsiness (45) and seizures (12) were the next most frequent severe events having some relation to the injection medication.

Seizure episodes have been described in the literature as having a possible connection with the use of intravenous heroin. Seizures related to heroin use are commonly associated with the co-use of other substances, especially crack cocaine and benzodiazepines. The latter was true of the NAOMI participants who underwent seizures.

It is important to note that none of the adverse events required the discontinuation of the treatment and almost all were resolved without sequellae (longer term complications). The pre- and post-injection assessment period allowed monitoring and treatment of the adverse events and the majority of them were easily resolved. For example, drowsiness was most often managed by asking subjects to remain for one or more additional observation periods until they were deemed fit to leave the clinic based on clinical assessment.

Serious Adverse Events (SAE): There were 61 serious adverse events in the injection arm. Many of these involved the co-morbidities associated with chronic heroin addiction and not with the injection medication. Of the 61 SAEs, only 29 were deemed to be possibly, probably or definitely related to the injection medication (1 per 3675 injections). Of the latter 29 instances, 13 and 7 involved oversedation and seizures respectively.

Seizures have been discussed above. In most cases, this was an exacerbation of a previous seizure disorder and/or related to the concomitant use of cocaine. In each instance, the episode resolved without sequellae.

The 13 episodes of oversedation represent those instances when intervention was required beyond observation. This included the administration of oxygen and naloxone as per emergency protocol. In all instances, the participants were aroused with naloxone injection. As per protocol, ambulances were called in every case; however, the participant either refused the ambulance transfer or refused emergency admission upon arrival at the hospital. These episodes were most often associated with recent use of benzodiazepines.

Deaths: At the time of analysis, there have been two deaths in the trial, both in participants randomized to the oral arm and both due to drug overdose. One participant (#3192) was in methadone treatment at the time of death; however (s)he had missed his/her methadone dose the day before the fatal event. The other participant (#3073) was an early drop-out from the oral arm who rejected methadone treatment after being informed of the results of the randomization; the death occurred two years later.

Community Impact

Prior to the study, there were concerns that the treatment clinics would have an adverse impact on the surrounding neighbourhoods. To address this in Vancouver, the study established a Neighourhood Advisory Committee (NAC) and posted a 24-hour telephone hotline to receive complaints from any concerned neighbours. During the course of the study, there were no complaints received from the NAC and zero calls to the hotline. Preliminary findings from a community impact study conducted by Simon Fraser University found no adverse effects of the clinic on the surrounding neighbourhood. There were also no negative impacts observed near the Montreal clinic.

CONCLUSIONS

1. Heroin-assisted therapy proved to be a safe and highly effective treatment for people with chronic, treatment-refractory heroin addiction. Marked improvements were observed including decreased use of illicit "street" heroin, decreased criminal activity, decreased money spent on drugs, and improved physical and psychological health.

2. The NAOMI trial attracted the most chronic and marginalized heroin users who were outside the treatment system and continued to use heroin despite numerous previous treatment attempts. Both heroin-assisted therapy and optimized methadone maintenance treatment achieved high retention rates and remarkable response rates in this difficult-to-treat group.

3. Contrary to pre-existing concerns, the treatment clinics appeared to have no negative impacts on the surrounding neighbourhoods.

4. Participants on hydromorphone did not distinguish this drug from heroin. Moreover, hydromorphone appeared to be equally effective as heroin although the study was not designed to test this conclusively. If this were proven to be true, hydromorphone-assisted therapy could offer legal, political and logistical advantages over heroin and could be made more widely available.