

## **North American Opiate Medication Initiative (NAOMI)**

### **Backgrounder**

#### **Harms and costs of opiate addiction**

Opiate addiction is a major public health problem in North America with an estimated 600,000 opiate-dependent persons in the United States and 60,000 to 90,000 in Canada. Untreated opiate addiction can lead to overdose, infectious disease, loss of regular social and economic functioning, and extensive engagement in both drug-related and drug acquisition crime. Research shows that these risks and harms impose major costs on our public health, health care, welfare and criminal justice systems.

Regarding overdose, in British Columbia alone, there was one injection drug use-related overdose death per day in 1998, and Canada in total reports approximately 1,000 such deaths per year.

Canadian HIV prevalence rates among injection drug users (IDUs) are estimated to be 20-25% or higher in cities like Vancouver and Montreal, and infection rates in other jurisdictions are rising. Similarly, hepatitis C infection rates among IDU populations in British Columbia and Ontario range from 55% to 88%, and hepatitis B rates range from 25% to 35%.

The social and economic costs of illicit drug use are considerable. Illicit drug use has been correlated with family dysfunction, violence and criminal behavior. Most users require funds in the realm of \$100-\$150 per day to support their drug use habits alone, and field studies have shown that the large part is generated by welfare assistance and illegal activities such as property crime. Most illicit opiate users have had multiple criminal arrests, convictions and sentences, and are often under some form of criminal justice supervision. In addition, many costs are incurred through a higher frequency of uninsured hospital visits for treatment of direct and indirect health effects.

In Canada, illicit drug use costs account for approximately 0.2% of the GNP. A recent cost-of-illness analysis on the basis of data from a cohort of untreated opiate addicts in Toronto yielded an estimate of over \$45,000 in societal costs per addict per year.

#### **Methadone and its limitations**

In North America the primary method for the treatment of opiate addiction is with methadone hydrochloride. Methadone is easily absorbed when taken orally and has a half-life of

approximately 25 hours, allowing once daily administration. Methadone maintenance therapy (MMT) was pioneered in the U.S. and Canada in the early 1960s. This therapy provides methadone orally on a regular (usually daily) basis to the patient. Studies have suggested that methadone is successful in blocking the effects of opiate withdrawal symptoms, thus reducing the major risks, harms and costs associated with untreated opiate addictions.

Studies show, however, that methadone maintenance therapy has limitations. It is available to only a limited number of addicted people and, where it is widely available, many prefer not to use it. In Canada only 15%-20% of the estimated opiate addict population are in methadone treatment, although this proportion is somewhat higher in the urban centres of Vancouver and Toronto.

While limited availability is certainly a contributing factor to the low uptake, the characteristics of MMT programs also play a role in deterring entry for many IDUs. In a recent Toronto survey of untreated opiate users who were offered immediate admission to MMT, 48% would have accepted treatment, 33% would have outrightly rejected it, and 19% were ambivalent.

Besides limited attraction, a further limitation to the overall effectiveness of existing MMT is its restricted success in retaining patients in treatment. Studies suggest that MMT programs lose one third of their original treatment population within the first 12 months and another third within the following 24 months.

### **Heroin-assisted therapy**

In light of the above limitations of methadone therapy, a number of countries have recently started to utilize the provision of injectable opiates to treatment-resistant opiate users as an alternative treatment. The United Kingdom has practiced controlled prescription of injectable heroin and methadone in the treatment of opiate addicts for decades. However, only limited, non-systematic evaluation of their programs has been conducted.

The idea of heroin-assisted therapy in North America is not new. From 1919-1923, several morphine and heroin-assisted therapy clinics were in operation until their termination by the U.S. government. Scarcity of data has prevented a proper analysis of the efficacy of opiate prescription in these clinics. In Canada in 1972, a Commission of Inquiry led by Mr. Justice Gerald LeDain recommended the implementation of a heroin prescription trial for addicts who could not be attracted into conventional forms of opiate addiction treatment.

### **Swiss heroin study**

More recently, Switzerland and the Netherlands have conducted studies examining the effectiveness of heroin prescription in the treatment of opiate addiction. The three-year multi-site Swiss study (1994-1997) provided injectable opiates to over 1,000 opiate addicts who indicated a long-term drug abuse history and multiple failed treatment attempts. Although not conducted as a controlled trial, the before-after study produced encouraging outcomes.

The program managed to retain 69% of its original sample of hard-core and treatment-resistant addicts in treatment throughout the 18-month study period; more than half of the dropouts switched to other treatments or went drug-free, and no deaths occurred as a direct consequence of the opiate drugs prescribed. Drop-out rates in other randomized and

double-blind studies of methadone and morphine were 3 to 13 times that of the heroin group. A substantial percentage (83%) of the patients switched to abstinence-based therapy during the course of the study. Importantly, self-reported drug use decreased dramatically during the course of the study.

### **Health improves, crime plummets**

Participants in the Swiss study experienced marked improvements in physical health and social indicators (e.g., social functioning, employment, illegal activities, housing). The overall death rate was 3%, a rate comparable to other reported death rates in cohorts of addicts. The proportion of participants with unstable housing fell during the 18 months (43% on admission to 21% at 18 months). The rate of employment doubled from 14% to 32% and the proportion who were debt-free increased from 15% at admission to 34% at 18 months. Arrests and illegal income generation decreased substantially from 69% to 10% and there was a greater than 50% reduction in criminal offences registered by the police over the time of the study.

The Swiss public has since voted in referenda in favour of continuing the trial as a long-standing program. The Swiss study, however, lacked a true control group and therefore allowed for possible biases.

### **Dutch heroin studies**

In response to these and other criticisms of the Swiss research, the Dutch government commissioned a multi-site randomized controlled trial co-prescribing injectable heroin to hard-core addicts that began in July 1998. The final report of the Dutch trial has recently become available ([www.ccbh.nl](http://www.ccbh.nl)). In contrast to the Swiss, the Dutch conducted two scientifically rigorous clinical trials: one examining injection heroin; the other inhalable heroin. Both trials had a similar design and consistent outcome measures. As maintenance therapy is widely available in the Netherlands, the Dutch trials targeted people in methadone maintenance treatment who continued to use illicit drugs. In both the injection and inhalation trials, the investigators found significantly greater improvements in drug use, physical and mental health and social functioning in those receiving heroin prescription in combination with methadone compared to those randomized to continue on oral methadone alone.

The Dutch results, therefore, demonstrate the effectiveness of heroin-assisted treatment but these results cannot be easily generalized to North America or elsewhere because of the wide availability of methadone therapy and the different treatment system in the Netherlands.

The NAOMI study aims to assess whether heroin-assisted therapy could be an effective treatment for Canadians who are chronically addicted to heroin and have failed to benefit from other therapies. Similar studies of heroin are also underway or being planned in Germany, Spain and Australia.

### **NAOMI study design**

NAOMI is a randomized controlled clinical trial that will enroll injection opiate users who have failed to benefit from other treatments. Two study centres (Vancouver and

Montreal) will enroll participants, beginning in February 2005. Entry criteria include being 25 or older, addiction to opioids for at least 5 years, daily injection opioid use for at least a year, and at least two episodes of methadone maintenance treatment for 30 or more consecutive days, or methadone maintenance and another form of treatment.

Forty-five percent of participants will be randomized to an “optimized” version of oral methadone treatment, which will serve as the control arm. Fifty-five percent of participants will be randomized to the injection arm. Within the injection arm, 45% will receive injectable heroin and will form the experimental arm. The remaining 10% in the injection arm will receive injectable hydromorphone (Dilaudid™), which is pharmacologically similar to heroin. Heroin and hydromorphone will be given on a double-blind basis within the injection arm (neither the participant nor the study staff will know who is receiving which medication). Participants in the injection arm are eligible to receive “optimized” methadone therapy as an adjunct, if desired, at any time during the treatment period. The reason for this is that some individuals in the injection arm, such as those who are employed, may wish to avoid having to visit the treatment clinic 3 times every day for injections.

The primary rationale for the smaller hydromorphone arm is to permit objective detection of illicit heroin use by urine testing.

Study treatments will be offered for 12 months followed by a 3-month period during which participants still being treated with injection drugs will be transitioned to conventional therapies such as methadone. Research data will be collected regularly for two years from the point of randomization.

### **Study sites**

Within each of the two study sites (Vancouver, Montreal) there will be two separate facilities: a treatment clinic, and a research centre. The treatment clinic will house the clinical staff and medication dispensing activities. The research centre is where the participants will be interviewed regularly and basic study outcomes are measured.

The treatment clinic and research centre will operate independently. Data collected by the research centre will not be shared with the treatment clinic and will not affect the clinical care received by the study participant.

The investigators believe that separating treatment from research data collection will aid in reducing bias. Second, because a significant degree of non-response in the treatment arms will be due to non-retention, it is imperative to collect research follow-up data on all participants, whether or not they are retained in treatment. The research centre will offer modest cash remuneration (an average of \$25) for each follow-up research visit and the time taken to fill in lengthy questionnaires.

### **Treatment clinic**

The treatment clinics will see participants on an outpatient basis. Each treatment clinic will be open 8 AM to 8 PM, seven days a week, because of the daily requirements of heroin injection. Clinical staff will include a clinic director (addiction medicine specialist), nurses to dispense medications, program assistants, and a pharmacist.

### **Medical care, social services**

People with untreated addictions often lead such troubled lives that they are unable to seek the help of primary care physicians, improve their housing, or access other social services. A premise of the NAOMI study is that heroin-assisted therapy could stabilize the addictions of participants and allow them to address other health issues and concerns. All participants will therefore have direct access to social workers and primary care physicians, who will be available at the research centres of the NAOMI sites. The study will also track the degree to which participants are able to improve their health and their lives.

### **Economic analysis**

The NAOMI study will include an analysis of the cost-effectiveness of the alternative treatment strategies will be assessed according to 1) the incremental cost per patient retained at 12 months; and 2) incremental cost per quality-adjusted life-year gained.

### **Ethical approval**

The NAOMI clinical trial has been approved by the ethical review boards of the University of British Columbia / Providence Health Care, and the Université de Montreal, as well as by the Canadian Institutes of Health Research, Canada's premier health research funding agency.